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DEPARTMENT OF PHYSICAL SCIENCES

CHANGE MANAGEMENT FOR VALUE ADDITION

Dr. Satya Prakash Sharma

ABSTRACT

Today change is normal. How the industry deals with the change can mean the difference between success & failure. The overall improvement depends upon the implementation of a prioritized change programme, with concentration of effort on change projects, a few at a time, and with frequent measurement of results to determine the extent to which success was being achieved. Managers and executives must be trained for the same.

After giving a brief about the change trilogy, change cycle and stages of acceptance, the paper highlights a proven path an integrated approach that identifies an improvement cycle, in order to achieve maximum output after implementing a project for improvement. Before launching a new effort, it is important to evaluate what's working well today, what is not and then to recommend what the correct actions are for improving the company/ professional practice. The concept and hazard of neutral zone which is time of great uncertainly and fear has also been explained briefly along with success ratio and dynamic stability. A case study of change management has been discussed.

Keywords: Change, improvement, neutral zone, change triology, change cycle, proven path.

1. INTRODUCTION

Change is a natural process. The mantra, "change or perish"? Like many corporate clichés happens to be true. Future is going to present even greater changes. In competitive environment of today, many manufacturing industries are implementing MRPII, JIT, CIM, FMS, KANBAN, TQM and other techniques to improve business competitiveness by increasing customer satisfaction, cash flow and productivity. While the theoretical benefits are enormous, very few implementations achieve their potential because of a failure to manage the changed process. How the industry deals with the change can mean the difference between success and failure. Successful management of change requires a clear understanding of the factors involved and effective planning to control the levers of change

Unfortunately, most of the leaders of a manufacturing industry have not been trained in the management of change. To be effective in a world class environment, managers must develop an understanding of the change process, and must master the skill involved in introducing and implementing change.

Skills must be developed in anticipating the need for change, rather than simply reacting to changes others are making. Skills must focus on preparing the organization for change. Significant efforts must be made to develop new approaches to managing the organization while it undergoes major change processes. Finally, new orientations to stablising the organization after a change, while simultaneously making it ready for the next generation of changes, must be developed.

Most change efforts do not fare so well as the change initiatives start with great enthusiasm, visibility and upper management support, but often die out long before the goal is reached. A common mistake people make when managing change is to assume that there is adequate commitment. In fact the commitment is actually far too week to withstand the challenges of change. Another, is the failure to measure and feedback tangible preliminary results and benefits of the change, while the change is still being established.

Aim should be to focus an organization the change objective, sustain commitment to the change effort, overcome the inevitable resistance and practical hurdles, keep the implementation on track, and reach the point where the change itself becomes the normal and it's benefits are tangible.

2. CHANGE IN INDUSTRIAL OUTLOOK

All in all, push and pull on industry will surely lead to very significant waste accumulation which necessarily requires elimination or reuse to improve the overall efficiency of the industry;

hence a change in our outlook and practice is becoming very essential. The questions that arise in this context are:

- Competitive pressure push
- Emerging technology push
- When to change
- How to change
- How to cause change
- Where to change
- What to change
- How to promote change so that the improvement cycle repeats
- Creating the environment for change
- Challenging past practices and excuses
- Removing the barriers and road blocks
- Rewarding the right things so that change continues to evolve.

Waste exists in all work activities, all process tasks, and at all levels in the organization. Challenging past practices and excuses involves, to a large extent, understanding the sources of waste and minimizing these wastages by implementing a change process.

3. CONTINUAL IMPROVEMENT & DYNAMIC STABILITY

Continual improvement refers to changes that are gradual and incremental as well as changes of a more dramatic nature.

There are two levels at which continual improvement takes place in a factory: the process level and the system level. Process improvement is detailed and narrow in scope, and system improvement is broad and holistic in scope. Both are necessary if the factory is to benefit from improvement efforts. Process improvement alone cannot produce system wide advantages, and system improvement requires that specific processes within the system be modified.

Process improvement is continual and incremental. It takes place on the shop floor with the people who are involved in the specific process. In practice, shop floor workers can improve their own processes without the assistance or involvement of engineers or managers, but there is no reason to exclude anyone who wishes to be involved in the improvement effort.

Process improvement focuses on the details and methods of a specific production process. It can include the placement of tools, presentation of material, or arrangement of machines in a work cell. Fixtures or devices that automatically load or unload machines are often installed as a result of process improvement. Process improvement involves scrutinizing how people get their work done, and its goal is to minimize the time needed for material to flow through the area. Activities that do not add value to the product, such as unnecessary walking to get supplies or looking for tools, are reduced or eliminated. Of course, as with any change, the standardized work procedure should be revised.

Improvement should not be a special event that takes place sporadically. It should be an ongoing part of the workday. To make sure factory improvement is continual, we recommend a cyclical approach. Figure 1 represents a typical improvement cycle. First a problem or area that needs improvement is selected. Then the root cause of the problem is identified and a possible solution devised. The solutions implemented and tested for effectiveness. If it works, the process is standardized to reflect the new method. If the solution is not effective, the "cause" that was identified is reexamined to make sure that it was truly the source of the problem. Once the true source of the problem has been verified, a new solution is developed, implemented, and tested. After the solution's effectiveness has been established, the standardize work procedures are updated, and the next problem or area needing improvement is addressed.

Change has been with us forever, and it always will be, but the idea of change itself is changing. Change creates initiative overload and organizational chaos, both of which provoke strong resistance from the people most affected. To change successfully, companies should stop changing all the time. Instead, they should intersperse a major change initiatives among carefully paced periods of smaller, organic change- an approach called dynamic stability.

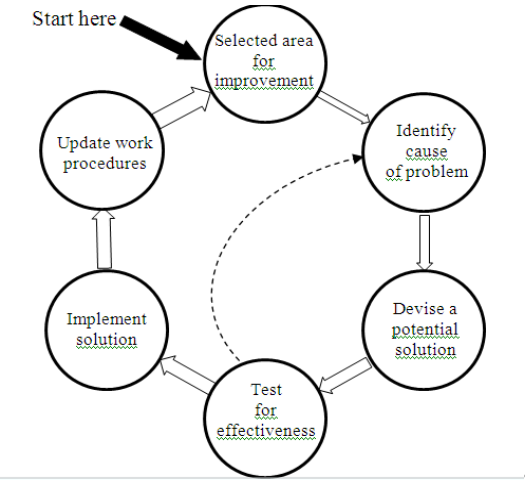


Figure 1 Improvement Cycle

Dynamic stability is a process of continual but relatively small change efforts that involve the reconfiguration of existing business models rather than the creation of new ones.

Oscillation between big changes and small changes helps ensure dynamic stability in organizations. More critically, it paves the way for change that succeeds

Achieving dynamic stability is more difficult than ramming audacious changes through an organization. However, dynamic stability has the great advantage of allowing change without fatal plan.

CHANGE TRILOGY – SILENT WAR

Indian industry is indeed engaged in a 'silent war'. To win it, we must be able to manage the change for improved productivity. Industry must rediscover the powerful effects of an allied effort which incorporates innovation, involvement of all employees and the management of technology. These three simulation efforts, combined with a never ending emphasis on continuous improvement are the primary strategic and technical initiatives which must be used in the silent war. Message is in one of the two forms. How we are managing ourselves into economic decline through the neglect of manufacturing or how to apply the winning techniques to improve our own performance.

What is saught today, is to move the innovative process out of the laboratories into the centre of the business – into manufacturing. Fig 2, suggests that for successful company, the goal must be continuous improvement, through a combination of innovative ideas and people involved in their implementation, using appropriate technology as needed. to win the silent war, companies must transform their operating environments. Employees must understand that continuous improvement is the norm and the change will be part of all operations. Instability must exist within the context of stability.

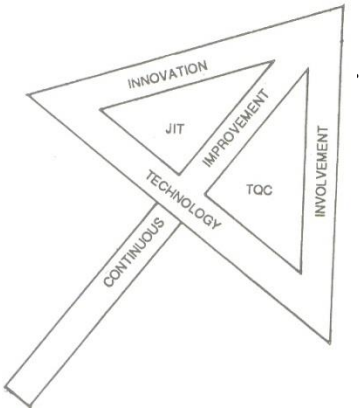


Figure 2 Managing Productivity and Change

WHY WINNERS ALWAYS SEEM TO WIN

It is noticed that some of the firms (like some people) come up as winners all the times where many fail. They march into MRP, expand into CIM and it ripples successfully through the whole firm. They take up TQM and the defects fall, they jump into JIT and things flow better. It does not make sense to credit their success to the methodologies and technologies- MRP, TQM, JIT etc. plenty of firms have tried these and failed, or experienced only marginal success/ results. Part of the answer is that these firms never forgot the message.

Three plus one = survival in white water

In today's turbulent economy, three things aid survival, and the fourth is essential or critical.

I. Read the river- listen to your market.
II. Know and grow your physical abilities and limits i.e. capabilities – listen to your work force. Assimilate the lessons of philosophy, skill, experimentation and improvement and listen to it's accumulated wisdom.
III. Master the techniques of maneuvering and righting yourself – listen to the relevent technology.

The fourth essential and critical point is,

- Keep your balance mentally, even more than physically when things get exciting, i.e. keep the above three in balance by clear strategies, measure every system or technology by its's support to these strategies.

This demands whole company vision, continuous learning, constant reassessment of system and technologies in support of goals.

6. STAGES OF ACCEPTANCE

Change acceptance is a process, which includes the following stages:

Awareness. Awareness consists of the first introduction to the potential change and the initial impressions formed by the stakeholder. An abstract concept of the changed environment is formed. Since project objectives and potential changes are often spread through rumors and half-truths until they are formally determined and disseminated, the potential exists for the awareness phase to extend over a significant period of time. A change implementer must be sure that all stakeholders do not form false concepts and build unnecessary resistance in the later stages of the acceptance process.

Self-concern. The self concern phase quickly follows the awareness phase. During this stage the stakeholder asks, "what's in this for me?". Each stakeholder will project the impact the change will have on his or her environment and begin to form an opinion. Positioning as a supporter or blocker will rely heavily on the stakeholder's thoughts developed during this stage.

Mental tryout. During the mental try out phase, stakeholders begin to process details about the change. Envisioning or mentally walking through the new environment or process is the key indicator that someone is in this stage of acceptance.

Hands on. At the hands on phase, stakeholders actually walk through the new process. They are exposed to the details and can see the impact the change will have on them. The last barriers to acceptance are exposed at this point, and the change integrator must identify and resolve them. These barriers may not have been objectively formed by the stakeholder and may reflect a failure by the stakeholder to perceive a win result in the change.

Acceptance. Once the final barriers have been mitigated, acceptance will follow. Unless the stakeholder perceives the result, this acceptance may be less than enthusiastic. Notice that each stage has a cumulative effect of stakeholder buy-in. their perception of a win result is building and reassured through these stages unless a net obstacle is not overcome. Figure 3 summarizes the stages of the change acceptance process

7. Change Formula

Change formula is a powerful tool that can help to plan change efforts. It identifies several key factors which must be present in sufficient degree to initiate and sustain a change effort. It is also a diagnostic tool that can be used to quickly assess what is missing or what is going wrong.

The difficulty of creating readiness for change, may be thought of in terms of the cost of changing to organizational members. Change will occur only when these costs are outweighed by a number of factors which can create positive motivation to change. This relationship between positive forces which support change, and the cost of change may be expressed as

$C_h = D \times M \times P > C$

Ch =Change

D=Dissatisfaction with the status quo
M =A new model for managing or organizing
P=A planned process for managing changes
C =Cost of change to individuals and groups

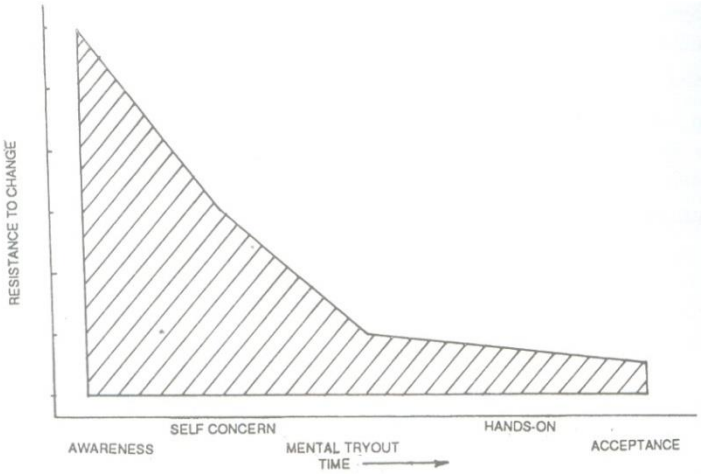


Figure 3 Sages of the Change Acceptance Process

For many purposes, substituting the concept of vision (V) for model (M) is more understandable and approachable. A vision can be thought of as a target to shoot for, or an extended wide angle 'photograph' of what the organization would look like in it's new status. The key factors for change are:

The "WHY" (Discomfort). The change will be difficult to implement unless the people who actually have to make the change feel the discomfort strongly. It may be necessary to "raise the level of discomfort" before people choose to support the change. Organization do not take on major changes unless there is very strong felt reason to do so due to the negative external threats.

The "WHAT" (Vision). Along with a sufficient level of discomfort, change effort will need a vision to move toward. The vision can provide a clear sense of direction, as well as positive motive for change. Organization lacking sufficiently clear and compelling vision often tend to waste their precious resources, time and energy.

The "HOW TO" (Process). A well thought out process for the implementation of change. (Which also requires adjustment process for people), has to be prepared. It may include reorientation of their job and perhaps a whole new way of thinking about their activities, career and the industry. Reviewing previous change efforts, pinpointing, what worked and what did not and why and applying those lessons can improve the probability of success in the current change efforts.

The "WHY NOT" (Cost or Resistance). It includes all forms of resistance to change, which must be overcome to initiate and sustain a change process.

In order to assess whether the situation to make change is favorable or not an overall comparison of:

a. Major driving forces that exist or could be developed to overcome the restraining forces.
b. Major resistive or restraining forces that must be overcome to initiate and sustain the change.

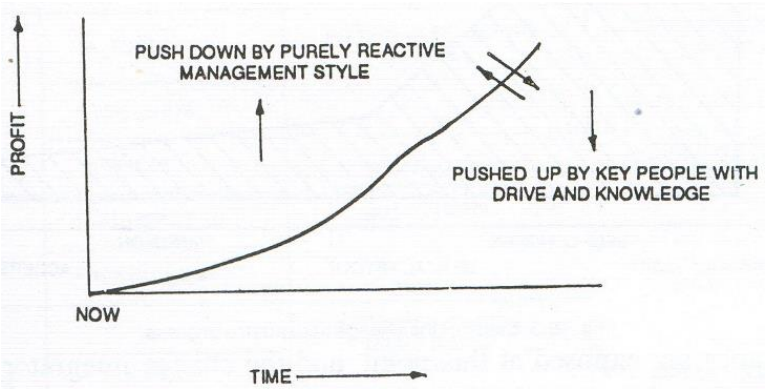


Figure 4. Illustrates the forces of change

Figure 4 Forces of Charge

Paradigms Against Change

People's believe in the technical and professional ranks that bog down the change process includes:

- My profession plays a vital role in the success of the business. I hold a responsibility to do the job

I am expected to do and if I accomplish this, I have done all I can to make the company successful.

- M responsibility ends at the point where my tasks have been successfully accomplished and passed on to the next function the chain.
- My hands are tied with regard to the tasks of other professions (functions) within the organization. I hold no direct responsibility for their success or failure other than to complete my part of the work they need to successfully complete their assigned responsibilities.
- I was educated in a professional field, then hired and trained by the company to perform a relatively clear set of professional duties and functional responsibilities, I may be asked to expand my duties and responsibilities within my function, given appropriate reasoning and/ or remuneration, but I should not be expected to step outside this basic role.
- There is a need for the various professions to work as separate and independent entities. Even functions that are closely related should never be combined.
- Change is good, in fact required, as long as the change does not affect the conventional or traditional way I am expected to do things within my profession.

9. CHANGE CYCLE

Change cycle is a road map that can be useful in choosing course, anticipating problems and helping keep track. The different stages of change cycle are:

1. **Choosing the target.** (strengthening competitive position, improving product line etc.)
2. **Setting goals.** (closer scrutiny of proposed change, purpose, scope, implementation plan, time duration etc.).
3. **Initiating action.** (individual commitment, collective, capabilities, shift from planning to action).
4. **Making connections.** (talking to others, looking for guidance, support, practical suggestions etc.)
5. **Rebalancing to accommodate the change.** (adjustment throughout the system, rebalancing of functional system relationship pattern and organizational structure etc.)
6. **Consolidating the learning.** (integration and reflection on the project as a whole).
7. **Moving to the new cycle.** (regarding time and completion, one cycle reaches completion and a new cycle may begin for the next change).

The challenges of the change cycle has it's own purpose and characteristics. In each stage some significant smaller change must take place to propel the cycle forward.

The challenges that manufacturing engineering/ management face in implementing change can be broadly put into two categories.

Functional Challenge, which relates to capability and structures of the system while the **People Challenge** includes attitudinal behavioral and emotional response to the change efforts.

10. COST OF CHANGE

Cost of change implies investment of both cash and personnel resources and all programmes require a commitment prior to the benefits being realized. At the company not al the costs were foreseen, but allowance had to be made for the following:

i. Training for revised work practice
ii. New plant layout
iii. New business systems
iv. Additional people resources
v. Organizational restructuring

Careful planning of change, with prioritizing of the necessary actions, can significantly reduce the effects of the potential profit dip, as shown figure 5.

Table 1 gives an idea for costing an engineering change.

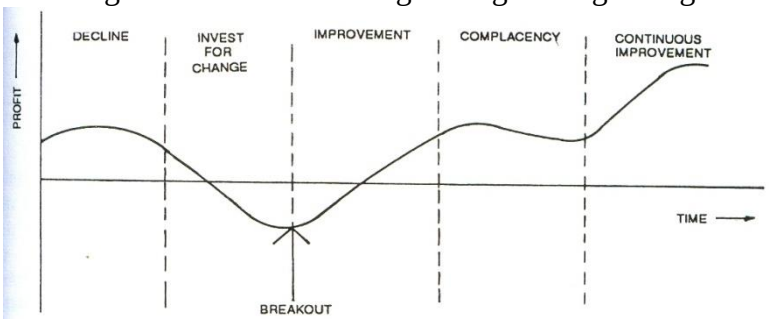


Figure 5 The Process of Change and Profit Dip

Notice that the analysis does not include the cost of surplus or obsolete material dispositions resulting from the change, nor the costs associated with the conversion or scrapping of tooling and fixture. It is only the direct administrative costs of processing each change to be implemented– a direct drain on the profitability of the organization, never recovered, seldom budgeted, and always detrimental.

11. THE NEUTRAL ZONE

The neutral zone is a time of great uncertainty and fear. It is like wading through a swamp full of snakes, insects, alligator, and quicksand with no way to see very far ahead. By being aware of the hazards of the neutral zone, one can help the factory to overcome them. There are six dangers of the neutral zone

- Anxiety rises and motivation falls.
- Absenteeism rises and productivity falls.
- Old weaknesses and past resentments resurface.
- Personnel are overloaded and turnover increases.
- People become polarized.
- The organization is vulnerable.

It might seem like the neutral zone should be avoided at all costs! Perhaps it seems much safer to let the factory keep running the old way. However, like the "ending" described above, the neutral zone can be navigated safely by understanding the dangers and taking a few simple precautions.

The neutral zone is not simply a difficult phase that must be endured before the factory can operate successfully in its new configuration. The neutral zone is a beneficial period that provides the necessary time for reorientation and redefinition. People need time for the old methods and patterns of behavior to take shape. As progress is made through the neutral zone, people begin to realize they wouldn't go back to the old way even if they could.

Table 1: Costing engineering changes

Costing the Engineering Changes				
Sr. no	**Function or Activity**	**Hours Required**	**Cost/Hour**	**Total Cost**
1	Design Engineering Change			
2	Detailing and Drafting			
3	Design Review Meeting			
4	Checking &Approval Process			
5	Document Control			
6	Document Distribution			
7	Manufacturing Engineering Review			
8	Process Design Change			
9	Tooling Design Change			
10	Quality Planning & Test			
11	Inventory Planning			

12	Purchase of New Materials			
13	Supplier Costs Exclusive of Materials			
14	Transportation Planning			
15	Receiving Inspection			
16	Material Handling &Storage			
17	Material Issue & Movement			
18	Production Time			
19	Cost of Approvals			
20	Other (Miscellaneous Changes)			
21	Total Cost of the Change			
22	Number of Changes Per Month			
	Total Monthly Financial Impact			

A manager, we must shield people from as much uncertainty as possible while in the neutral zone. We can do this by instituting temporary systems and policies, redefining reporting relationships, and setting measurable and achievable shorter goals. It is also important to give people the opportunity to succeed. If the goals are too ambitious, people will not achieve them and may begin to lose confidence. For example, the neutral zone is not the time to try to break productivity records. Also, people should be given the tools to succeed. It may be necessary to send workers and managers to special training. People may not understand fully what is going on around them, and they may feel forlorn. For this reason, it is important to strengthen interpersonal relationships and feeling of trust and loyalty while in the neutral zone. Top management should communicate regularly, reminding people why the change is necessary, where the company is going, how the company is doing. This information bears repeating over and over at every opportunity.

12. SUCCESS RATIO

$$\text{Success ratio} = \frac{\text{Business need}}{\text{full/active employee support}}$$

The formula pertains to the potential success or failure, management can expect in moving forward aggressively with a significant change. It deals with a thoughtful consideration of business need on one hand and the potential for full and active employee support on the other. Full support would mean no uncertainty or doubt. The interpretation of formula is like this: the business need should always be considered to be 100 percent in other words, something that must be done in order for the company to remain competitive or in some cases just to survive. If it is not 100 percent, then simply forget it! If, in turn, the full and active support of employees is deemed to be 50 percent at best (expressed as 1.0-0.5 = 0.5), then the success ratio would probably be no better than 2.0, on a scale of 1 to 10 (1.0/0.5=2.0), which is obviously a very low potential for success.

With this formula you will find that the ratio both increases and depresses disproportionally with the estimated degree of support. While 50 percent only yields a 2.0 on a scale of 1 to 10, 85 percent still only provides an estimated success ratio that is less than 7, which still is not the best of odds. Conversely, 25 percent full and active support sets forth a success ratio of 1.3, which is certainly still lower than the 2.0 projected for 50 percent support. What this formula uncovers is that you need full and active support of at least 90 percent or implementation of the need is going to be very difficult, unless, of course, you conduct a great deal of persuasive communicating with

the work force on the front end. And, even with that, any absolute assurance of success would still remain highly questionable.

This does not mean if the success ratio ends up being 5 or even 2, that change should not proceed. It would say, however, that a good deal of communication of how this change will affect employees should precede the change and that employees should have a forum that provides the opportunity for both challenge and debate- until they understand the underlying principles of economical manufacturing and its benefits. But, the fact is, if a leader is not in a position to accept debate and challenge to any change being proposed, then he or she simply isn't ready to lead it.

13. CASE STUDY: CHANGE MANAGEMENT

Newage food products Ltd. is one of the oldest and pioneer companies manufacturing fruit syrups and other eatable products in Delhi. It has established a high reputation for many of its products distributed through a wide network of sales outlets throughout the country. Due to increasing competition, it was obliged to make a serious effort to reduce total product cost. But due to steep and steady rise in raw materials, this seems immediately impossible. Then on giving a second thought to the second largest group of items of purchases, i.e. packaging materials, see table 2, which gives group wise annual purchase requirements of the company in money value. It will be seen that out of total annual requirements of stores of Rs. 19.86 millions, packaging materials stand next to raw materials. Therefore, even a slight reduction in the cost of these items would yield a large sum of savings.

Table 2: Group Wise Total Annual Requirements

Sr. No	Items	Money value in lakhs
1	Raw Material	95.2
2	Packaging Materials	78.4
3	Miscellaneous Items	15.2
4	Spare Parts	6.0
5	Printing etc	3.8
	Total	**198.6**

High level officers were appointed to form a team in order to explore the possibilities of cost reduction. The team comprises of the company's cost accountant, the purchasing officer, the engineering design manager, planning officer, the sales manager, manufacturing manager, market research officer, all acting under the coordination of the plant manager.

The plant manager called a meeting to discuss the problem and decided to take a particular item to see the ultimate effects. The project under consideration is glass bottles for fruit syrups. This particular problem or project was discussed and the terms of reference were established. Terms of reference are as follows:

- The container was a bottle for fruit syrup to be considered.
- The capacity of bottle was 50 ml and its maximum height 25 cm.
- The bottle should protect and dispense the syrup easily.
- The bottle should be attractive to customers.
- It must cost less than Rs. 1.00

It was further decided that in case of any difficulty the problem may be referred to SKAA Consultants. After analyzing and discussing the problem was referred to SKAA consultants. They form a committee and the procedure followed by them is as follows:

First Step: Data Collection Originally the company made its own glass bottles for syrups, but the local supply of silica for glass making became exhausted and transporting supplies from many kilometers away increased the cost of bottle excessively.

Subsequently, to consider alternative containers or alternative suppliers at the right price, the members of the team collected data on suitable types of bottles, from information in the Newage Food Products Ltd. and also from the market in general.

Second Step: Analysis

At the first meeting of the consultants committee all the data collected was analyzed and the whole bottling process was reviewed in order to create an idea for reducing costs. A summary of the costs for making the current glass bottles was prepared.

Materials:	Silica for Glass	:Rs 0.354/Bottle
	Metal Cap	:Rs 0.130/Bottle
Machinery :	Bottle Making	:Rs. 0.090/Bottle
	Filling	:Rs .0. 050/Bottle
	Sealing	:Rs .0.048/Bottle
Labour :	Bottle Making	:Rs. 0.074/Bottle
	Bottling	:Rs. 0.030/Bottle
	Packing	:Rs. 0.024/Bottle
Overheads:	Production Charges	:Rs. 0. 384/Bottle
	Total	1.184/Bottle

It was obvious that reducing the total cost from Rs. 1.184 to Rs. 1.00 could not be obtained from the materials alone; therefore, it was decided to look for suppliers of readymade bottles. Also, several ideas for alternative bottles were put forward, but the only idea worth considering was a bottle made of plastic. It will also avoid heavy breakages of glass bottles. A detailed probe revealed that in many cases bottle design and shape could also be conveniently changed to standard sizes and shapes.

Third Step: Record of Ideas:

The one person was chosen as the secretary and he recorded minutes of the analysis meeting. He recorded that the present bottle cost of Rs. 1.184 was too expensive and that streamlining the production method, looking for an outside source of bottles and manufacturing bottles from plastics should be considered at the speculation meeting.

Fourth Step: Speculation Meetings

At this meating members considered different ways of reducing the bottle costs, appreciable saving could not be obtained from any improved bottling method and alternative suppliers of bottles were unavailable locally. Plastics could be used, the thickness of the bottles would be reduced and possibly the glass moulding machinery could be modified to use plastics. Replacing glass with plastic was capable of reducing the materials cost between Rs. 0.10 and Rs. 0.30 per bottle and this suggestion was worth investigating.

Fifth Step: Investigation

More information and plastic samples were collected and the summary of new costs is:

Plastics for bottle	Rs 0.250/bottle
Metal cap	Rs 0.130/bottle
Machinery costs	Rs 0.0190/bottle
Labour costs	Rs 0.120/bottle
Direct overheads	Rs .360/bottle
Total	**1.050/bottle**

Sixth Step: Recommendation Meetings

The members met to consider the practical investigations in order to prepare a recommendation report for New Age Food Products Ltd. The use of plastic bottles for syrups was perfectly

feasible, there were no objection chemically or mechanically and existing machinery and labor skills could be modified. It requires no extra hands. However, the maximum cost reductions possible were unable to comply with the terms of reference. When considering the transportation cost saving (approx. Rs 0.024 per bottle) that should result from a reduced bottle weight by using plastic, it was thought that this change should be recommended. Also, it was thought that a light weight bottle would assist sales promotion too.

The suggestion that a plastic bottle would be more attractive and almost unbreakable was investigated further. It was also felt that plastic bottles could increase sales marginally which may increase profit. Therefore, a recommendation report was prepared saying that making plastic bottles should be implemented; it gave full details of the method, including the advice that the current bottle cost could be reduced from Rs. 1.184 to Rs. 1.050 and its utility would be improved at the same time. If reduction in transport cost is considered the current bottle cost comes out to be Rs. 1.026. After implementation the extra profit from increased sales may be considered that may bring the cost to Rs. 1.00 per bottle or even less.

Seventh Step: Acceptance and Implementation

To get the proposal accepted the plant manager (chairman of the committee) called a meeting. A number of problems came up. Some of them are:

Mohan (chairman): In reviewing the study, it appears that the SKAA Consultants have come up with something. According to their report, if we change this bottle from silica to one that of plastic, we can reduce our cost. Dr. Chum, as engineer on this project, what do you think of the idea?

Dr. Chum (engineer): I just do not know. I have studied their proposal, and everything seems O.K. But we already have a bottle that works; I don't think we should fool with it.

Mohan (chairman): Are you saying that you don't think it will work?

Dr. Chum(Engineer): No, I am not, what I am saying is that no matter how good it looks on paper, we still don't know what will happen in actual practice. I shall admit that the cost reduction is attractive. But don't forget that we now have a bottle that has been in market for quite a while, it does well. I don't think we should take any chance by changing it.

Bell (Manufacturing): I agree with Dr. Chum. Let's not ruin a good thing.

Mohan (chairman): It is not often I get to hear manufacturing agree with engineering. What is really on your mind?

Bell(manufacturing) : If you want to know what's bothering me, I will tell you. I read the old man's memo on cost reduction, too; but on this job we are following a nice 90 percent learning curve. In future we can show a good cost reduction. But this study cuts my budget. If I have to lay off people because of this study, man in the shop won't cooperate on any more cost reduction programmes. By the way, if my budget is cut, what will it do to my overhead? Don't get me wrong, I am all in favour of reducing cost, but let's keep the shop busy!

Mohan (chairman): Well, at least we won't hear any complaints from Raghu. This study will keep his procurement people busy.

Raghu (procurement): You think so? We have been ordering materials for the current design of bottle for quite a while. Now that we have some quantity, we can finally negotiate for a good price break. The other day my boss said that he wanted to see the cost of these materials continues to go down. He is happy because procurement is doing its part to reduce cost. I am happy because he is happy. Now you are asking me to go for another material. Proposal is very good, but my boss is interested in the department's performance.

Dr. Gupta (planning): Let me interrupt for a minute. I wasn't going to mention this. But since it appears this study for change is causing some trouble, I might as well throw in my two paise worth. According to this study, engineering needs at least four weeks to design this and another

two weeks to test it. The vendor/manufacturing section claims he will deliver the first production article 12 weeks after the go ahead is given. That means we will have an 18 weeks delay that we would not have if we stuck to the old design. This is not an overwhelming problem, provided someone can guarantee me that nothing will go wrong and that we can start using the new design 18 weeks after we give go ahead. Can anyone be sure that the 18 week is firm? Dr. Chum? (He shakes his head no.) Raghu? (He shakes his head no.) If that is the case, you guys can save me a lot of trouble by sticking with the old design!

Mohan (chairman): Tirkey. You have been quite through all this. As a Sales Manager, what do you think of the study?

Tirkey (Sales/Marketing) : First let me say that I am all in favour of reducing cost, especially expenses. I object to the proposal on the ground that such a sudden switchover will create some marketing problems since this has to be heavily advertised and brought to the notice of ultimate consumers who have been accustomed to use fruit syrup in glass bottle. Since the company name is etched on each glass bottle, apprehend a shift of custom to other company's products and unscrupulous traders will take advantage of this situation.

Mohan (chairman): Gentlemen, I assume from your comments that we should recommend no action on this proposal. In light of the arguments you have offered, it may also mean the end of this change effort. Just so I can complete my report and keep everything legal. How many are in favour of dropping this value engineering study? (No hands are raised). How many are in favour of incorporating this study? (No hands are raised). Come now, gentlemen, a little while ago I heard a lot of reasons for not accepting this study. It would seem that you are all in favour of cost reduction, and since the report is ready with me, let us get together on our recommendations to implement it.

After implementation, it was found that sales increased by 18 percent and that freight charges were reduced by Rs. 0.025 per bottle. Therefore, additional savings include:

Extra profit from increased sales	Rs. 0.127/bottle
Reduced freight per bottle	Rs. 0.025/bottle
Total	**Rs. 0.152/bottle**

Table 3

After marketing syrups in plastic bottles for six months the actual costs were Rs. 0.898 and management was very pleased with the results since the new bottle complied with the terms of reference.

CONCLUSION

Most change efforts do not fare so well as the change initiatives start with great enthusiasm, visibility and upper management support, but often die out long before the goal is reached.

Aim should be to focus an organization on the change process objective, sustain commitment to the change effort, overcome the inevitable resistance and practical hurdles, keep the implementation on track, and reach the point where the change itself becomes the normal and it's benefits are tangible.

REFERENCES

1. Charles Standard and Dale Davis, Running Today's Factory' Hanser Gardner publications, Cincinnati, 1999.
2. W. J. Hopp and Spearman M.L, "Factory Physics: Foundation of Manufacturing Management, " Chicago, Irwin, 1996.
3. W. Davis John, Fast Track to Waste Free Manufacturing, Productivity Press, Portland, USA, 1999.
4. Michael J. Termini, "The New Manufacturing Engineer", Society of Manufacturing Engineers, Dearborn, Michigan 48121, 1996.
5. Kumar, Surender, Khan, B.K., "Computer Aided Manufacturing", Satya Prakashan, New Delhi, 2011.

ANTIMICROBIAL ACTIVITY OF AZETIDINONE DERIVATIVES

Pallavi Bhardwaj, S.P.Sharma and Monika Chahar

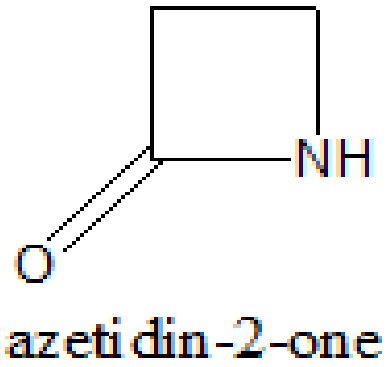
Baba Mastnath University Asthal Bohar Rohtak-124021, Haryana Email id: pallavi198277@gmail.com

Abstract

Azetidinone is the simplest β-lactam known for a number of pharmacological activities. Azetidinones exhibits a wide range of biological activities which includes anti-tubercular, anti-inflammatory, anti-tumor anti-HIV, anti-parkinsonian, anti-diabetic activities etc. In addition, the azetidinone moiety is reposted as a potent mechanism based inhibitor of several enzymes like human tryptase, chymase, thrombin, leukocyte elastase, human cytomegalovirus protease and serine protease enzyme. The four membered heterocyclic β-lactam is well known for its antibacterial and antifungal activities. They have shown significant antibacterial activity against a wide range of microorganisms like fungi, Gram positive strains such as Staphylococcus aureus, Bacillus subtilis and Bacillus lintus and Gram negative strains such as Escheria coli, Vibrio cholera and Pseudomonas aeruginosa. The present review reports the methods of synthesizing some of the 1,3,4-oxadiazole derivatives and their anti-microbial activity.

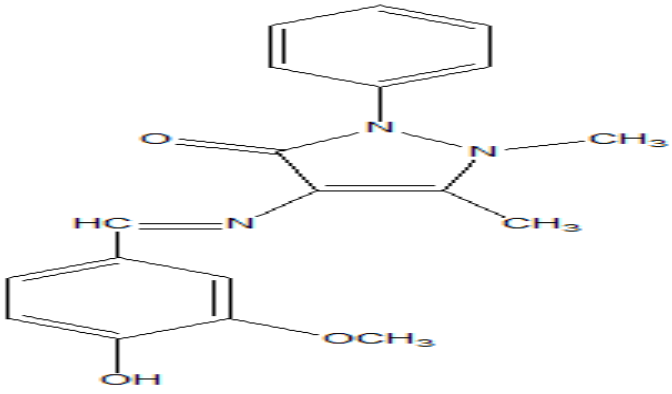
INTRODUCTION

A β-lactam ring, is a four-membered lactam. It is named as such, because the nitrogen atom is attached to the β-carbon atom relative to the carbonyl group. The simplest β-lactam possible is 2-azetidinone.

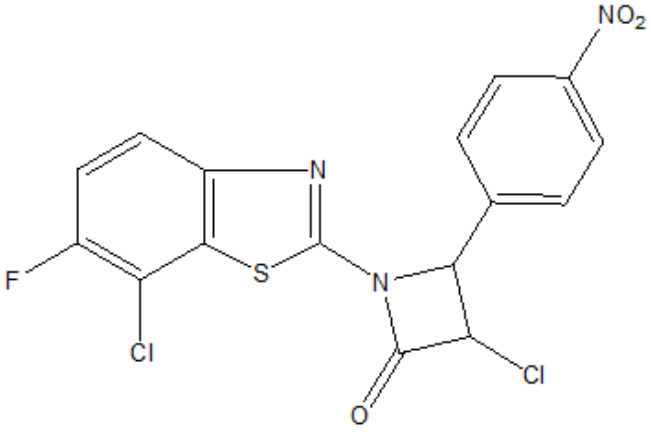


2-Azetidinones shows various biological activities such as antifungal, antibacterial, antitubercular, anticonvulsant, analgesic, anti- inflammatory, antiviral activities. It is also known as a potent mechanism based inhibitor of several enzymes like human tryptase, chymase, thrombin, leukocyte elastase, human cytomegalovirus protease and serine protease enzyme. The four membered heterocyclic β-lactam is well known for its antibacterial and antifungal activities. This review article highlights the recent work that has been carried out on azetidinones reporting the antimicrobial properties of 2-azetidinones.

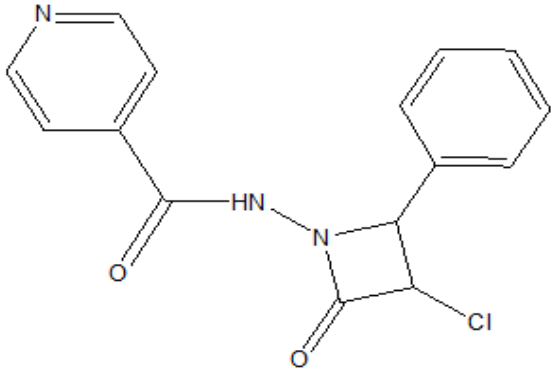
J. Senthil Kumaran *et al* [1] synthesized transition metal complexes from Schiff bases derived from 4-aminoantipyrine and 4-hydroxy-3-methoxy benzaldehyde.



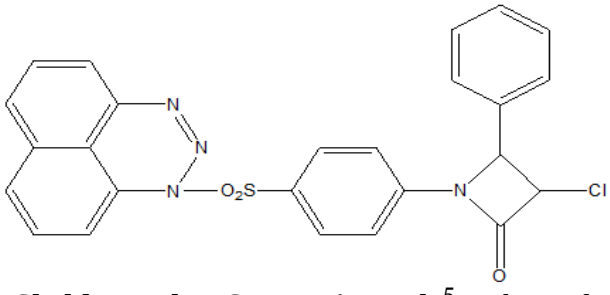
Sathe Bushankumar S. *et al* [2]synthesized and screened various derivatives of flourobenzothiazole incorporated azetidinones. The titled compounds exhibited significant antimicrobial, anthelmintic and anti-inflammatory activity.



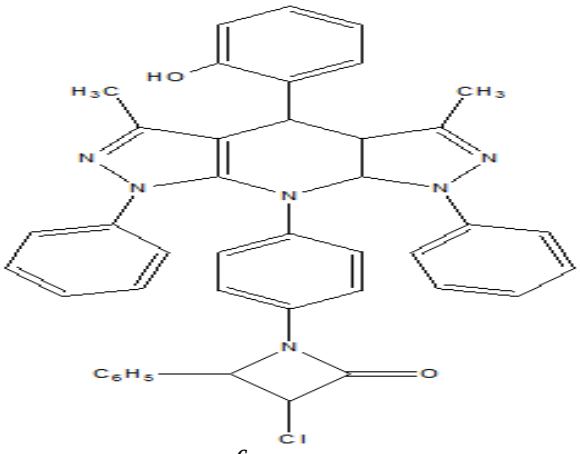
V. Harinadha Babu *et al* [3](synthesized a new series of azetidin-2-ones from isoniazid. The synthesized compounds have shown promising anti-bacterial activity.



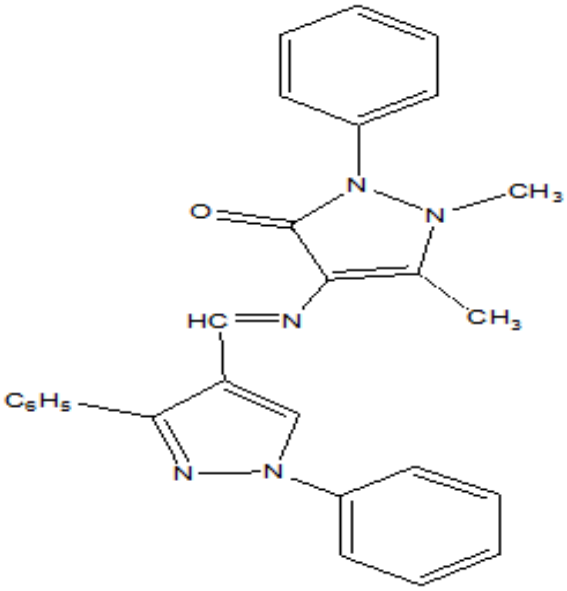
Amit M. Patel and Tarun M. Patel *et al* [4] synthesized a new series of azetidinone derivatives from 4-(1H-napthol(1,8-de)(1,2,3) triazin-1-ylsulfonyl)aniline. The newly synthesized compounds showed moderate to good antibacterial and antifungal activities.



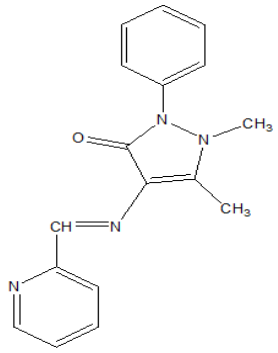
Ravindra kumar, Abha Shukha and D.S. Tyagi *et al* [5]synthesized a new series of bioactive azetidinones and were found to have good activity against all bacterial strains used.



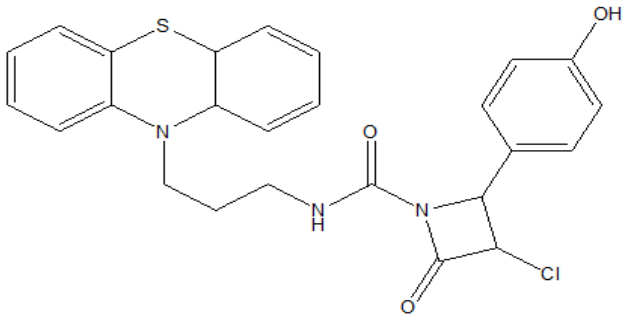
Akash R. Patel and Jabali J. Vora *et al* [6]synthesized Schiff bases from 4-amino antipyrine and 1,3-diphenyl-1H-pyrazole-4-carbaldehyde. Some of the derivatives showed promising antibacterial and antifungal activity.



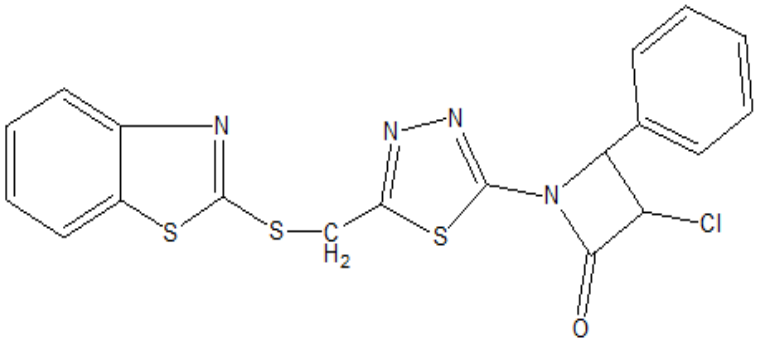
Anand P. Mishra and Rajendra Jain *et al* [7]synthesized the metal complexes of Schiff bases of 4-amino antipyrine and 2-pyridine caboxaldehyde. The Schiff bases formed were found to have good antibacterial activity.



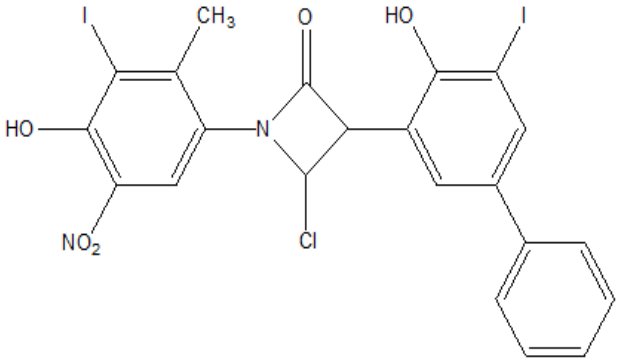
Pushkal Samadhiya *et al* [8]synthesized a new series of 2-azetidinone derivatives from phenothiazine. The synthesized derivatives showed varying range of antibacterial, antifungal and antitubercular activity depending on the substituents.



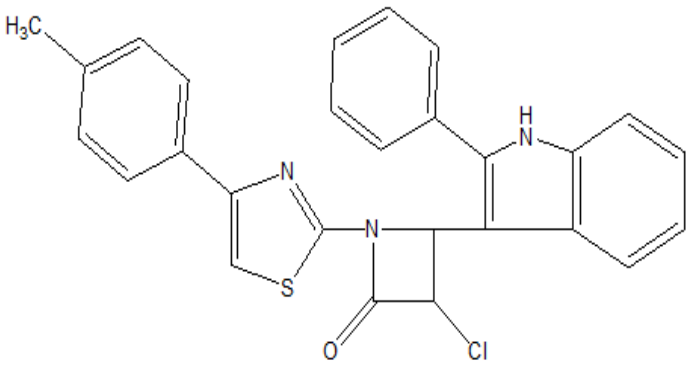
Chavi Raj Singh *et al* [9]synthesized a series of azetidinone derivatives from 2-amino-5-(benzothiazol-2'-yl-thiomethyl)-1,3,4-thiadiazole. It appeared from the screening results that most of the synthesized compounds inhibited the mycelia growth of test fungi at 1000ppm.



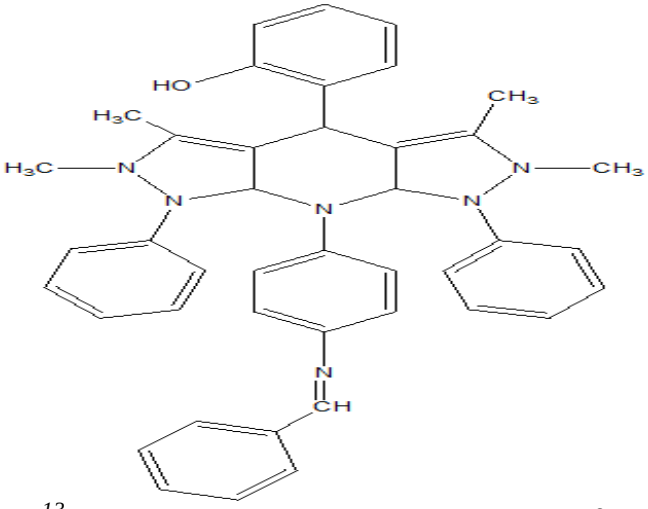
Subash B. Junne *et al* [10]synthesized some new Schiff bases and 2-azetidinones from iodo hydroxyl biphenyl moiety. Some of the synthesized compounds showed potential antibacterial activity.



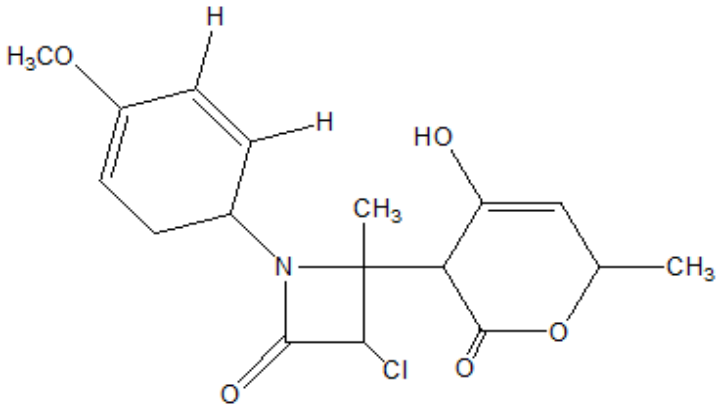
A.R. Sundane and Prabhakar Walmik *et al* [11]synthesized azetidinone derivatives linked to indole nucleus. The compounds were screened for their antioxidant, antimicrobial, antimycobacterial and cytotoxic activities. Some of them displayed excellent activity.



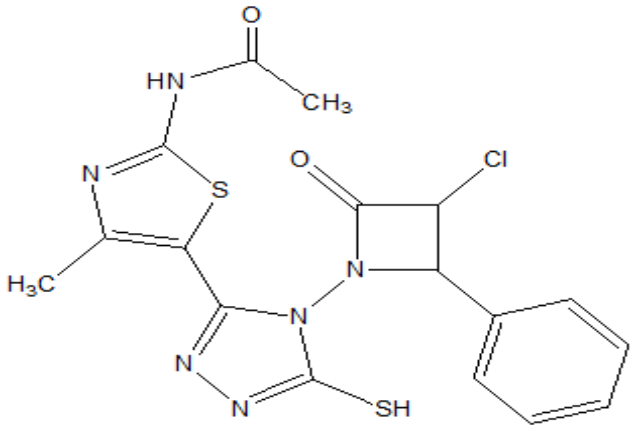
Jyotsana S. Meshram *et al* [12] synthesized a novel series of azetidinones from 1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one under microwave methods. The compounds showed potent antibacterial activity.



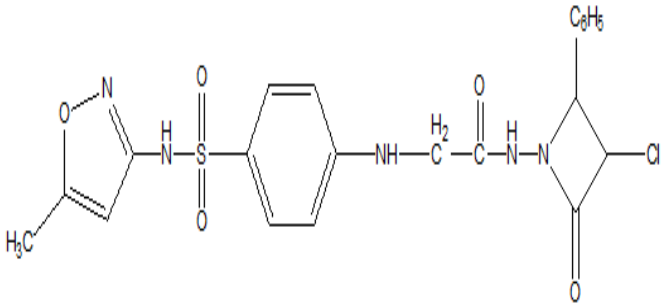
Chetan P. Pulate *et al* [13] synthesized novel azetidinone derivatives from dehydroacetic acid by using microwave system. The compounds showed moderate to good antimicrobial activity against some bacteria and fungi.



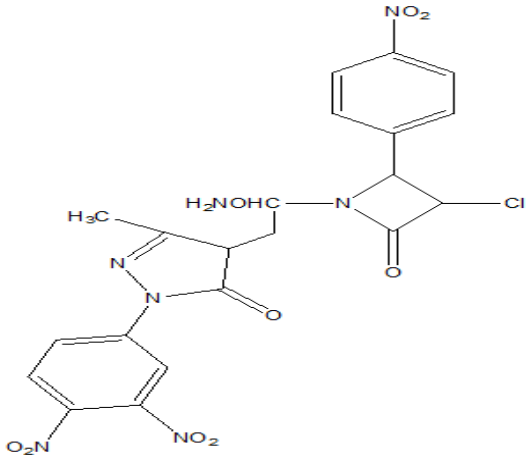
B.A. Baviskar *et al* [14] synthesized thiazolyltriazole substituted azetidinone derivatives. The new analogues, among which five of them showed maximum antibacterial activity and others showed moderate to good activity.



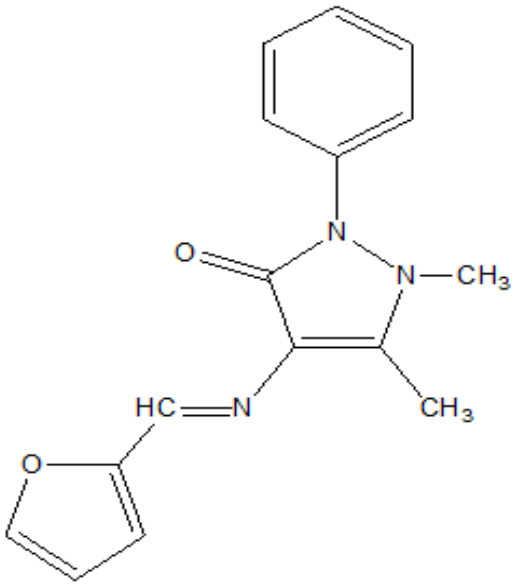
Jainey P. James *et al* [15]synthesized a novel series of azetidinone derivatives from sulphamethoxazole moiety. The resultant compounds showed moderate to good antimicrobial activity against some bacteria and fungi.



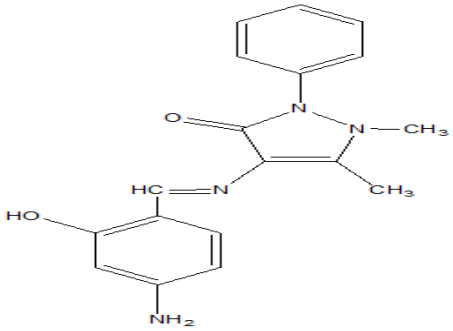
Rahul B. Shete *et al* [16]synthesized novel azetidinone derivatives of pyrazolone. The products showed moderate to good antibacterial activity.



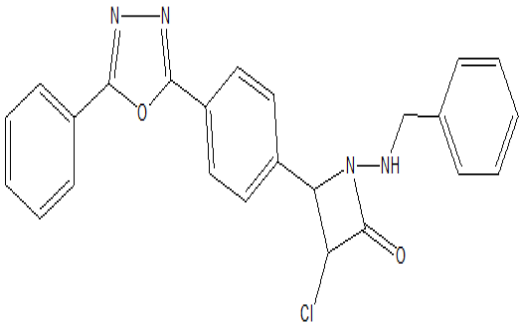
V. Prakash and M.S. Suresh *et al* [17]prepared chelates of Schiff base derived from 4-aminoantipyrine, furfural and o-phenylenediamine. The MIC values showed that the intermediate Schiff bases also exhibited antibacterial activity.



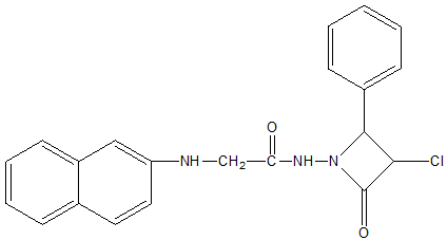
Amit Rai *et al* [18]also synthesized and characterized Schiff base ligands derived from 4-amino antipyrine and 4-aminosalicylaldehyde, benzene-1,2-diamine and its metal complexes.



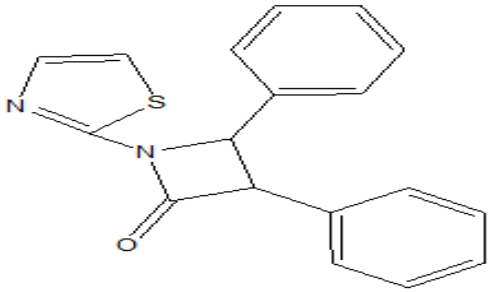
Kokila Parmer, Rinku Patel and Sarju Prajapati *et al* [19]synthesized new azetidinone derivatives from aryl amino-1,3,4-oxadiazole. The new derivatives were screened for their antibacterial and antifungal activity and were found to have promising activities.



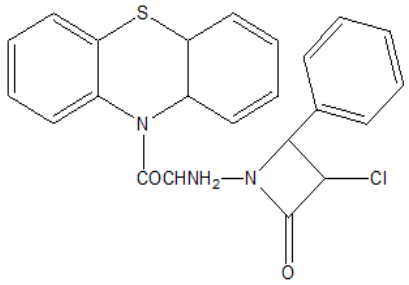
Ajay Bhagerwal *et al* [20]synthesized azetidinone derivatives from napthylamine moiety. The synthesized compounds exhibited good antibacterial and antifungal activities.



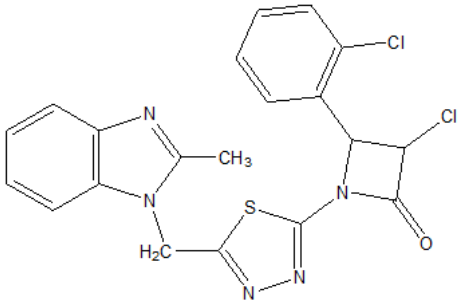
Jyotsna Meshram *et al* [21]synthesized 3-phenyl-4-substituted phenylazetidin-2-ones from 2-aminothiazoles. The antibacterial screening data shows that the compounds are active against the used strains.



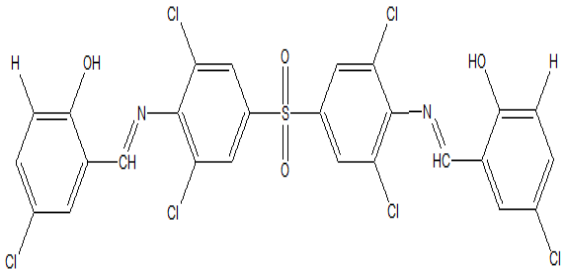
A. Rajasekharan *et al* [22]synthesized a series of seven novel azetidinones by cyclocondensation of various Schiff bases of phenothiazine with chloroacetyl chloride in the presence of triethylamine. The titled compounds were found to have antitubercular, antibacterial, antifungal and anti-inflammatory activities.



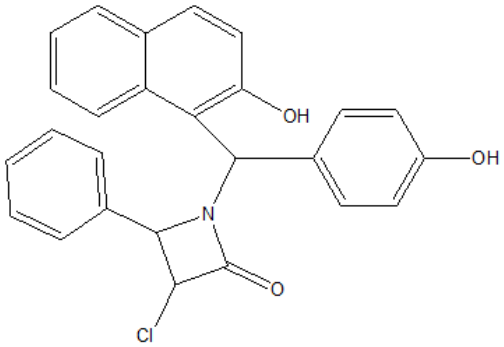
Rajiv Dua and S.K. Sonwane *et al* [23]synthesized some new 2-azetidinone derivatives of 2-methylbenzimidazole. The derived compounds were screened for their antimicrobial activity whose results showed that some of them displayed pronounced biological activity.



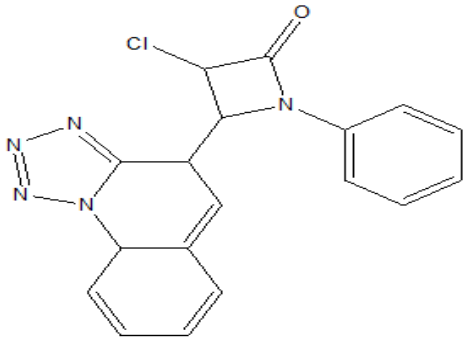
Yeshwant B. Vibhute *et al* [24]synthesized novel Schiff bases of 4,4'-sulfonyldianiline by using microwave assisted synthesis. The results of the antibacterial activity indicated that the synthesized compounds had moderate to potent activities at low and high concentrations with reference to their appropriate reference standards.



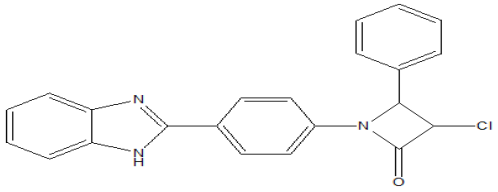
Jyotsna Meshram, Parvez Ali and Vandana Tiwari *et al* [25]synthesized a series of 3-chloro-1[(2-hydroxynapthalen-1-yl-substituted phenylmethyl)]-4-substituted phenylazetidin-2-ones under microwave irradiation. The synthesized compounds were screened for their antibacterial activity and were found to be promising candidates as new antibacterial agents.



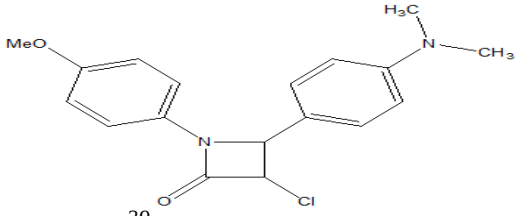
Bhupendra Mistry and Smitha Jahuari *et al* [26]synthesized and characterized some quinoline based azetidinones. The results of antimicrobial studies and bioassays showed that the newly synthesized analogues emerged as lead molecules with excellent MIC.



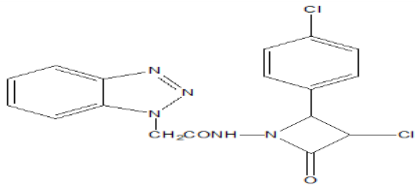
N. Anbalagan *et al* [27]synthesized 2-(4-(azetidin-2-one)-3-chloro-4-phenyl)-1H-phenyl benzimidazole. The synthesized compounds showed significant activity of antibacterial, antifungal, analgesic and anti-inflammatory comparable to that of a standard.



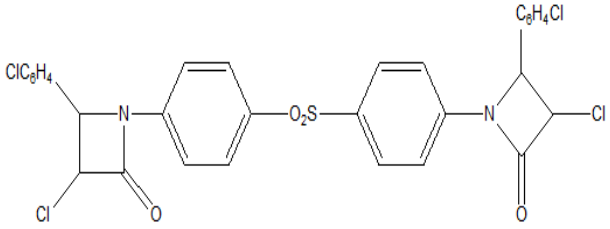
S. Jubie *et al* [28]synthesized different derivatives of 2-azetidinones from p-anisidine and different aldehydes. All the derivatives showed comparable antimicrobial activities. Among these, the one having 2,4-dimethylaminophenyl at 2nd position have shown good activity in all species.



Marunmayee P. Toraskar *et al* [29]synthesized novel N-substituted-2-azetidinone derivatives using Schiff bases synthesized from ethyl-1H-benzotriazole-1-acetate. The synthesized compounds exhibited moderate to good antifungal activity when tested in-vitro against C. albicans.



S.J. Wadher *et al* [30]synthesized a series of Schiff bases and 2-azetidinones of 4,4'-diaminodiphenylsulphone. The compounds were characterized and some derivatives were found to exhibit potent antibacterial activity.



REFERENCES:

1 Senthil Kumaran J., Priya S., Jayachandramani S. and Mahalakshmi S. (2013). Synthesis, Spectroscopic Characterization and Biological activities of Transition Metal Complexes derived from Tridentate Schiff base. Journal of Chemistry, 32, 67-78.

2 Bushankumar S.S. and Saneer S.S. (2012). Synthesis and biological screening of various different derivatives of Flourobenzothiazole incorporated Azetidinones. Journal of Pharmaceutical and Scientific innovation, 13, 32-45.
3 Babu H.V., Rani S.E., Parmeshwar R., Ranganath S.Y., Naveen B.K. and Kumar A.G. (2012). Synthesis and antibacterial screening of some novel N-(3-chloro-2-oxosubstituted phenyl azetidin-1-yl) isonicotinamide and 4-(5-substituted phenyl-1,3,4-oxadiazol-2-yl)pyridine derivatives. International Journal of Pharmacy and Pharmaceutical Sciences, 4, 23-34.
4 Patel A.M. and Tarun M.P. (2012). Synthesis and Anti-microbial activity of some new Azetidinone derivatives. Der Pharmacia Lettre, 4, 579-583.
5 Kumar R., Shukla A. and Tyagi T.S. (2012). An efficient synthesis of Bioactive Azetidinones and Thiazolidinones of 3-methyl-1-phenyl-1H-pyrazol-5-ol.International Journal Of Scientific and Research Publications, 2, 47-59.
6 R.P. Akash, Jabali J.V., Dinesh R.P. and Sandip D. (2012). Synthesis and Antimicrobial activity of some new 4-(substituted aryl)-1,3-diphenyl-1H-pyrazole-4-ylmethyleneamino)-1,5-dimethyl-2-phenylpyrazolidin-3-one derivatives, International Journal of Pharmaceutical Science Research, 3, 68-79.
7 Mishra A.M., Rudra M., Rajendra J. and Santosh G. (2012). Synthesis of new Cobalt, Nickel and Copper complexes with Isatin-3-chloro-4-flouroaniline and 2-pyridinecarboxylidiene-4-aminoantipyrine and their Anti-microbial studies. Journal of Microbiology, 40, 20-26.
8 Pushkal S., Ritusharma S., Srivastava S.D. and Srivastava S.K. (2012). Synthesis and Pharmaceutical importance of 2-azetidinone derivatives of phenothiazine. Journal of Chemical Science, 124, 633-637.
9 Singh C.R. and Singhal A. (2012). Synthesis of novel Schiff base and azetidinone derivatives and their Anti-microbial activity. European Journal of Chemistry, 34, 272-276.
10 Junne S.B., Archana B.K., Sainath B.Z., Saheb L.S. and Yeshwant B.V. (2012). Synthesis and Antibacterial activity of some new Schiff bases and 2-Azetidinones containing iodohydroxybiphenyl moiety. International Multidisciplinary Research Journal, 2, 44-47.
11 Sundane A.R. and Walmik P. (2012). Synthesis, Antioxidant, Anti-microbial, Anti-microbial, Anti-mycobacterial and Cytotoxic activities of Azetidinone and Thiazolidinone moieties linked to Indole nucleus. Journal of Chemistry, 28, 49-56.
12 Meshram S.J. , Himani N.C., Ramakanth P. and Venkateshwar J. (2012). An efficient synthesis of novel bioactive Azetidinones and Thiazolidinones of 1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one. International Journal of Pharma and Bio Sciences, 2, 24-32.
13 Pulate C.C., Swamy G., Rishikesh V. and Goli D. (2011). Microwave assisted synthesis and Antimicrobial activity of novel Azetidinone from Dehydroacetic acid. International Journal of Drug Discovery and Design, 2, 483-487.
14 Baviskar B.A., Shiradhkar M.R., Khadabadi S.S., Deore S.L. and Bothara K.G. (2011). Synthesis of thiazolyltriazole substituted azetidinones as antimicrobial agents. Indian Journal of Chemistry, 50B, 321-325.
15 James P.J., Ishwar B.K., Sunil K.M., Shastry C.S. (2011). Antimicrobial studies of azetidinone derivatives from sulphamethoxazole moiety. Journal of Chemical and Pharmaceutical Research, 6, 234-243.
16 Shete B.R., Rishikesh V.A., Rajesh J.O., Sandip S.K., Sampada S.J. and Hemlata M.N. (2011). New 4-(substituted)-pyrazolone, Part 1 : Microwave assisted synthesis and antibacterial activity of novel 4-substituted azetidinone derivatives of pyrazolone. International Journal of Drug Design and Discovery, 2, 648-653.
17 Prakash V. and Suresh M.S. (2011). Preparation, Characterization and Antibacterial studies of Chelates of Schiff base derived from 4-aminoantipyrine, furfural and o-phenylenediamine. E-Journal of Chemistry, 28, 1408-1416.
18 Rai A., Ashish K.R. and Sirohi R. (2011). Synthesis and Characterization of Schiff base ligands derived from 4-aminoantipyrine and 4-nitrosalicylaldehyde, Benzene-1,2-diamine and its complex with Molybedenum Tricarbonyl. VSRD Technical and Non-Technical Journal, 8, 352-357.
19 Parmar K., Modi V., Prajapati S. and Patel R. (2011). A Facile and Expeditious approach for the synthesis of 2-azetidinone derivatives with antimicrobial activity. Asian Journal of Biochemical and Pharmaceutical Research, 1, 36-47.
20 Bhagerwal A., Ashish B., Rakesh K. and Dinesh K.P. (2011). Synthesis and Antimicrobial studies of Azetidinone derivatives from Napthylamine Moiety. International Journal of Chem Tech Research, 3, 274-279.
21 Meshram J., Parvez A. and Vandana T. (2010). Microwave mediated cyclocondensation of 2-aminothiazole into β-lactam derivatives: Virtual Screening and In-vitro Antimicrobial activity with various microorganisms. International Journal of Chem Tech Research, 2, 956-964.

22 Rajasekharan A., Periasamy M. and Venkatesan S. (2010). Synthesis, Characterization and Biological activity of some novel azetidinones . Journal of Developmental Biology and Tissue Engineering, 2, 5-13.
23 Dua R., Sonwane S.K., Srivastava S.K. and Srivastava S.D. (2010). Synthesis of some novel 2-azetidinone derivatives of 2-methylbenzimidazole by conventional and microwave assisted synthesis and evaluation of their antimicrobial efficacy. Der Pharmacia Lettre, 2, 483-487.
24 Vibhute B.Y., Omprakash G., Bhanusree S., Sainath B.Z. and Shivaji B.C. (2010). Comparative study of Conventional and Microwave assisted synthesis of novel Schiff bases and their antimicrobial screening. Journal of Chemical and Pharmaceutical Research, 6, 234-243.
25 Meshram J., Vandana T. and Pervez A. (2010). Synthesis and Antibacterial activity of 3-chloro-1-[(2-hydroxynapthalen-1-yl-(substituted)-phenylazetidin-2-ones and Thiazolidin-4-ones encompassing Benzthiazole. Indian Journal of Pharmaceutical Science, 12, 34- 42.
26 Mistry B. and Jauhari S. (2010). Synthesis and Characterization of some quinoline based azetidinones and thiazolidinones as antimicrobial agents. Archives of Applied Science Research, 6, 332-343.
27 Anbalagan N., Shanmugapandiyan P., Denshing K.S., Illavarasan R. and Nirmal R. (2010). Synthesis and biological activity of 2-[(thiazolidin-4-one) phenyl]-1H-phenylbenzimidazoles and 2-[4-(azetidin-2-one)-3-chloro-4-phenyl]-1H-phenylbenzimidazoles. International Journal of Pharmaceutical Sciences and Drug Research, 2, 115-119.
28 Jubie S., Gowramma B., Nitin K., Kalirajan R., Gomathi S. and Elango K. (2009), International Journal of Chem Tech Research, 1, 153-157.
29 Toraskar M.P., Vilasrao M., Kadam P., Vithal D. and Kulkarni M. (2009). Synthesis and antifungal activity of some Azetidinones. International Journal of Chem Tech Research, 1, 1194-1199.
30 Wadher S.J., Pauranik M.P., Karanke N.A. and Yeole P.G. (2009). Synthesis and Biological evaluation of Schiff base of Dapsone and their derivatives as Antimicrobial agents.International Journal of Pharma Tech Research, 1, 22-33.

OPTICAL STUDY OF NEODYMIUM CHLORIDE EMBEDDED PMMA BASED MATERIAL

Monika Chahar[1*], Sushil Kumar[2], Pallavi Bhardwaj[1]

1.Baba Mastnath University, Asthal Bohar, Rohtak- 124 021, India.
2 Chaudhary Devi Lal University, Sirsa-125 055, India.

ABSTRACT

The Chemical modification by embedded rare earths in polymethylmethacrylate (PMMA) matrix may open up the possibility in the development of advanced materials. Laser materials made by polymerization of rare earths in the polymer host matrix are an advanced class of materials with great deal of future promise for potential applications as high performance materials and play an important role in the vast area of materials research. In the present work neodymium chloride as dopant is embedded in the polymethylmethacrylate (PMMA) matrix by chemical doping process. The optical characterization of doped (PMMA) matrix has been carried out with different concentration of dopant by using UV- visible spectroscopy to measure the effect of embedded dopant.

Keywords: Kiton red-620, PMMA, Chemical doping, FTIR, UV-Visible studies.

INTRODUCTION

Solid-state laser materials are commonly made by "doping" a crystalline solid host with ions that provide the required energy states. The population inversion is actually maintained in the "dopant" such as chromium or neodymium. Neodymium is a common "dopant" in various solid state laser crystals including yttrium orthovanadate (Nd: YVO_4), yttrium lithium aluminum garnet (Nd:YAG). All these lasers can produce high powers in the infrared spectrum at 1064 nm. So we can say that laser materials are that type of substance in which the majority of atoms or molecules are in an excited energy state [1-2]. They are used for cutting, welding and marking of metals, spectroscopy and for pumping of dye lasers. These lasers are also commonly frequency doubled tripled or quadrupled to produce 532 nm (green, visible), 355nm (UV) and 266 nm (UV) light when those wavelengths are needed ytterbium, holmium, thulium and erbium are other common dopants in solid state lasers.Ytterbium is used in crystals such as Yb: YAG< Yb: KGW, Yb: KYW, Yb: SYS, Yb: BOYS, Yb: COF2, typically operating around 1020-1050 nm. They are potentially very efficient and high powered due to a small quantum defect. Extremely high powers in ultra short pulses can be achieved with Yb: YAG. Holmium-doped YAG crystals emit at 2097 nm and form an efficient laser operating at infrared wavelengths sobbingly absorbed by water bearing tissues. The Ho-YAG is usually operated in a pulsed mode, and passed through optical fiber surgical devices to resurface joints, remove rot from teeth, vaporize cancers, pulverize kidney and gall stones. Titanium doped sapphire (Ti-sapphire) produces a highly tunable infrared laser, commonly used for spectroscopy as well as the most common ultra short pulse lasers. So we can say that laser materials play an important role in advancement in the field of science and technology. Lasers range in size from microscopic diode lasers with numerous applications, to football field sized neodymium glass lasers used for inertial confinement fusion, nuclear weapons research and other high energy density physics experiments [3]. Laser materials made by polymerization of rare earths in the polymer host matrix are a advanced class of materials with great deal of future promise for potential applications as high performance materials. In the present study, we use polymethylmethacrylate(PMMA) as a host matrix for rare earth doping due to their good transperancy, resistivity, mechanical strength and optical homogeneity which can play an important role to built up advanced optical materials.

Several research groups are engaged in the development and interpretation of these types of advanced materials.Rongwei Fan et al. [4] have reported the solid state dye lasers based on LDS 698 doped in modified polymethylmethacrylate, Yoshi Okamoto et al. [5] have reported plastic optical fiber lasers and amplifiers containing lanthanide complexes, Brian J. Scott et al. [6] have

reported mesoporous and mesostructured materials for optical applications. In the present study, we use polymethylmethacrylate (PMMA) as a host matrix for rare earth doping due to their good transperancy, resistivity, mechanical strength and optical homogeneity which can play an important role to built up advanced optical materials. The samples were prepared with different concentration of dye in polymethylmethacrylate (PMMA) matrix. The optical characterization of prepared samples is made by the help of UV-Visible spectroscopy. We have recorded absorption spectra at different concentration of doped PMMA matrix that shows considerable change in the absorption peak.

EXPERIMENTAL Details

Chemicals: Perspex (PMMA) Ruchi Enterprises Mumbai, India, Acetone (A.R.Grade, Spectrochem Pvt. Ltd., Mumbai, India, neodymium chloride.

Methodolog: The Polymethylmethacrylate(PMMA) films doped with neodymium chloride have been prepared by dissolving perspex in acetone by stirring with the help of magnetic stirring. Chemical doping of neodymium chloride is carried out into PMMA host matrix. For preparing the samples of different concentration doped now put these samples into oven at 45°C so that the evaporation of acetone from the samples for completing the homogeneous incorporation of dopant with this slow drying process.

RESULTS AND DISCUSSION

UV-visible study:

The UV-visible study of neodymium chloride doped polymethylmethacrylate based material has been done by recording optical absorption using Spectrophotometer (Perkin Elmer Lambda). The absorption spectra of pure PMMA and neodymium chloride doped PMMA are shown in Fig. 1(a) and 1(b).

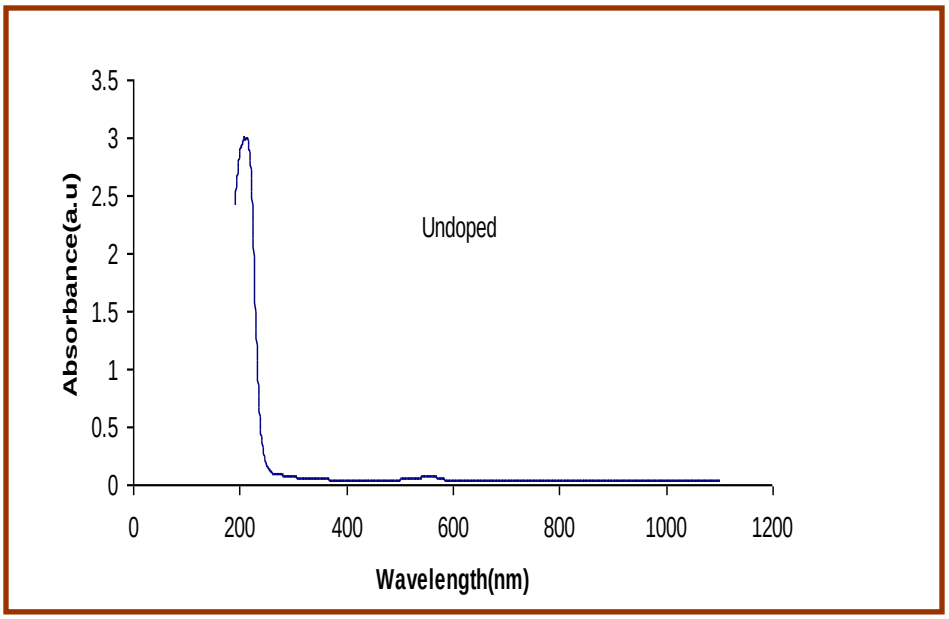


Fig.1 (a): Absorption spectra of PMMA

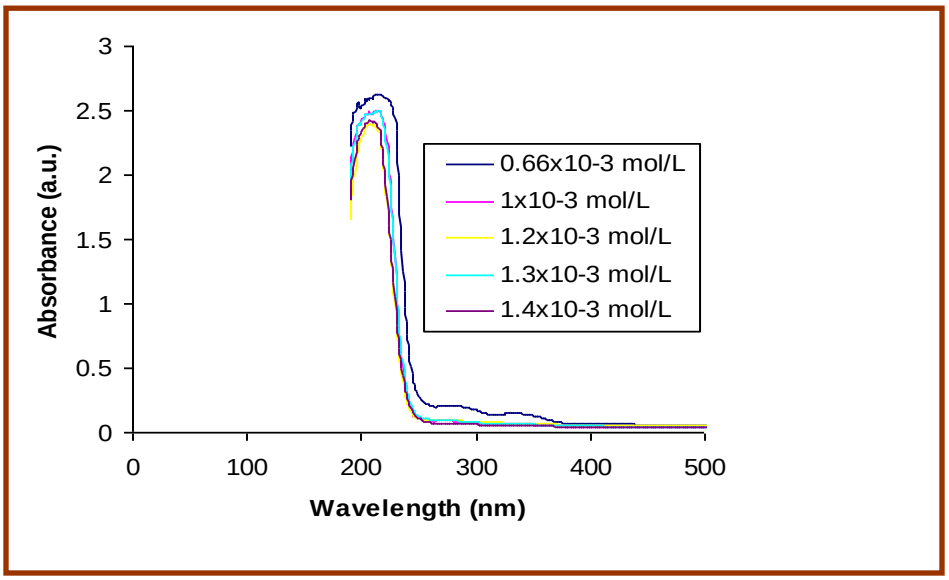


Fig.1 (b): Absorption spectra of neodymium chloride doped PMMA

It has been observed that the absorption peaks appears at wavelengths 224, 219, 214, 217 and 215 nm as the concentration of dopant varies as $0.66x10^{-3}$, $1x10^{-3}$, $1.2x10^{-3}$, $1.3x10^{-3}$ and $1.4x10^{-3}$ mol/L in PMMA matrix respectively. The shifting occurred in the spectra may be due to the polarity of solvent used in the synthesis or may be due to the dispersion of rare earth chloride particles in the PMMA matrix [7-10].

CONCLUSIONS

The neodymium chloride is embedded in synthesized PMMA matrix by chemical doping process and the films of neodymium chloride doped PMMA based optical material has been prepared by casting method. The concentration of neodymium chloride in PMMA matrix varies from $0.66x10^{-3}$ to $1.4x10^{-3}$ mol/L and characterize by UV-visible spectroscopic technique. UV-visible study showed that a slight shifting appears in the absorption spectra as the concentration of dopant increases. The absorption peaks appear in wavelength range 212-225 nm.

REFERENCES:

[1] Hollow cathode ion lasers for deep ultraviolet Raman spectroscopy and fluorescence imaging Storrie-Lombardia et al. Review of scientific instruments Volume 72, Number 12 December 2001.

[2] M. Tokurakawa; K. Takaichi, A. Shirakawa, K. Ueda, H. Yagi, T. Yanagitani, and A. A. Kaminskii(2007).”Diode-pumped 188fs mode- locked Yb^{3+}: Y2O3 ceramic laser”. Appl. Phys.Lett. 90:071101. doi: 10.1063/1.247-6385

[3] F. J. Duarte, “ organic dye lasers: brief history and recent developments.” Opt. Photon. News 14, 20-25(2003).

[4] Rong wui fan, Yuanqin Xia and Deying chem., 23 June 2008/ Vol. 16, No. 13/ optics express 9804.

[5] Yoshi Okamota, Ken Kuriki and Yasuhiro Koike, Chem. Rev. 2002, 102, 2347- 2356.

[6] Brian J. Scott, Gernat Wirnsberger and Galon D. Stucky, chem.. Mater. 2001, 13, 3140-3150.

[7] Y. Cho, Y. Choi and K. Sohn, Appl. Phys. Lett., **89** (2006) 5.

[8] Y. Xie, Applied Surface Science **221** (2004) 17.

[9] J.M. Drake, R.I. Morse, R.N. Steppel and D.Young, Chem. Phys. Lett., **35** (1975), 181.

[10] W.V. Moreshead, J.L.R. Nogues and R.H. Krabill, J. Non-Cryst. Solids, **121** (1990) 267.

ROLE OF QUANTUM MECHANICS IN PHYSICS

Sunita Dahiya

BMU, Asthal Bohar, Rohtake-mail Id: sunitadahiya@gmail.com

Abstract:

The rules of quantum mechanics are fundamental. They assert that the state space of a system is a Hilbert space and that observables of that system are Hermitian operatorsacting on that space—although they do not tell us which Hilbert space or which operators. These can be chosen appropriately in order to obtain a quantitative description of a quantum system. An important guide for making these choices is the correspondence principle, which states that the predictions of quantum mechanics reduce to those of classical mechanics when a system moves to higher energies or, equivalently, larger quantum numbers, i.e. whereas a single particle exhibits a degree of randomness, in systems incorporating millions of particles averaging takes over and, at the high energy limit, the statistical probability of random behaviour approaches zero. In other words, classical mechanics is simply a quantum mechanics of large systems. This "high energy" limit is known as the classical or correspondence limit. One can even start from an established classical model of a particular system, then attempt to guess the underlying quantum model that would give rise to the classical model in the correspondence limit.

QUANTUM MECHANICS AND CLASSICAL PHYSICS

Predictions of quantum mechanics have been verified experimentally to an extremely high degree of accuracy. According to the correspondence principle between classical and quantum mechanics, all objects obey the laws of quantum mechanics, and classical mechanics is just an approximation for large systems of objects (or a statistical quantum mechanics of a large collection of particles). The laws of classical mechanics thus follow from the laws of quantum mechanics as a statistical average at the limit of large systems or large quantum numbers. However, chaotic systems do not have good quantum numbers, and quantum chaos studies the relationship between classical and quantum descriptions in these systems.

Quantum coherence is an essential difference between classical and quantum theories as illustrated by the Einstein–Podolsky–Rosen (EPR) paradox — an attack on a certain philosophical interpretation of quantum mechanics by an appeal to local realism. Quantum interference involves adding together probability amplitudes, whereas classical "waves" infer that there is an adding together of intensities. For microscopic bodies, the extension of the system is much smaller than the coherence length, which gives rise to long-range entanglement and other nonlocal phenomena characteristic of quantum systems. Quantum coherence is not typically evident at macroscopic scales, though an exception to this rule may occur at extremely low temperatures (i.e. approaching absolute zero) at which quantum behavior may manifest itself macroscopically. This is in accordance with the following observations:

- Many macroscopic properties of a classical system are a direct consequence of the quantum behavior of its parts. For example, the stability of bulk matter (consisting of atoms and molecules which would quickly collapse under electric forces alone), the rigidity of solids, and the mechanical, thermal, chemical, optical and magnetic properties of matter are all results of the interaction of electric charges under the rules of quantum mechanics.
- While the seemingly "exotic" behavior of matter posited by quantum mechanics and relativity theory become more apparent when dealing with particles of extremely small size or velocities approaching the speed of light, the laws of classical, often considered "Newtonian", physics remain accurate in predicting the behavior of the vast majority of "large" objects (on the order of the size of large molecules or bigger) at velocities much smaller than the velocity of light.

Relativity and quantum mechanics

Even with the defining postulates of both Einstein's theory of general relativity and quantum theory being indisputably supported by rigorous and repeated empirical evidence, and while they do not directly contradict each other theoretically (at least with regard to their primary claims), they have proven extremely difficult to incorporate into one consistent, cohesive model. Einstein himself is well known for rejecting some of the claims of quantum mechanics. While clearly contributing to the field, he did not accept many of the more "philosophical consequences and interpretations" of quantum mechanics, such as the lack of deterministic causality. He is famously quoted as saying, in response to this aspect, "My God does not play with dice". He also had difficulty with the assertion that a single subatomic particle can occupy numerous areas of space at one time. However, he was also the first to notice some of the apparently exotic consequences of entanglement, and used them to formulate the Einstein–Podolsky–Rosen paradox in the hope of showing that quantum mechanics had unacceptable implications if taken as a complete description of physical reality. This was 1935, but in 1964 it was shown by John Bell (see Bell inequality) that - although Einstein was correct in identifying seemingly paradoxical implications of quantum mechanical nonlocality - these implications could be experimentally tested. Alain Aspect's initial experiments in 1982, and many subsequent experiments since, have definitively verified quantum entanglement. According to the paper of J. Bell and the Copenhagen interpretation—the common interpretation of quantum mechanics by physicists since 1927 - and contrary to Einstein's ideas, quantum mechanics was not, at the same time a "realistic" theory and a "local" theory.

The Einstein–Podolsky–Rosen paradox shows in any case that there exist experiments by which one can measure the state of one particle and instantaneously change the state of its entangled partner - although the two particles can be an arbitrary distance apart. However, this effect does not violate causality, since no transfer of information happens. Quantum entanglement forms the basis of quantum cryptography, which is used in high-security commercial applications in banking and government. Gravity is negligible in many areas of particle physics, so that unification between general relativity and quantum mechanics is not an urgent issue in those particular applications. However, the lack of a correct theory of quantum gravity is an important issue in cosmology and the search by physicists for an elegant "Theory of Everything" (TOE). Consequently, resolving the inconsistencies between both theories has been a major goal of 20th and 21st century physics. Many prominent physicists, including Stephen Hawking, have labored for many years in the attempt to discover a theory underlying everything. This TOE would combine not only the different models of subatomic physics, but also derive the four fundamental forces of nature - the strong force, electromagnetism, the weak force, and gravity - from a single force or phenomenon. While Stephen Hawking was initially a believer in the Theory of Everything, after considering Gödel's Incompleteness Theorem, he has concluded that one is not obtainable, and has stated so publicly in his lecture "Gödel and the End of Physics" (2002).

APPLICATIONS

Quantum mechanics has had enormous success in explaining many of the features of our universe. Quantum mechanics is often the only tool available that can reveal the individual behaviors of the subatomic particles that make up all forms of matter (electrons, protons, neutrons, photons, and others). Quantum mechanics has strongly influencedstring theories, candidates for a Theory of Everything . Quantum mechanics is also critically important for understanding how individual atoms combine covalently to form molecules. The application of quantum mechanics to chemistryis known as quantum chemistry. Relativistic quantum mechanics can, in principle, mathematically describe most of

chemistry. Quantum mechanics can also provide quantitative insight into ionic and covalent bonding processes by explicitly showing which molecules are energetically favorable to which others and the magnitudes of the energies involved. Furthermore, most of the calculations performed in modern computational chemistry rely on quantum mechanics. A working mechanism of a resonant tunneling diode device, based on the phenomenon of quantum tunneling through potential barriers

A great deal of modern technological inventions operate at a scale where quantum effects are significant. Examples include the laser, the transistor (and thus the microchip), the electron microscope, and magnetic resonance imaging(MRI). The study of semiconductors led to the invention of the diode and the transistor, which are indispensable parts of modern electronics systems and devices. Researchers are currently seeking robust methods of directly manipulating quantum states. Efforts are being made to more fully develop quantum cryptography, which will theoretically allow guaranteed secure transmission of information. A more distant goal is the development of quantum computers, which are expected to perform certain computational tasks exponentially faster than classical computers. Instead of using classical bits, quantum computers use qubits, which can be in superpositions of states. Another active research topic is quantum teleportation, which deals with techniques to transmit quantum information over arbitrary distances.

Quantum tunneling is vital to the operation of many devices. Even in the simple light switch, the electrons in the electric current could not penetrate the potential barrier made up of a layer of oxide without quantum tunneling. Flash memory chips found in USB drives use quantum tunneling to erase their memory cells. While quantum mechanics primarily applies to the smaller atomic regimes of matter and energy, some systems exhibit quantum mechanical effects on a large scale. Superfluidity, the frictionless flow of a liquid at temperatures near absolute zero, is one well-known example. So is the closely related phenomenon of superconductivity, the frictionless flow of an electron gas in a conducting material (an electric current) at sufficiently low temperatures. Quantum theory also provides accurate descriptions for many previously unexplained phenomena, such as black-body radiation and the stability of the orbitals of electrons in atoms. It has also given insight into the workings of many different biological systems, including smell receptors and protein structures. Recent work on photosynthesis has provided evidence that quantum correlations play an essential role in this fundamental process of plants and many other organisms.[72] Even so, classical physics can often provide good approximations to results otherwise obtained by quantum physics, typically in circumstances with large numbers of particles or large quantum numbers. Since classical formulas are much simpler and easier to compute than quantum formulas, classical approximations are used and preferred when the system is large enough to render the effects of quantum mechanics insignificant.

REFERENCES

The following titles, all by working physicists, attempt to communicate quantum theory to lay people, using a minimum of technical apparatus.

1. Chester, Marvin (1987) Primer of Quantum Mechanics. John Wiley. ISBN 0-486-42878-8
2. Cox, Brian; Forshaw, Jeff (2011). The Quantum Universe: Everything That Can Happen Does Happen:. Allen Lane. ISBN 1-84614-432-9.
3. Richard Feynman, 1985. QED: The Strange Theory of Light and Matter, Princeton University Press. ISBN 0-691-08388-6. Four elementary lectures on quantum electrodynamics and quantum field theory, yet containing many insights for the expert.
4. Ghirardi, GianCarlo, 2004. Sneaking a Look at God's Cards, Gerald Malsbary, trans. Princeton Univ. Press. The most technical of the works cited here. Passages using algebra, trigonometry, and bra–ket notation can be passed over on a first reading.

5. N. David Mermin, 1990, "Spooky actions at a distance: mysteries of the QT" in his Boojums all the way through. Cambridge University Press: 110-76.
6. Victor Stenger, 2000. Timeless Reality: Symmetry, Simplicity, and Multiple Universes. Buffalo NY: Prometheus Books. Chpts. 5-8. Includes cosmological and philosophical considerations.
7. Bryce DeWitt, R. Neill Graham, eds., 1973. The Many-Worlds Interpretation of Quantum Mechanics, Princeton Series in Physics, Princeton University Press. ISBN 0-691-08131-X
8. Dirac, P. A. M. (1930). The Principles of Quantum Mechanics. ISBN 0-19-852011-5. The beginning chapters make up a very clear and comprehensible introduction.
9. Hugh Everett, 1957, "Relative State Formulation of Quantum Mechanics", Reviews of Modern Physics 29: 454-62.
10. Feynman, Richard P.; Leighton, Robert B.; Sands, Matthew (1965). The Feynman Lectures on Physics 1–3. Addison-Wesley. ISBN 0-7382-0008-5.

OVER VIEW OF LIQUID CRYSTALS

SUNITA DAHIYA, KUSAM RANI

Department of Physics Baba Mastnath Universty,Asthal Bohar, Rohtak,124021 E-Mail: sunitadahiya@GMAIL.COM

ABSTRACT:

The study of liquid crystals began in 1888 when an Austrian botanist named Friedrich Reinitzer observed that a peculiar melting behavior of a material known as cholesteryl benzoate (C6H5COOC27H45). He found that the crystals of this substance melted sharply to form anopaque, cloudy melt instead of the usual clear melt. The conclusion Reinitzer drew from this observation was that some type of order still existed in the molten state. Furthermore Reinitzer observed that the opacity vanished at a higher temperature and the material changed again into a clear,transparent liquid at this high temperature. Shortly thereafter, Lehmann reported that ammonium oleateand *p*-azoxyphenetole exhibited turbid states between the truly anisotropic crystalline and the trulyisotropic fluid state. To describe the strange behavior of the new state, Lehmann introduced the term"Flussige Kristalle," or liquid crystals. Because of the early work, Reinitzer is often credited withdiscovering a new phase of matter - the liquid crystal phase.

Definition of a liquid crystal: Liquid crystals (LCs), are substances that exhibit long-range order in one or two dimensions, but not all three. Liquid crystals are substances that exhibit a phase ofmatter that has properties between those of a conventional liquid, and those of a solid crystal.A large number of organic molecules with long chain such as cholesteryl acetate (CH3COOC27H45),cholesteryl benzoate (C6H5COOC27H45), etc show LC behavior. A liquid crystal (LC) may flow like aordinary liquid, but have the molecules in the liquid arranged and/or oriented in a crystal-like way orthey show anisotropy and double refraction like crystalline solids.A liquid crystal is a thermodynamic stable phase characterized by anisotropy of properties without the existence of a three-dimensional crystal lattice, generally lying in the temperature rangebetween the anisotropic solid and isotropic liquid phase, hence the term **mesophase**.

Both small molecules and polymers may exist in the liquid crystalline state, but generally special spatial structures like rigid rod like or disc like molecules are required. Here define a new term **mesogen**, is rigid rod like or disc like molecules which are components of liquid crystalline materials.

Liquid substances are more or less entirely disordered and crystalline materials are ordered in all three dimensions, the LCs lie in-between in properties. Liquid crystals are ordered in one or twodimensions only. Liquid crystals all exhibit some degree of fluidity. The formation of liquid crystals isa direct consequence of molecular asymmetry. It arises because two molecules cannot occupy the samespace at the same time and is largely entropically derived.

As research into this field continues and as new applications are developed, liquid crystals will play an important role in modern technology.2The first polymeric liquid crystal discovered was poly(g-benzyl l-glutamate), in 1950.Engineering advances utilizing polymers that go through an LC stage include new classes of highmodulusfibers, high-temperature plastics, and a host of new electronic and data storage materials.

What are Liquid Crystals? Liquid crystal materials generally have several common characteristics. Among these are rod-like molecular structures, rigidness of the long axis, and strongdipoles and/or easily polarizable substituents.

The distinguishing characteristic of the liquid crystalline state is the tendency of the molecules to point along a common axis, called the director (the molecular direction of preferred orientation inliquid crystalline mesophases). This is in contrast to molecules in the liquid phase, which havenointrinsic order. In the solid state, molecules are highly ordered and have little translational freedom.The characteristic orientational order of the liquid crystal state is between the traditional

solid andliquid phases and this is the origin of the term mesogenic state, used synonymously with liquid crystalstate. Note the average alignment of the molecules for each phase in the following diagram.It is sometimes difficult to determine whether a material is in a crystal or liquid crystalstate.Crystalline materials demonstrate long range periodic order in three dimensions. By definition, anisotropic liquid has no orientational order. Substances that aren't as ordered as a solid, yet have somedegree of alignment are properly called liquid crystals.

Characterizing Liquid Crystals: The following parameters describe the liquid crystalline structure: [1] Orientational Order [2] Positional Order. Each of these parameters describes the extent towhich the liquid crystal sample is ordered. **Orientational order:** Measure of the tendency of the molecules to align along thedirector on a long-range basis. **Positional order:** The extent to which the position of an average molecule or group ofmolecules shows translational symmetry.3Most liquid crystal compounds exhibit polymorphism or a condition where more than one phaseis observed in the liquid crystalline state. The term mesophase is used to describe the "subphases" ofliquid crystal materials. Mesophases are formed by changing the amount of order in the sample, eitherby imposing order in only one or two dimensions, or by allowing the molecules to have a degree of translational motion. The following section describes the mesophases of liquid crystals in greater detail.

Liquid Crystal Phases: The liquid crystal state is a distinct phase of matter observed between the crystalline (solid) and isotropic (liquid) states. There are many types of liquid crystal states,depending upon the amount of order in the material. This section will explain the phase behavior ofliquid crystal materials.

Nematic Phases: The nematic liquid crystal phase is characterized by molecules that have no positional order but tend to point in the same direction (along the director). In the following diagram,notice that the molecules point vertically but are arranged with no particular order. Liquid crystals are anisotropic materials, and the physical properties of the system vary with the average alignment with the director. If the alignment is large, the material is very anisotropic. Similarly, if the alignment is small, the material is almost isotropic.Nematic

Smectic Phases: The smectic phase is another distinct mesophase of liquid crystal substances. Molecules in this phase show a positional order, not present in the nematic. In the smectic state, themolecules maintain the general orientational order of nematics. The increased order means that the smectic state is more "solid-like" than the nematic.

Many compounds are observed to form more than one type of smectic phase. As many as twelve of these variations have been identified, however only the most distinct phases are smectic-A and smectic-C. In the **smectic-C** mesophase, molecules are arranged as in the smectic-A mesophase, but the director is at a constant tilt angle measured normally to the smectic plane.4 Smectic A Smectic C

Cholesteric Phases: A special class of nematic liquid crystals is called chiral nematic. Chiral refers to the unique ability to selectively reflect one component of circularly polarized light.The term chiral nematic is used interchangeably with cholesteric.

The cholesteric (or chiral nematic) liquid crystal phase is typically composed of nematic mesogenic molecules containing a chiral center which produces intermolecular forces that favor alignment between molecules at a slight angle to one another. This leads to the formation of a structure which can be visualized as a stack of very thin 2-D nematic-like layers with the director in each layer twisted with respect to those above and below. Cholesteric (or chiral nematic)

Columnar Phases: Columnar (or discotic) liquid crystals are different from the previous types because they are shaped like disks instead of long rods. This mesophase is characterized by stacked columns of molecules. The columns are packed together to form a two-dimensional

crystalline array.The arrangement of the molecules within the columns and the arrangement of the columns themselvesleads to new mesophases.
Columnar (or discotic)5
Highlights Liquid Crystalline Mesophases
Mesophase Topologies: Liquid crystalline structures can be organized into several classes, muchthe same as crystalline materials are organized into body-centered, triclinic, and so on lattices. The major LC mesophase topologies are (a) *Nematic*, (b) *Smectic*, (c) *discotic* and (d) *Cholesteric*. The ***nematic LCs*** are organized in one dimension only, with their chains lying parallel to each other at equilibrium. Molecules have no positional order in this mesophase.
The ***smectic LCs*** are ordered in two dimensions. Molecules in this phase show a positional order. Two of the more important mesophases are the smectic A and C structures. The ***cholesteric (chiral nematic)*** mesophase is like a two dimensional twisted nematicmesophase.
The ***columnar (discotic)*** mesophase resembles stacks of dishes or coins.Nematic state SmecticA Smectic C Cholesteric (Chiral nematic) Columnar (Discotic)6A LC-forming molecule may exhibit multiple mesophases at different temperatures or pressures.The kinetics of forming many LC mesophases is fairly slow. Again, it must be emphasized that not all molecules go through LC mesophases. Usually the conditions for liquid crystal formation are best met when the molecules have at least some portion of their structure in the form of rods or disks.
Liquid crystals can be classified into two main categories:
Thermotropic Liquid Crystals, and Lyotropic Liquid Crystals. These two types of liquid crystals aredistinguished by the mechanisms that drive their self-organization, but they are also similar in manyways. **Thermotropic transactions** occur in most liquid crystals, and they are defined by the fact thatthe transitions to the liquid crystalline state are induced thermally. That is, one can arrive at the liquidcrystalline state by raising the temperature of a solid and/or lowering the temperature of a liquid.Thermotropic liquid crystals can be classified into two types: ***enantiotropic liquid crystals***,which can be changed into the liquid crystal state from either lowering the temperature of a liquid orraising of the temperature of a solid, and ***monotropic liquid crystals***, which can only be changed into the liquid crystal state from either an increase in the temperature of a solid or a decrease in the temperature of a liquid, but not both. In general, thermotropic mesophases occur because of anisotropic dispersion forces between the molecules and because of packing interactions.In contrast to thermotropic mesophases, **lyotropic liquid crystal transitions** occur with the influence of solvents, not by a change in temperature. Lyotropic mesophases occur as a result of solvent-induced aggregation of the constituent mesogens into micellar structures. Lyotropic mesogens are typically amphiphilic, meaning that they are composed of both lyophilic (solvent-attracting) and lyophobic (solvent-repelling) parts. This causes them to form into micellar structures in the presence of a solvent, since the lyophobic ends will stay together as the lyophilic ends extend outward toward the solution. As the concentration of the solution is increased and the solution is cooled, the micelles increase in size and eventually coalesce. This separates the newly formed liquid crystalline state from the solvent.

REFERENCES:

1. Chandrasekhar, S. (1992). *Liquid Crystals* (2nd ed.). Cambridge: Cambridge University Press. ISBN 0-521-41747-3.
2. Reinitzer, Friedrich (1888). "Beiträge zur Kenntniss des Cholesterins". *Monatshefte für Chemie (Wien)* **9** (1): 421–441.doi:10.1007/BF01516710.
3. Lehmann, O. (1889). "Über fliessende Krystalle". *Zeitschrift für Physikalische Chemie* **4**: 462–72.
4. ^ Jump up to:[a b] Sluckin, T. J.; Dunmur, D. A. and Stegemeyer, H. (2004). *Crystals That Flow – classic papers from the history of liquid crystals*. London: Taylor & Francis. ISBN 0-415-25789-1.
5. ^ Gray, G. W. (1962) *Molecular Structure and the Properties of Liquid Crystals*, Academic Press

6. ^ Stegemeyer, H (1994). "Professor Horst Sackmann, 1921 – 1993". *Liquid Crystals Today* **4**: 1.doi:10.1080/13583149408628630.
7. ^ Liquid Crystals. kfupm.edu.sa
8. ^ Jump up to:[a b c d] Castellano, Joseph A. (2005). *Liquid Gold: The Story of Liquid Crystal Displays and the Creation of an Industry*. World Scientific Publishing. ISBN 978-981-238-956-5.
9. ^ Goldmacher, Joel E. and Castellano, Joseph A. "Electro-optical Compositions and Devices," U.S. Patent 3,540,796, Issue date: November 17, 1970.
10. ^ Heilmeier, G. H.; Zanoni, L. A.; Barton, L. A. (1968). "Dynamic Scattering in Nematic Liquid Crystals". *Applied Physics Letters* **13**: 46. Bibcode:1968ApPhL..13...46H. doi:10.1063/1.1652453.
11. ^ Kelker, H.; Scheurle, B. (1969). "A Liquid-crystalline (Nematic) Phase with a Particularly Low Solidification Point". *Angew. Chem. Int. Ed.* **8** (11): 884. doi:10.1002/anie.196908841.
12. ^ Gray, G.W.; Harrison, K.J.; Nash, J.A. (1973). "New family of nematic liquid crystals for displays". *Electronics Lett.* **9** (6): 130.doi:10.1049/el:19730096.
13. ^ "History and Properties of Liquid Crystals". Nobelprize.org. Retrieved June 6, 2009.
14. de Gennes, P.G. and Prost, J (1993). *The Physics of Liquid Crystals*. Oxford: Clarendon Press. ISBN 0-19-852024-7.
15. ^ Jump up to:[a b c] Dierking, I. (2003). *Textures of Liquid Crystals*. Weinheim: Wiley-VCH. ISBN 3-527-30725-7.
16. ^ Jump up to:[a b c d] Collings, P.J. and Hird, M (1997). *Introduction to Liquid Crystals*. Bristol, PA: Taylor & Francis. ISBN 0-7484-0643-3

NANOTECHNOLOGY IN ELECTRONICS –REVIEW ARTICLE

Sanjay Kumar

Baba Mastnath University, Asthal Bohar, Rohtak-124001

ABSTRACT:

Nanoelectronics *refer to the use of nanotechnology in electronic components. The term covers a diverse set of devices and materials, with the common characteristic that they are so small that inter-atomic interactions and quantum mechanical properties need to be studied extensively. Some of these candidates include: hybrid molecular/semiconductor electronics, one-dimensionalnanotubes or advanced molecular electronics. Recent silicon CMOS technology generations, such as the 22nm node, are already within this regime. Nanoelectronics are sometimes considered as disruptive technology because present candidates are significantly different from traditional transistors.*

Keywords: Nanoelectronics, nanotechnology, semiconductor.

INTRODUCTION:

In 1965 Gordon Moore observed that silicon transistors were undergoing a continual process of scaling downward, an observation which was later codified as Moore's law. Since his observation transistor minimum feature sizes have decreased from 10 micrometers to the 28-22 nm range in 2011. The field of nanoelectronics aims to enable the continued realization of this law by using new methods and materials to build electronic devices with feature sizes on the nanoscale.

The volume of an object decreases as the third power of its linear dimensions, but the surface area only decreases as its second power. This somewhat subtle and unavoidable principle has huge ramifications. For example the power of a drill (or any other machine) is proportional to the volume, while the friction of the drill's bearings and gears is proportional to their surface area. For a normal-sized drill, the power of the device is enough to handily overcome any friction. However, scaling its length down by a factor of 1000, for example, decreases its power by 1000^3 (a factor of a billion) while reducing the friction by only 1000^2 (a factor of only a million). Proportionally it has 1000 times less power per unit friction than the original drill. If the original friction-to-power ratio was, say, 1%, that implies the smaller drill will have 10 times as much friction as power; the drill is useless.

For this reason, while super-miniature electronic integrated circuits are fully functional, the same technology cannot be used to make working mechanical devices beyond the scales where frictional forces start to exceed the available power. So even though you may see microphotographs of delicately etched silicon gears, such devices are currently little more than curiosities with limited real world applications, for example, in moving mirrors and shutters. Surface tension increases in much the same way, thus magnifying the tendency for very small objects to stick together. This could possibly make any kind of "micro factory" impractical: even if robotic arms and hands could be scaled down, anything they pick up will tend to be impossible to put down. The above being said, molecular evolution has resulted in working cilia, flagella, muscle fibers and rotary motors in aqueous environments, all on the nanoscale. These machines exploit the increased frictional forces found at the micro or nanoscale. Unlike a paddle or a propeller which depends on normal frictional forces (the frictional forces perpendicular to the surface) to achieve propulsion, cilia develop motion from the exaggerated drag or laminar forces (frictional forces parallel to the surface) present at micro and nano dimensions. To build meaningful "machines" at the nanoscale, the relevant forces need to be considered. We are faced with the development and design of intrinsically pertinent machines rather than the simple reproductions of macroscopic ones.

All scaling issues therefore need to be assessed thoroughly when evaluating nanotechnology for practical applications.

APPROACHES TO NANOELECTRONICS

Nanomaterials Electronics

Besides being small and allowing more transistors to be packed into a single chip, the uniform and symmetrical structure of nanotubes allows a higher electron mobility (faster electron movement in the material), a higher dielectric constant (faster frequency), and a symmetrical electron/hole characteristic [1-4].

Also, nanoparticles can be used as quantum dots.

Molecular Electronics

Single molecule devices are another possibility. These schemes would make heavy use of molecular self-assembly, designing the device components to construct a larger structure or even a complete system on their own. This can be very useful for reconfigurable computing, and may even completely replace present FPGA technology.

Molecular electronics is a new technology which is still in its infancy, but also brings hope for truly atomic scale electronic systems in the future. One of the more promising applications of molecular electronics was proposed by the IBM researcher Ari Aviram and the theoretical chemist Mark Ratner in their 1974 and 1988 papers *Molecules for Memory, Logic and Amplification*, (see Unimolecular rectifier) [5-7].

This is one of many possible ways in which a molecular level diode / transistor might be synthesized by organic chemistry. A model system was proposed with a spiro carbon structure giving a molecular diode about half a nanometre across which could be connected by polythiophene molecular wires. Theoretical calculations showed the design to be sound in principle and there is still hope that such a system can be made to work.

Other Approaches

Nanoionics studies the transport of ions rather than electrons in nanoscale systems.Nanophotonics studies the behavior of light on the nanoscale, and has the goal of developing devices that take advantage of this behavior.

Nanoelectronic Devices

Current high-technology production processes are based on traditional top down strategies, where nanotechnology has already been introduced silently. The critical length scale of integrated circuits is already at the nanoscale (50 nm and below) regarding the gate length of transistors in CPUs or DRAM devices.

COMPUTERS

Nanoelectronics hold the promise of making computer processors more powerful than are possible with conventional semiconductor fabrication techniques. A number of approaches are currently being researched, including new forms of nanolithography, as well as the use of nanomaterials such as nanowires or small molecules in place of traditional CMOS components. Field effect transistors have been made using both semiconducting carbon nanotubes and with hetero structured semiconductor nanowires.

In 1999, the CMOS transistor developed at the Laboratory for Electronics and Information Technology in Grenoble, France, tested the limits of the principles of the MOSFET transistor with a diameter of 18 nm (approximately 70 atoms placed side by side). This was almost one tenth the size of the smallest industrial transistor in 2003 (130 nm in 2003, 90 nm in 2004, 65 nm in 2005 and 45 nm in 2007). It enabled the theoretical integration of seven billion junctions on a €1 coin. However, the CMOS transistor, which was created in 1999, was not a simple research experiment to study how CMOS technology functions, but rather a demonstration of how this technology functions now that we ourselves are getting ever closer to working on a molecular

scale. Today it would be impossible to master the coordinated assembly of a large number of these transistors on a circuit and it would also be impossible to create this on an industrial level.

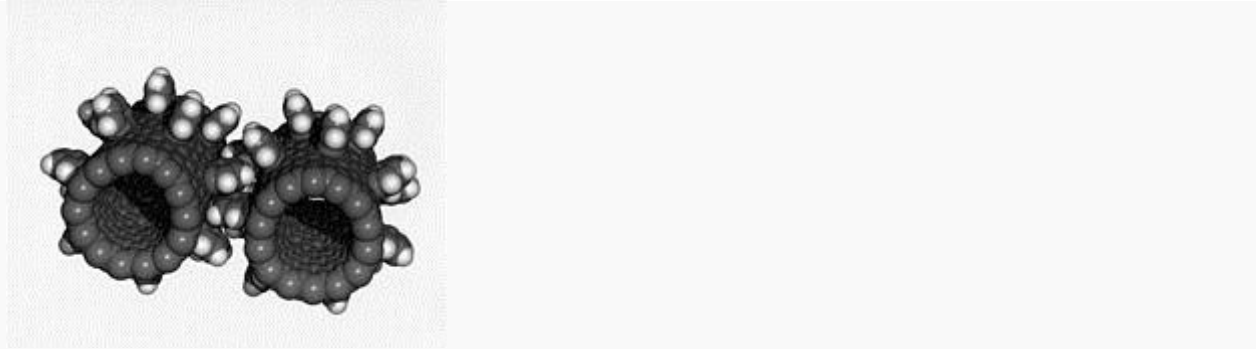
Memory Storage

Electronic memory designs in the past have largely relied on the formation of transistors. However, research into crossbar switch based electronics have offered an alternative using reconfigurable interconnections between vertical and horizontal wiring arrays to create ultra high density memories. Two leaders in this area are Nantero which has developed a carbon nanotube based crossbar memory called Nano-RAM and Hewlett-Packard which has proposed the use of memristor material as a future replacement of Flash memory.

An example of such novel devices is based on spintronics.The dependence of the resistance of a material (due to the spin of the electrons) on an external field is calledmagnetoresistance. This effect can be significantly amplified (GMR - Giant Magneto-Resistance) for nanosized objects, for example when two ferromagnetic layers are separated by a nonmagnetic layer, which is several nanometers thick (e.g. Co-Cu-Co). The GMR effect has led to a strong increase in the data storage density of hard disks and made the gigabyte range possible. The so-called tunneling magnetoresistance (TMR) is very similar to GMR and based on the spin dependent tunneling of electrons through adjacent ferromagnetic layers. Both GMR and TMR effects can be used to create a non-volatile main memory for computers, such as the so-called magnetic random access memory or MRAM.

Novel Optoelectronic Devices

In the modern communication technology traditional analog electrical devices are increasingly replaced by optical or optoelectronic devices due to their enormous bandwidth and capacity, respectively. Two promising examples are photonic crystals and quantum dots.Photonic crystals are materials with a periodic variation in the refractive index with a lattice constant that is half the wavelength of the light used. They offer a selectable band gap for the propagation of a certain wavelength, thus they resemble a semiconductor, but for light or photons instead of electrons. Quantum dots are nanoscaled objects, which can be used, among many other things, for the construction of lasers. The advantage of a quantum dot laser over the traditional semiconductor laser is that their emitted wavelength depends on the diameter of the dot. Quantum dot lasers are cheaper and offer a higher beam quality than conventional laser diodes.



Displays

The production of displays with low energy consumption might be accomplished using carbon nanotubes (CNT). Carbon nanotubes are electrically conductive and due to their small diameter of several nanometers, they can be used as field emitters with extremely high efficiency for field emission displays (FED). The principle of operation resembles that of the cathode ray tube, but on a much smaller length scale.

Quantum Compute

Entirely new approaches for computing exploit the laws of quantum mechanics for novel quantum computers, which enable the use of fast quantum algorithms. The Quantum computer

has quantum bit memory space termed "Qubit" for several computations at the same time. This facility may improve the performance of the older systems.

Radios

Nanoradios have been developed structured around carbon nanotubes.

Energy Production

Research is ongoing to use nanowires and other nanostructured materials with the hope to create cheaper and more efficient solar cells than are possible with conventional planar silicon solar cells. It is believed that the invention of more efficient solar energy would have a great effect on satisfying global energy needs.

There is also research into energy production for devices that would operate *in vivo*, called bio-nano generators. A bio-nano generator is a nanoscale electrochemical device, like a fuel cell or galvanic cell, but drawing power from blood glucose in a living body, much the same as how the body generates energy from food. To achieve the effect, anenzyme is used that is capable of stripping glucose of its electrons, freeing them for use in electrical devices. The average person's body could, theoretically, generate 100 wattsof electricity (about 2000 food calories per day) using a bio-nano generator. However, this estimate is only true if all food was converted to electricity, and the human body needs some energy consistently, so possible power generated is likely much lower. The electricity generated by such a device could power devices embedded in the body (such as pacemakers), or sugar-fed nanorobots. Much of the research done on bio-nano generators is still experimental, with Panasonic's Nanotechnology Research Laboratory among those at the forefront.

Medical Diagnostics

There is great interest in constructing nanoelectronic devices that could detect the concentrations of biomolecules in real time for use as medical diagnostics, thus falling into the category of nanomedicine.A parallel line of research seeks to create nanoelectronic devices which could interact with single cells for use in basic biological research. These devices are called nanosensors. Such miniaturization on nanoelectronics towards in vivo proteomic sensing should enable new approaches for health monitoring, surveillance, and defense technology.

REFERENCES:

1. "MEMS Overview". Retrieved 2009-06-06.
2. Das, S.; Gates, A.J.; Abdu, H.A.; Rose, G.S.; Picconatto, C.A. &Ellenbogen, J.C. (2007). "Designs for Ultra-Tiny, Special-Purpose Nanoelectronic Circuits". *IEEE Trans. on Circuits and Systems I* **54** (11): 11. doi:10.1109/TCSI.2007.907864.
3. Melosh, N.; Boukai, Abram; Diana, Frederic; Gerardot, Brian; Badolato, Antonio; Petroff, Pierre & Heath, James R. (2003). "Ultrahigh density nanowire lattices and circuits".*Science* **300** (5616): 112–5. Bibcode:2003Sci...300..112M.doi:10.1126/science.1081940. PMID 12637672.
4. Goicoechea, J.; Zamarreñoa, C.R.; Matiasa, I.R. &Arregui, F.J. (2007). "Minimizing the photobleaching of self-assembled multilayers for sensor applications". *Sensors and Actuators B: Chemical* **126** (1): 41–47. doi:10.1016/j.snb.2006.10.037.
5. Aviram, A.; Ratner, M. A. (1974). "Molecular Rectifier". *Chemical Physics Letters* **29** (2):277. Bibcode:1974CPL....29..277A. doi:10.1016/0009-2614(74)85031-1.
6. Aviram, A. (1988). "Molecules for memory, logic
7. Petty, M.C.; Bryce, M.R. & Bloor, D. (1995). *An Introduction to Molecular Electronics*. London: Edward Arnold. ISBN 0-19-521156-1

2D MATERIALS FOR EXCELLENCE IN NANOELECTRONICS

Neha Katyal*[1], Ashish Katyal[2],Dr.S.P Sharma[1]

[1] Department of Physics, Baba Mastnath University, Rohtak- 124001, India
[2]Department of Biotechnology, Meerut Institute of Engineering and Technology, Meerut-250005, India

ABSTRACT:
The compelling demand for higher performance and lower power consumption in electronic systems is the main driving force of the electronics industry's quest for devices and/or architectures based on new materials. As nanoelectronic devices and integrated circuits become smaller and denser, performance degradation and excess heat dissipation on the chip become big issues. Atomically thin, inherently 2D semiconductors offer excellent thickness scaling capabilities to improve electrostatic control. In this paper, we first review the impressive properties of two-dimensional (2D) nanocrystals , outlining perspective on the advantages offered by this class of materials for future.

INTRODUCTION

As nanoelectronic devices and integrated circuits become smaller and denser, performance degradation and excess heat dissipation on the chip become big issues. Atomically thin, inherently 2D semiconductors such as transition metal dichalcogenides (MX2, M=Mo, W, X=S, Se, Te) offer excellent thickness scaling capabilities to improve electrostatic control. In addition, at the limit of a single layer, MX2 become direct gap semiconductors with excellent response in the near IR and visible part of the solar spectrum making it suitable for light emitting devices and energy harvesting. Besides, these materials have high mechanical strength and because they are atomically thin they are bendable and stretchable so they can be used for transparent flexible displays and a number of low power versatile applications. Graphene – composed of a single layer of carbon atoms arranged in a hexagonal lattice with extraordinary physical properties was first experimentally demonstrated by Novoselov et al. [1] in 2004 and has drawn worldwide attention. It has shown that it is not only possible to exfoliate stable, single-atom or single-polyhedral-thick 2D materials from van der Waals solids, but that these materials can exhibit unique and fascinating physical properties. In single-layer graphene's band structure, the linear dispersion at the K point gives rise to novel phenomena, such as the anomalous room-temperature quantum Hall effect. Stimulated by the rise of graphene, various 2D crystals including layered hexagonal-boron nitride (h-BN) and TMDs i.e., transition metal dichalcogenides (such as MoS2) ,topological insulators (TI) such as Bi2Se3 and Bi2Te3, as well as graphene provide the option of ultimate thin "channel" transistors and the opportunity for new device concepts

. These 2D crystals can be easily prepared by the micromechanical exfoliation technique used on the layered structures of their 3D bulk materials, where adjacent layers are held together by the relatively weak van der Waals (vdW) bonds, while the in-plane atoms are bonded by the strong valence bonds.It is quite impressive that advanced devices and integrated circuits have already been realized showing that they can impact Nanoelectronics . However, most of the device work worldwide has been performed on small (micron size) flakes exfoliated from bulk. For real world applications, large area synthesis of these materials is required. These emerging 2D materials have attracted tremendous attention due to their unique 2D nature that not only enriches the world of low-dimensional physics, but also provides unique platform for transformative technical innovations. Different from conventional materials, their unique

properties include (1) pristine interfaces free of dangling bonds leading to low density of interface trap states and reduced scattering (**Fig. 1a, b**); (2) ultra-thin and uniform thickness leading to fluctuation-immune environment and excellent device electrostatics (**Fig. 1c, d**); and (3) wide range of choices from metals, insulators and semiconductors with controllable band gaps (**Fig. 1e**).

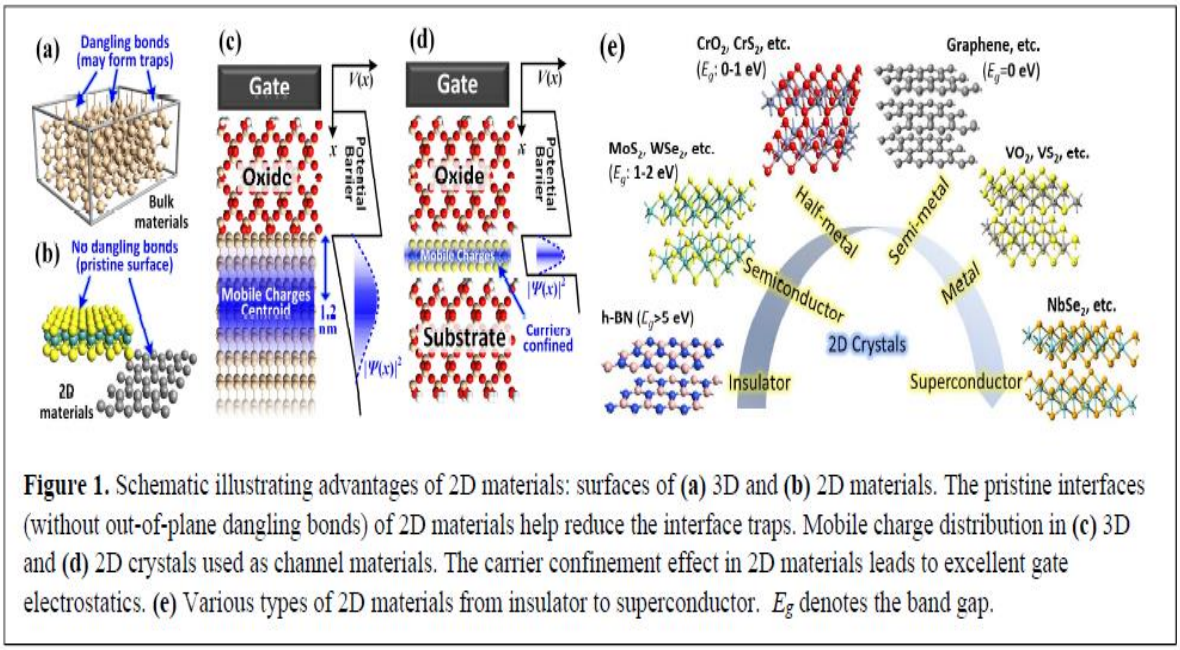


Figure 1. Schematic illustrating advantages of 2D materials: surfaces of **(a)** 3D and **(b)** 2D materials. The pristine interfaces (without out-of-plane dangling bonds) of 2D materials help reduce the interface traps. Mobile charge distribution in **(c)** 3D and **(d)** 2D crystals used as channel materials. The carrier confinement effect in 2D materials leads to excellent gate electrostatics. **(e)** Various types of 2D materials from insulator to superconductor. E_g denotes the band gap.

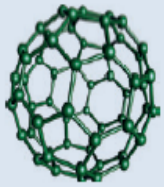
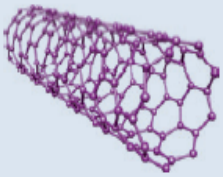
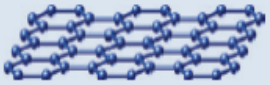
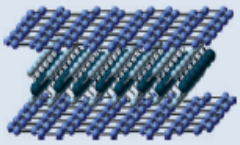
APPLICATIONS

Graphene and its derivatives are very versatile materials. As a result of their electrical, mechanical and optical properties they have, in the past 10 years, been proposed for use in a wide range of applications ranging from flexible electronics to DNA sequencing. They offer the promise to significantly improve existing products and to enable the design of materials and devices with novel functionalities.

One of the most striking features of graphene is its high charge-carrier mobility, and electronic and optoelectronic applications that could exploit this, as well as other characteristics, were among the first to be envisaged for the material. Developments in electronics based on graphene and related layered materials, which could potentially replace silicon-based electronic components in both digital and analog applications by leveraging on the ultimate thickness of these materials and on their excellent mobility. Development of graphene materials and devices is more mature in some areas, such as flexible electronics and conductive inks, but is at a more conceptual stage in others, such as biomedical and aerospace technologies. Several challenges towards commercialization remain that are application-dependent. Energy storage is a grand challenge for future energy infrastructure, transportation and consumer electronics. Jun Liu discusses how graphene may — or may not — be used to improve various electrochemical energy storage devices. Corrosion is one of the greatest challenges faced by the steel industry. It is triggered by environmental factors, such as water, oxygen and electrolytes. Graphene can be used to prevent corrosion of metals such as steel. Graphene applications in biomedicine, even though still in their infancy, can be divided into several main areas: transport (delivery) systems, sensors, tissue engineering and biological agents (for example antimicrobials). The use of various carbon nanoforms in such

biomedical applications has been actively pursued for the past decade or more[3]. Therefore, determination of the unique features offered by GMs (and other 2D structures) is of critical importance in the design and development of truly novel constructs of enhanced or previously unattainable functionality. Table 1 illustrates how the most widely explored nanocarbons (fullerenes and carbon nanotubes) compare with graphene and other 2D heterostructures in terms of their biomedical applicability and potential

Table 1 | Opportunities and challenges in biomedical applications for different forms of nanocarbon.

	Fullerenes	Carbon nanotubes	Graphene materials	2D heterostructures
				
Unique properties used in biomedical and life science	Free radical scavenging	Cylindrical shape Photothermal capability Inner space (for filling)	2D flat shape Large available surface area Flexibility Electrical conductivity Absence of bandgap Aqueous solubility (in the case of graphene oxide) Versatility of chemical functionalization	Similar to graphene materials in shape and structure More variability in the 'mix' of physical properties from different single layers
Biomedical application (most mature or intensively explored)	Antimicrobials	Molecular transporters (drug delivery) Near-infrared imaging agents	Highly sensitive biosensors Molecular transporters Coatings/substrates for tissue engineering and implants	Almost no such applications reported Biosensing and biodetection will be prime candidates
Opportunity	Interaction with double-stranded nucleic acids (for example mitochondrial DNA)	Translocation of biological membranes and barriers	Responsive to a wide range of parameters High sensitivity Multiple read-out routes Ease and speed of degradation	'Fabricate-by-design' based on the selection of layers
Challenge	Aqueous dispersibility Non-specific DNA binding leading to cytotoxicity	Controlled manufacturing and surface functionalization Aqueous dispersibility Adverse (inflammatory) responses related to fibre shape Slow kinetics of biodegradation	Unknown cytotoxic limitations Controllable dimensions Determination of *in vivo* biodegradability kinetics	Interaction with biological matter is currently unknown

CONCLUSION

The question that faces us today is "do we have the right new materials and a device or devices that will enable the industry to develop new nanoelectronic systems with the potential of revolutionizing the industry"? Due to the atomically-thin, flexible, bio-compatible, and transparent nature of these 2D materials, along with the wide range of electronic band gaps offered by them, a completely new generation of ultra-low power and ultra-dense green electronic devices and circuits to DNA sequencing can be envisioned. These properties can also be exploited for building various bio/chemical and gas sensors, energy harvesters, as well as "wearable", "implantable" and "invisible" electronics, which will usher unprecedented opportunities in electronics innovation during the next few decades.

REFERENCES

[1] International Technology Roadmap for Semiconductors (ITRS).

[2] K. S. Novoselov, A. K. Geim, S. V Morozov, D. Jiang, Y. Zhang, S. V Dubonos, I. V Grigorieva, and A. A. Firsov, "Electric field effect in atomically thin carbon films.," *Science*, vol. 306, no. 5696, pp. 666–9, Oct. 2004.
[3] K. S. Novoselov, D. Jiang, F. Schedin, T. J. Booth, V. V Khotkevich, S. V Morozov, and a K. Geim, "Two-dimensional atomic crystals.," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 102, no. 30, pp. 10451–3, Jul. 2005.
[4] K. F. Mak, C. Lee, J. Hone, J. Shan, and T. F. Heinz, "Atomically thin MoS2: a new direct-gap semiconductor," *Phys. Rev. Lett.*, vol. 105, no. 13, p. 136805, Sep. 2010
[5] B. Radisavljevic et al., ACS Nano **5**, 9934 (11); [2] P. Tsipas et al.,Appl. Phys. Lett. **103**, 251605 (2013); [3] P. Tsipas et al., ACS Nano (2014), **DOI:** 10.1021/nn502397x
[6] H. Li, C. Xu, N. Srivastava, and K. Banerjee "Carbon nanomaterials for next-generation interconnects and passives: physics, status, and prospects," *IEEE Trans. Electron Devices*, vol. 56, no. 9, pp. 1799–1821, 2009.
[7] H. Li, C. Xu and K. Banerjee, "Carbon nanomaterials: the ideal interconnect technology for next-generation ICs," *IEEE Des. Test Comput.*, vol. 27, no. 4, pp. 20–31, Jul. 2010.
[8] J. Kang, D. Sarkar, Y. Khatami, and K. Banerjee, "Proposal for all-graphene monolithic logic circuits," *Appl. Phys. Lett.*, vol. 103, no. 8, p. 083113, 2013.
[9] W. Cao, J. Kang, W. Liu, Y. Khatami, D. Sarkar, and K. Banerjee, "2D electronics: Graphene and beyond," in *43rd European Solid-State Device Research Conference (ESSDERC)*, Bucharest, Romania, 2013, pp. 1–8.
[10] J. Kang, D. Sarkar, W. Liu, D. Jena, and K. Banerjee, "A computational study of metal-contacts to beyond-graphene 2D semiconductor materials," in *IEEE International Electron Devices Meeting*, 2012, pp. 407–410.
[11] Novoselov, K. S. *et al*. *Science* **306,** 666–669 (2004).

LATEST APPROACHES OF NANO FABRICATION

Kusum Rani[1],Sheetal[1]

[1]Baba Mastnath University, Rohtak- 124001 , India(Vatskusum6@gmail.com),M-9034323301

Abstract

This chapter outlines and discusses important micro- and nanofabrication techniques. We start with the most basic methods borrowed from the integrated circuit (IC) industry, such as thin film deposition, lithography and etching, and then move on to look at MEMS and nanofabrication technologies. We cover a broad range of dimensions, from the micron to the nanometer scale. Although most of the current research is geared towards the nanodomain, a good understanding of top-down methods for fabricating micron-sized objects can aid our understanding of this research. Due to space constraints, we have focused here on the most important technologies; in the microdomain these include surface, bulk and high aspect ratio micromachining; in the nanodomain we concentrate on e-beam lithography, epitaxial growth, template manufacturing and self-assembly. MEMS technology is maturing rapidly, with some new technologies displacing older ones that have proven to be unsuited to manufacture on a commercial scale. However, the jury is still out on methods used in the nanodomain, although it appears that bottom-up methods are the most feasible, and these will have a major impact in a variety of application areas such as biology, medicine, environmental monitoring and nanoelectronics.

Key words: Nanometer ,Nanodomain ,Nanoelectronics ,Microdomain

INTRODUCTION

"Nanofabrication" is the process of making functional structures with arbitrary patterns having minimum dimensions currently defined (more-or-lessarbitrarily) to be e100 nm. Microelectronic devices and information technologies have improved and will continue to improve as a result of large-scale, commercial implementation of nanofabrication. The motivationfor these improvements is to increase the density of components, lower their cost, and increase their performance per device and per integrated circuit.

The smallest physical gate length of a microprocessor currently in production is 37 nm,1 and currenthalf-pitch, or periodicity, of manufactured dynamic random-access memory (DRAM) is 90 nm. The International Technology Roadmap for Semiconductors (ITRS), published by the Semiconductor Industry Association (SIA), projects reaching the 45-nm node in 2010 (corresponding to transistor gate lengths down to 18 nm and DRAM spacing of 45 nm).1 It is likely that a number of new technologies will evolve with further developments in nanofabrication. Many materials with minimum dimensions on the nanoscale have properties different than those observed for the bulk material.

Methods used to generate nanoscale structures and nanostructured materials are commonly characterized as "top-down" and "bottom-up". The top-down approach uses various methods of lithography to pattern nanoscale structures. This approach includes serial and parallel techniques for patterning features typically in two-dimensions (2D)sover length scales approximately 4 orders of magnitude larger (in linear dimension) than an individual structure. The bottomup approach uses interactions between molecules or colloidal particles to assemble discrete nanoscale structures in two and three dimensions. This manuscript first briefly reviews "conventional" techniques for nanofabrication; this review serves as background for discussions of "unconventional" techniques. These top-down techniques include photolithography and scanning beam (or maskless) lithography (e.g., electron beam and focused ion beam lithography). The first area of unconventional nanofabrication that we review is a set of techniques that uses organic materials to replicate nanoscale patterns or masters. These patterns are transferred into the materials by molding, embossing, or printing. The second area of

unconventional nanofabrication that we review (albeit in less detail) is scanning probe lithography (SPL). Techniques based on SPL are serial but can pattern features on a surface with atomic resolution. 28,52 We also sketch advances in the development of a parallel approach to SPL. Our review of SPL is brief as this technique has been reviewed elsewhere. 32,34,53,54 The last two areas that we reviewsedge lithography and self-assemblysare more limitedthan conventional lithography in generating arbitrary patterns but are promising approaches to lowcost, regular arrays of nanostructures. We believe that these approaches will be useful in research laboratories wishing to explore ideas in nanoscience. There are many forms of edge lithography; generally, they are techniques in which the *edges* of one pattern become the *features* of a second pattern. One approach to edge lithography converts films that are thin in the vertical direction into structures that are thin in the lateral direction. A second approach toedge lithography transfers the edges of a patterned thin film into another material. Self-assembly (both templated and untemplated) offers a final set of new approaches to nanofabrication. We believe that template self-assembly will be very important in nanoscience but is early in its development

CONVENTIONAL TECHNIQUES FOR NANOFABRICATION

Overview

The microelectronics industry has developed a sophisticated
infrastructure for patterning nanoscale features by conventional lithography. There are two dominant methods for conventional lithography: photolithography and particle beam lithography.

Photolithography

In current semiconductor nanofabrication photolithography can pattern 37-nm wide features with 193- nm wavelength light. The microelectronics industry plans to pattern minimum features below 37 nm using photolithography.1 Continuing this trend with 193-nm light will require optical proximity correction (OPC) or phase-shifting mask technology, which significantly increases the cost of photomasks. Another potential route to features with sub-50- nm resolution using 193-nm light is "immersion lithography". Immersion lithography is analogous to the better known concept of immersion microscopy often used with biological specimens.65 Imaging resolution for immersion microscopy is improved by increasing the refractive index of the medium between the imaging lens and the imaging approaches to nanofabrication. We believe that template self-assembly will be very important in nanoscience but is early in its development. Photolithography has a number of advantages over scanning beam lithography in nanofabrication, but the time and cost required to fabricate the photomasks typically patterned by scanning beam lithography scan be a significant drawback. There is, however, one photolithographic method that can produce simple patterns (e.g., diffraction gratings) without using a photomask. This process is interferometric lithography ,78,79 which involves the constructive and destructive interference of multiple laser beams at the surface of a photoresist. This method does not require a photomask or most of the expensive projection optics, but the projected patterns are restricted to regularly spaced arrays of lines or dots. Some of the smallest featuresspatterns of 40-nm wide parallel lines separated by 57 nm produced by photolithography have, however, been generated using interferometric lithography.

SCANNING BEAM LITHOGRAPHY

Scanning beam lithography is a slow process relative to photolithography. This serial technique can, however, generate high-resolution features with arbitrary patterns. There are three main classes of scanning beam lithography: (i) scanned laser beams with _250-nm resolution are the least expensive; (ii) focused electron beams with sub-50-nm resolution (depending on tool settings and the choice of photoresist) are expensive to purchase and maintain; and (iii) focused

ion beam (FIB) systems with sub-50- nm resolution are primarily (and extensively) used research. Typically, high-resolution photomasks are patterned using laser writers and electron-beam tools.There are tradeoffs for high resolution patterning with an electron or ion beam. Increasing the resolution requires decreasing the diameter of the particle beam, which decreases the beam current (charge repulsion makes small, high-current beams unstable). These changes increase the time necessary to achieve the same imaging dose. Some improvements can be realized by using very sensitive resists. Resists that require a lower dose of electrons or ions, however, usually have lower resolution than photoresists that require a higher dose. A chemically

amplified photoresist requires a low dose of electrons (_10 *í*C/cm2 for an accelerating potential of 100 kV) to pattern features with a resolution >50 nm.81 A photoresist requiring a higher dose of electrons, such as poly(methyl methacrylate) (PMMA), however, can have resolution below 20 nm but requires a dose of _400 *í*C/cm2 (at 50 kV).82 A cold developer (<10 °C) may improve the resolution and clarity of features in both types of resists.83 A focused ion beam can write patterns into a photoresist or directly onto the substrate .This technique can "mill" substrates by selectively removing material through ion bombardment or create patterns in an additive process by ion deposition or a localized chemical vapor deposition. This lithography technique can pattern features in a semiconductor with resolution down to _20 nm and with the smallest lateral dimensions down to _5 nm.

NON TEMPLATED SELF-ASSEMBLY

One of the most appealing aspects of self-assembly is the *spontaneous* assembly of components into a desired structure. The notion that a fabrication strategy requires only the mixing of components toachieve an ordered structure is appealing both for its simplicity and its potential efficiency. We refer to this type of self-assembly as "nontemplated selfassembly."

Templated Self-Assembly

By templating self-assembly it is possible to introduce an element of pattern into the self-assembled structure and sometimes increase the order of the self-assembled structure. Templated self-assembly is an alternative to non template self-assembly for the controlled fabrication of patterned structures with nanometer-scale local order and for the generation of micrometer-size, or larger, domains of defect-free patterns.

CONCLUSION

The expectations surrounding nanotechnology and nanofabrication are high Nanoscience and nanotechnology cover many different areas, but one key set of methods for both is nanofabrication. The development of microelectronic circuits with <100-nm-scale features is proceeding rapidly by extensions of existing, conventional photolithographic techniques. Unconventional techniques and new materials will be required, if at all, for structures with dimensions below _20 nm and to change the cost structure of this very capitalintensive industry. New products and technologies outside the field of microelectronics, but still requiring nanoscale fabrication, are being developed in widely different areas such as biology, materials science, and optics. Our intuition is that there will be many opportunities for the application of unconventional nanofabrication in these areas. Some possible areas of application include the following: (i) printed, low-cost organic microelectronics; (ii) subwavelength optics; (iii) tools for biology for investigating individual cells and cell-cell interactions; (iv) nanofluidics; (v) nanoelectrical mechanical systems (NEMS); and (vi) single-molecule studies.

References

(1) Anon (http://public.itrs.net/Files/2003ITRS/Home2003.htm).
(2) Brus, L. E. *J. Chem. Phys.* **1984**, *80*, 4403.

(3) Feldheim, D. L.; Keating, C. D. *Chem. Soc. Rev.* **1998**, *27*, 1.
(4) Kastner, M. A. *Phys Today* **1993**, *46*, 24.
(5) Klein, D. L.; Roth, R.; Lim, A. K. L.; Alivisatos, A. P.; McEuen, P. L. *Nature* **1997**, *389*, 699.
(6) Venema, L. C.; Wildoer, J. W. G.; Janssen, J. W.; Tans, S. J.;
Tuinstra, H. L. J. T.; Kouwenhoven, L. P.; Dekker, C. *Science* **1999**, *283*, 52.
(7) Avouris, P. *Acc. Chem. Res.* **2002**, *35*, 1026.
(8) Zhou, C.; Kong, J.; Yenilmez, E.; Dai, H. *Science* **2000**, *290*, 1552.
(9) Liang, W.; Bockrath, M.; Bozovic, D.; Hafner, J. H.; Tinkham, M.; Park, H. *Nature* **2001**, *411*, 665.
(10) Bockrath, M.; Liang, W.; Bozovic, D.; Hafner, J. H.; Lieber, C. M.; Tinkham, M.; Park, H. *Science* **2001**, *291*, 283.
(11) Bockrath, M.; Cobden, D. H.; McEuen, P. L.; Chopra, N. G.; Zettl, A.; Thess, A.; Smalley, R. E. *Science* **1997**, *275*, 1922.
(12) Baughman, R. H.; Cui, C.; Zakhidov, A. A.; Iqbal, Z.; Barisci, J. N.; Spinks, G. M.; Wallace, G. G.; Mazzoldi, A.; De Rossi, D.; Rinzler, A. G.; Jaschinski, O.; Roth, S.; Kertesz, M. *Science* **1999**, *284*, 1340.
(13) Torres, J. A.; Nealey, P. F.; de Pablo, J. J. *Phys. Rev. Lett.* **2000**, *85*, 3221.

A NEW FORMULATION FOR LINEAR PROGRAMMING PROBLEM : ISO L.P.P

G C SHUKLA

Department of Mathematics, Baba Mastnath University Asthal Bohar , Rohtak (Haryana) drgcshukla@gmail.com

ABSTRACT.

Linear program roblem develop by dentizing have been extensively use by many coworkers. We have shown that it is not unique and by presenting ISO L.P.P we have extended and further works will elebrate its importants.

INTRODUCTIONS

Linear programming problem was developed by G.Dantzig and his coworkers In 1947 and extremely used by various research workers.

This formulation uses basic linear variable Xi and a combination of these ,

Known as objective function to be maximized or minimized w.r.t set of linear constants with sign $\geq$ or $\leq$ or = . In mathematical notation L.PP

Is suppressed in matrix form Max / Min $z = CX^T$

Subject to $Ax=b$, $b\geq 0$

$x \rightarrow 0$

$x = (x1, x2 \ldots . x_m)$

$C=(c1, c2 \ldots \ldots . c_n)$

$A=[a_{11} , a_{12} , \ldots . a_{1n} , 1 , 0\ 0 \ldots 0$

$a_{21}, a_{22} \ldots \ldots . a_{2n}$

$a_{m1}, a_{m2} \ldots \ldots . a_{mn} , 0 , 0 , 1 \ ]$

We now exploit the solution of $Ax \leq b$ or $\geq b$ or $= b$

Let us take the case $Ax=b$, We know that by gauss-jordan method ,

Elementary row transformation for $Ax \leq b$ leaves solution unaltered this

Gives us Iso L.P.P.

Further for given L.P.P one formulates dual and we note that each L.P.P is called primal L.P.P , has a dual for it. In dual of L.P.P max becomes min and coefficient of objective function in primal becomes b's of dual and number of constant in dual changes of primal L.P.P has more constants that decision variable than dual is better choice for this

We illustrate all these concepts for a simple problem whenever many problems have been solved elsewhere.

Ex Solve

$$\text{Max } Z=2X_1+5X_2$$

$$\text{S.t} \quad X_1+4X_2 \leq 24$$

$$3X_1+X_2 \leq 21$$

$$X_1+X_2 \leq 9$$

$$X_1 , , X_2 \geq 0$$

Since number of constant(3) is more than number of base value(2)
So one choice is to consult dual of this process

$$\text{Dual Min } Z = 24Y_1+21Y_2+7Y_3$$
$$\text{S.t} \quad Y_1+3Y_2+Y_3 \le 2$$
$$Y_1, Y_2, Y_3 \ge 0 \quad 4Y_1+Y_2+Y_3 \le 5$$

We write constant equation

$$\begin{bmatrix} 1 & 4 \\ 3 & 1 \\ 1 & 1 \end{bmatrix} \begin{bmatrix} x1 \\ x2 \end{bmatrix} \le \begin{bmatrix} 24 \\ 21 \\ 9 \end{bmatrix}$$

Apply ERT ,

R1→R2-R3
R2→R2-R3

We got

$$\begin{bmatrix} 0 & 1 \\ 1 & 0 \\ 1 & 1 \end{bmatrix} \begin{bmatrix} x1 \\ x2 \end{bmatrix} \le \begin{bmatrix} 5 \\ 6 \\ 9 \end{bmatrix}$$

Thus Iso L.PP I
Note that constant 2^{nd} is redundant
This gives Iso L.P.P

$$\begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} X1 \\ X2 \end{bmatrix} \le \begin{bmatrix} 5 \\ 4 \end{bmatrix}$$

Note that Iso L.P.P II is easy to solve say , by graphical solution , and its solution is
Max Z=33
X2=5
X1=4
We have worked out solved examples in ref(3)

WE CONCLUDE

1 Iso LPP makes LPP non uniques and its economic interpretation gives us new insight
2 dual of L.P.P loses its charm as shown in as shown in an example solved here
3 There maybe many dual from ISO lp[p
4 its open us various avenues as to remove degeneracy , cycles in lpp by formulation iso l.P.P of problem associated with difficulties it will be tackled elsewhere

REFERENCES

1. Dantzig G.B linear programming of extensions 1963 , Princeton university press
2. 2 fundamentals of operations research 1968 new york Wiley operations research
3. 3 H.A . Taha , 2008 P.H.I Delhi
4. 4 G.C.Shukla operations research - Book under preparation

HILBERT SPACE AND IT'S PROPERTIES

Minakshi

Baba Mastnath University, Asthal Bohar, Rohtak-124021, E-mail: mann80m@gmail.com

ABSTRACT

The mathematical concept of a **Hilbert space**, named after David Hilbert, generalizes the notion of Euclidean space. It extends the methods of vector algebra and calculus from the two-dimensional Euclidean plane and three-dimensional space to spaces with any finite or infinite number of dimensions. A Hilbert space is an abstract vector space possessing the structure of an inner product that allows length and angle to be measured. Furthermore, Hilbert spaces are complete: there are enough limits in the space to allow the techniques of calculus to be used.

Hilbert spaces arise naturally and frequently in mathematics and physics, typically as infinite-dimensional function spaces. The earliest Hilbert spaces were studied from this point of view in the first decade of the 20th century by David Hilbert, Erhard Schmidt, and Frigyes Riesz. They are indispensable tools in the theories of partial differential equations, quantum mechanics, Fourier analysis (which includes applications to signal processing and heat transfer)—and ergodic theory, which forms the mathematical underpinning of thermodynamics. John von Neumann coined the term *Hilbert space* for the abstract concept that underlies many of these diverse applications. The success of Hilbert space methods ushered in a very fruitful era for functional analysis. Apart from the classical Euclidean spaces, examples of Hilbert spaces include spaces of square-integrable functions, spaces of sequences, Sobolev spaces consisting of generalized functions, and Hardy spaces of holomorphic functions.

INTRODUCTION

A Hilbert space H is a real or complex inner product space that is also a complete metric space with respect to the distance function induced by the inner product. To say that H is a complex inner product space means that H is a complex vector space on which there is an inner product $\langle x, y\rangle$ associating a complex number to each pair of elements x, y of H that satisfies the following properties:

- The inner product of a pair of elements is equal to the complex conjugate of the inner product of the swapped elements:
  $\langle y, x\rangle = \overline{\langle x, y\rangle}$.
- The inner product is linear in its first argument. For all complex numbers a and b,
  $\langle ax_1 + bx_2, y\rangle = a\langle x_1, y\rangle + b\langle x_2, y\rangle$.
- The inner product of an element with itself is positive definite:
  $\langle x, x\rangle \geq 0$
  where the case of equality holds precisely when $x = 0$.

It follows from properties 1 and 2 that a complex inner product is antilinear in its second argument, meaning that

$$\langle x, ay_1 + by_2\rangle = \bar{a}\langle x, y_1\rangle + \bar{b}\langle x, y_2\rangle.$$

A real inner product space is defined in the same way, except that H is a real vector space and the inner product takes real values. Such an inner product will be bilinear: that is, linear in each argument.

The norm is the real-valued function

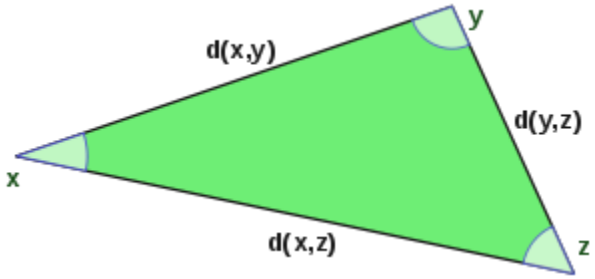
$$\|x\| = \sqrt{\langle x, x\rangle},$$

and the distance d between two points x,y in H is defined in terms of the norm by

$$d(x, y) = \|x - y\| = \sqrt{\langle x - y, x - y\rangle}.$$

That this function is a distance function means (1) that it is symmetric in x and y, (2) that the distance between x and itself is zero, and otherwise the distance between x and y must be positive, and (3) that the triangle inequality holds, meaning that the length of one leg of a triangle xyz cannot exceed the sum of the lengths of the other two legs:

$$d(x, z) \leq d(x, y) + d(y, z).$$



This last property is ultimately a consequence of the more fundamental Cauchy–Schwarz inequality, which asserts

$$|\langle x, y\rangle| \leq \|x\| \, \|y\|$$

with equality if and only if x and y are linearly dependent.

Relative to a distance function defined in this way, any inner product space is a metric space, and sometimes is known as a pre-Hilbert space. Any pre-Hilbert space that is additionally also a complete space is a Hilbert space. Completeness is expressed using a form of the Cauchy criterion for sequences in H: a pre-Hilbert space H is complete if every Cauchy sequence converges with respect to this norm to an element in the space. Completeness can be characterized by the following equivalent condition: if a series of vectors $\sum_{k=0}^{\infty} u_k$ converges absolutely in the sense that

$$\sum_{k=0}^{\infty} \|u_k\| < \infty,$$

then the series converges in H, in the sense that the partial sums converge to an element of H.

As a complete normed space, Hilbert spaces are by definition also Banach spaces. As such they are topological vector spaces, in which topological notions like the openness and closedness of subsets are well-defined. Of special importance is the notion of a closed linear subspace of a Hilbert space that, with the inner product induced by restriction, is also complete (being a closed set in a complete metric space) and therefore a Hilbert space in its own right.

Examples

Lebesgue spaces

Lebesgue spaces are function spaces associated to measure spaces (X, M, μ), where X is a set, M is a σ-algebra of subsets of X, and μ is a countably additive measure on M. Let $L^2(X, \mu)$ be the space of those complex-valued measurable functions on X for which the Lebesgue integral of the square of the absolute value of the function is finite, i.e., for a function f in $L^2(X,\mu)$,

$$\int_X |f|^2 d\mu < \infty,$$

and where functions are identified if and only if they differ only on a set of measure zero.

The inner product of functions f and g in $L^2(X, \mu)$ is then defined as

$$\langle f, g\rangle = \int_X f(t)\overline{g(t)}\, d\mu(t).$$

For f and g in L^2, this integral exists because of the Cauchy–Schwarz inequality, and defines an inner product on the space. Equipped with this inner product, L^2 is in fact complete. The Lebesgue integral is essential to ensure completeness: on domains of real numbers, for instance, not enough functions are Riemann integrable.

The Lebesgue spaces appear in many natural settings. The spaces L^2(R) and L^2([0,1]) of square-integrable functions with respect to the Lebesgue measure on the real line and unit interval, respectively, are natural domains on which to define the Fourier transform and Fourier series. In other situations, the measure may be something other than the ordinary Lebesgue measure on the real line. For instance, if w is any positive measurable function, the space of all measurable functions f on the interval [0, 1] satisfying

$$\int_0^1 |f(t)|^2 w(t)\,dt < \infty$$

is called the weighted L^2 space $L2$ w([0,1]), and w is called the weight function. The inner product is defined by

$$\langle f, g\rangle = \int_0^1 f(t)\overline{g(t)}w(t)\,dt.$$

The weighted space $L2$ w([0,1]) is identical with the Hilbert space L^2([0,1],μ) where the measure μ of a Lebesgue-measurable set A is defined by

$$\mu(A) = \int_A w(t)\,dt.$$

Weighted L^2 spaces like this are frequently used to study orthogonal polynomials, because different families of orthogonal polynomials are orthogonal with respect to different weighting functions.

Sobolev spaces

Sobolev spaces, denoted by H^s or $W^{s,2}$, are Hilbert spaces. These are a special kind of function space in which differentiation may be performed, but that (unlike other Banach spaces such as the Hölder spaces) support the structure of an inner product. Because differentiation is permitted, Sobolev spaces are a convenient setting for the theory of partial differential equations. They also form the basis of the theory of direct methods in the calculus of variations.

For s a non-negative integer and $\Omega \subset \mathrm{R}^n$, the Sobolev space $H^s(\Omega)$ contains L^2 functions whose weak derivatives of order up to s are also L^2. The inner product in $H^s(\Omega)$ is

$$\langle f, g\rangle = \int_\Omega f(x)\bar{g}(x)\,dx + \int_\Omega Df(x)\cdot D\bar{g}(x)\,dx + \cdots + \int_\Omega D^s f(x)\cdot D^s\bar{g}(x)\,dx$$

where the dot indicates the dot product in the Euclidean space of partial derivatives of each order. Sobolev spaces can also be defined when s is not an integer.

Sobolev spaces are also studied from the point of view of spectral theory, relying more specifically on the Hilbert space structure. If Ω is a suitable domain, then one can define the Sobolev space $H^s(\Omega)$ as the space of Bessel potentials; roughly,

$$H^s(\Omega) = \{(1-\Delta)^{-s/2} f | f \in L^2(\Omega)\}.$$

Here Δ is the Laplacian and $(1-\Delta)^{-s/2}$ is understood in terms of the spectral mapping theorem. Apart from providing a workable definition of Sobolev spaces for non-integer s, this definition also has particularly desirable properties under the Fourier transform that make it ideal for the study of pseudodifferential operators. Using these methods on a compact Riemannian manifold, one can obtain for instance the Hodge decomposition, which is the basis of Hodge theory.

Spaces of holomorphic functions

Hardy spaces

The Hardy spaces are function spaces, arising in complex analysis and harmonic analysis, whose elements are certain holomorphic functions in a complex domain. Let U denote the unit disc in the complex plane. Then the Hardy space $H^2(U)$ is defined as the space of holomorphic functions f on U such that the means

$$M_r(f) = \frac{1}{2\pi} \int_0^{2\pi} |f(re^{i\theta})|^2 \, d\theta$$

remain bounded for $r < 1$. The norm on this Hardy space is defined by

$$\|f\|_2 = \lim_{r \to 1} \sqrt{M_r(f)}.$$

Hardy spaces in the disc are related to Fourier series. A function f is in $H^2(U)$ if and only if

$$f(z) = \sum_{n=0}^{\infty} a_n z^n$$

where

$$\sum_{n=0}^{\infty} |a_n|^2 < \infty.$$

Thus $H^2(U)$ consists of those functions that are L^2 on the circle, and whose negative frequency Fourier coefficients vanish.

Bergman spaces

The Bergman spaces are another family of Hilbert spaces of holomorphic functions. Let D be a bounded open set in the complex plane (or a higher-dimensional complex space) and let $L^{2,h}(D)$ be the space of holomorphic functions f in D that are also in $L^2(D)$ in the sense that

$$\|f\|^2 = \int_D |f(z)|^2 \, d\mu(z) < \infty,$$

where the integral is taken with respect to the Lebesgue measure in D. Clearly $L^{2,\,h}(D)$ is a subspace of $L^2(D)$; in fact, it is a closed subspace, and so a Hilbert space in its own right. This is a consequence of the estimate, valid on compact subsets K of D, that

$$\sup_{z \in K} |f(z)| \leq C_K \|f\|_2,$$

which in turn follows from Cauchy's integral formula. Thus convergence of a sequence of holomorphic functions in $L^2(D)$ implies also compact convergence, and so the limit function is also holomorphic. Another consequence of this inequality is that the linear functional that evaluates a function f at a point of D is actually continuous on $L^{2,h}(D)$. The Riesz representation theorem implies that the evaluation functional can be represented as an element of $L^{2,h}(D)$. Thus, for every $z \in D$, there is a function $\eta_z \in L^{2,h}(D)$ such that

$$f(z) = \int_D f(\zeta) \overline{\eta_z(\zeta)} \, d\mu(\zeta)$$

for all $f \in L^{2,h}(D)$. The integrand

$$K(\zeta, z) = \overline{\eta_z(\zeta)}$$

is known as the Bergman kernel of D. This integral kernel satisfies a reproducing property

$$f(z) = \int_D f(\zeta) K(\zeta, z) \, d\mu(\zeta).$$

A Bergman space is an example of a reproducing kernel Hilbert space, which is a Hilbert space of functions along with a kernel $K(\zeta,z)$ that verifies a reproducing property analogous to this one.

The Hardy space $H^2(D)$ also admits a reproducing kernel, known as the Szegő kernel. Reproducing kernels are common in other areas of mathematics as well. For instance, in harmonic analysis the Poisson kernel is a reproducing kernel for the Hilbert space of square-integrable harmonic functions in the unit ball. That the latter is a Hilbert space at all is a consequence of the mean value theorem for harmonic functions.

Properties

Pythagorean identity

Two vectors *u* and *v* in a Hilbert space *H* are orthogonal when $\langle u, v \rangle = 0$. The notation for this is $u \perp v$. More generally, when *S* is a subset in *H*, the notation $u \perp S$ means that *u* is orthogonal to every element from *S*.

When *u* and *v* are orthogonal, one has

$$\|u+v\|^2 = \langle u+v, u+v\rangle = \langle u,u\rangle + 2\,\mathrm{Re}\langle u,v\rangle + \langle v,v\rangle = \|u\|^2 + \|v\|^2.$$

By induction on *n*, this is extended to any family $u_1,\ldots,u_n$ of *n* orthogonal vectors,

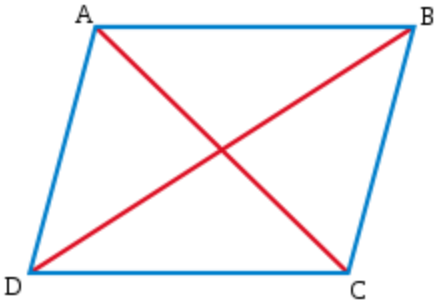
$$\|u_1 + \cdots + u_n\|^2 = \|u_1\|^2 + \cdots + \|u_n\|^2.$$

Whereas the Pythagorean identity as stated is valid in any inner product space, completeness is required for the extension of the Pythagorean identity to series. A series $\Sigma\, u_k$ of *orthogonal* vectors converges in *H* if and only if the series of squares of norms converges, and

$$\Big\| \sum_{k=0}^{\infty} u_k \Big\|^2 = \sum_{k=0}^{\infty} \|u_k\|^2.$$

Furthermore, the sum of a series of orthogonal vectors is independent of the order in which it is taken.

Parallelogram identity and polarization



Geometrically, the parallelogram identity asserts that $AC^2 + BD^2 = 2(AB^2 + AD^2)$. In words, the sum of the squares of the diagonals is twice the sum of the squares of any two adjacent sides.

By definition, every Hilbert space is also a Banach space. Furthermore, in every Hilbert space the following parallelogram identity holds:

$$\|u+v\|^2 + \|u-v\|^2 = 2(\|u\|^2 + \|v\|^2).$$

Conversely, every Banach space in which the parallelogram identity holds is a Hilbert space, and the inner product is uniquely determined by the norm by the polarization identity. For real Hilbert spaces, the polarization identity is

$$\langle u, v\rangle = \frac{1}{4}\left(\|u+v\|^2 - \|u-v\|^2\right).$$

For complex Hilbert spaces, it is

$$\langle u, v\rangle = \frac{1}{4}\left(\|u+v\|^2 - \|u-v\|^2 + i\|u+iv\|^2 - i\|u-iv\|^2\right).$$

The parallelogram law implies that any Hilbert space is a uniformly convex Banach space.

Best approximation

This subsection employs the Hilbert projection theorem. If C is a non-empty closed convex subset of a Hilbert space H and x a point in H, there exists a unique point $y \in C$ that minimizes the distance between x and points in C,

$$y \in C, \quad \|x - y\| = \operatorname{dist}(x, C) = \min\{\|x - z\| : z \in C\}.$$

This is equivalent to saying that there is a point with minimal norm in the translated convex set $D = C - x$. The proof consists in showing that every minimizing sequence $(d_n) \subset D$ is Cauchy (using the parallelogram identity) hence converges (using completeness) to a point in D that has minimal norm. More generally, this holds in any uniformly convex Banach space.

When this result is applied to a closed subspace F of H, it can be shown that the point $y \in F$ closest to x is characterized by

$$y \in F, \quad x - y \perp F.$$

This point y is the *orthogonal projection* of x onto F, and the mapping $P_F : x \to y$ is linear (see Orthogonal complements and projections). This result is especially significant in applied mathematics, especially numerical analysis, where it forms the basis of least squares methods.

In particular, when F is not equal to H, one can find a non-zero vector v orthogonal to F (select x not in F and $v = x - y$). A very useful criterion is obtained by applying this observation to the closed subspace F generated by a subset S of H.

> A subset S of H spans a dense vector subspace if (and only if) the vector 0 is the sole vector $v \in H$ orthogonal to S.

Duality

The dual space H^* is the space of all continuous linear functions from the space H into the base field. It carries a natural norm, defined by

$$\|\varphi\| = \sup_{\|x\|=1, x \in H} |\varphi(x)|.$$

This norm satisfies the parallelogram law, and so the dual space is also an inner product space. The dual space is also complete, and so it is a Hilbert space in its own right.

The Riesz representation theorem affords a convenient description of the dual. To every element u of H, there is a unique element φ_u of H^*, defined by

$$\varphi_u(x) = \langle x, u \rangle.$$

The mapping $u \mapsto \varphi_u$ is an antilinear mapping from H to H^*. The Riesz representation theorem states that this mapping is an antilinear isomorphism. Thus to every element φ of the dual H^* there exists one and only one u_φ in H such that

$$\langle x, u_\varphi \rangle = \varphi(x)$$

for all $x \in H$. The inner product on the dual space H^* satisfies

$$\langle \varphi, \psi \rangle = \langle u_\psi, u_\varphi \rangle.$$

The reversal of order on the right-hand side restores linearity in φ from the antilinearity of u_φ. In the real case, the antilinear isomorphism from H to its dual is actually an isomorphism, and so real Hilbert spaces are naturally isomorphic to their own duals.

The representing vector u_φ is obtained in the following way. When $\varphi \neq 0$, the kernel $F = \operatorname{Ker}(\varphi)$ is a closed vector subspace of H, not equal to H, hence there exists a non-zero vector v orthogonal to F. The vector u is a suitable scalar multiple λv of v. The requirement that $\varphi(v) = \langle v, u \rangle$ yields

$$u = \langle v, v \rangle^{-1} \overline{\varphi(v)}\, v.$$

This correspondence $\varphi \leftrightarrow u$ is exploited by the bra–ket notation popular in physics. It is common in physics to assume that the inner product, denoted by $\langle x|y\rangle$, is linear on the right,

$$\langle x|y\rangle = \langle y, x\rangle.$$

The result $\langle x|y\rangle$ can be seen as the action of the linear functional $\langle x|$ (the *bra*) on the vector $|y\rangle$ (the *ket*).

The Riesz representation theorem relies fundamentally not just on the presence of an inner product, but also on the completeness of the space. In fact, the theorem implies that the topological dual of any inner product space can be identified with its completion. An immediate consequence of the Riesz representation theorem is also that a Hilbert space H is reflexive, meaning that the natural map from H into its double dual space is an isomorphism.

Weakly convergent sequences

In a Hilbert space H, a sequence $\{x_n\}$ is weakly convergent to a vector $x \in H$ when

$$\lim_n \langle x_n, v\rangle = \langle x, v\rangle$$

for every $v \in H$.

For example, any orthonormal sequence $\{f_n\}$ converges weakly to 0, as a consequence of Bessel's inequality. Every weakly convergent sequence $\{x_n\}$ is bounded, by the uniform boundedness principle.

Conversely, every bounded sequence in a Hilbert space admits weakly convergent subsequences (Alaoglu's theorem). This fact may be used to prove minimization results for continuous convex functionals, in the same way that the Bolzano–Weierstrass theorem is used for continuous functions on R^d. Among several variants, one simple statement is as follows:

> If $f: H \to \mathrm{R}$ is a convex continuous function such that $f(x)$ tends to $+\infty$ when $\|x\|$ tends to ∞, then f admits a minimum at some point $x_0 \in H$.

This fact (and its various generalizations) are fundamental for direct methods in the calculus of variations. Minimization results for convex functionals are also a direct consequence of the slightly more abstract fact that closed bounded convex subsets in a Hilbert space H are weakly compact, since H is reflexive. The existence of weakly convergent subsequences is a special case of the Eberlein–Šmulian theorem.

REFERENCES

1. B.M. Levitan (2001), "Hilbert space", in Hazewinkel, Michiel.
2. Kolmogorov, Andrey; Fomin, Sergei V. (1970), *Introductory Real Analysis* (Revised English edition, trans. by Richard A. Silverman (1975) ed.), Dover Press, .
3. Krantz, Steven G. (2002), *Function Theory of Several Complex Variables*, Providence, R.I.: American Mathematical Society
4. Lanczos, Cornelius (1988), *Applied analysis* (Reprint of 1956 Prentice-Hall ed.), Dover Publications
5. O'Connor, John J.; Robertson, Edmund F. (1996), "Abstract linear spaces", *MacTutor History of Mathematics archive*, University of St Andrews..
6. Bers, Lipman; John, Fritz; Schechter, Martin (1981), *Partial differential equations*, American Mathematical Society.
7. Bourbaki, Nicolas (1986), *Spectral theories*, Elements of mathematics, Berlin: Springer-Verlag.
8. Bourbaki, Nicolas (1987), *Topological vector spaces*, Elements of mathematics, Berlin: Springer-Verlag.
9. Boyer, Carl Benjamin; Merzbach, Uta C (1991), *A History of Mathematics* (2nd ed.), John Wiley & Sons, Inc.
10. Brenner, S.; Scott, R. L. (2005), *The Mathematical Theory of Finite Element Methods* (2nd ed.), Springer.
11. Dieudonné, Jean (1960), *Foundations of Modern Analysis*, Academic Press.
12. Dunford, N.; Schwartz, J.T. (1958), *Linear operators, Parts I and II*, Wiley-Interscience.
13. Duren, P. (1970), *Theory of H^p-Spaces*, New York: Academic Press.
14. Folland, Gerald B. (2009), *Fourier analysis and its application* (Reprint of Wadsworth and Brooks/Cole 1992 ed.), American Mathematical Society Bookstore.

15. Folland, Gerald B. (1989), *Harmonic analysis in phase space*, Annals of Mathematics Studies 122, Princeton University Press.
16. Giusti, Enrico (2003), *Direct Methods in the Calculus of Variations*, World Scientific.
17. Grattan-Guinness, Ivor (2000), *The search for mathematical roots, 1870–1940*, Princeton Paperbacks, Princeton University Press.
18. Halmos, Paul (1957), *Introduction to Hilbert Space and the Theory of Spectral Multiplicity*, Chelsea Pub. Co
19. Halmos, Paul (1982), *A Hilbert Space Problem Book*, Springer-Verlag.
20. Hewitt, Edwin; Stromberg, Karl (1965), *Real and Abstract Analysis*, New York: Springer-Verlag.
21. Kadison, Richard V.; Ringrose, John R. (1997), *Fundamentals of the theory of operator algebras. Vol. I*, Graduate Studies in Mathematics 15, Providence, R.I.: American Mathematical Society.
22. Kline, Morris (1972), *Mathematical thought from ancient to modern times, Volume 3* (3rd ed.), Oxford University Press (published 1990).

INTRODUCTION OF LAURENT SERIES

VINOD BHATIA

Baba Mastnath University, Asthal Bohar,Rohtak-124021 E-mail: bhatiavinod@ymail.com

The **Laurent series** of a complex function *f*(*z*) is a representation of that function as a power series which includes terms of negative degree. It may be used to express complex functions in cases where a Taylor series expansion cannot be applied. The Laurent series was named after and first published by Pierre Alphonse Laurent in 1843. Karl Weierstrass may have discovered it first but his paper, written in 1841, was not published until much later, after Weierstrass' death.[1]
The Laurent series for a complex function *f*(*z*) about a point *c* is given by:

$$f(z) = \sum_{n=-\infty}^{\infty} a_n (z-c)^n$$

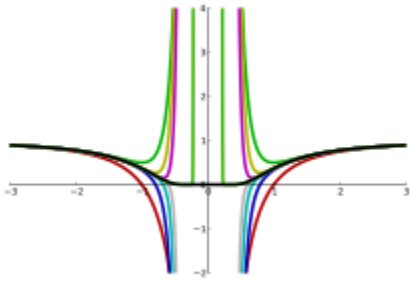
where the a_n are constants, defined by a line integral which is a generalization of Cauchy's integral formula:

$$a_n = \frac{1}{2\pi i} \oint_\gamma \frac{f(z)\,\mathrm{d}z}{(z-c)^{n+1}}.$$

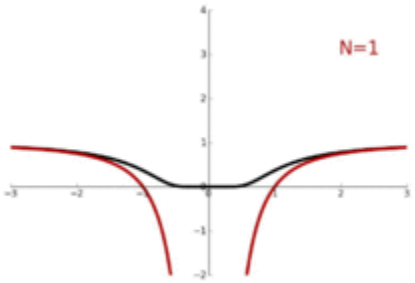
The path of integration γ is counterclockwise around a closed, rectifiable path containing no self-intersections, enclosing *c* and lying in an annulus *A* in which $f(z)$ is holomorphic (analytic). The expansion for $f(z)$ will then be valid anywhere inside the annulus. The annulus is shown in red in the diagram on the right, along with an example of a suitable path of integration labeled γ. If we take γ to be a circle $|z-c| = \varrho$, where $r < \varrho < R$, this just amounts to computing the complex Fourier coefficients of the restriction of f to γ. The fact that these integrals are unchanged by a deformation of the contour γ is an immediate consequence of Green's theorem.
In practice, the above integral formula may not offer the most practical method for computing the coefficients a_n for a given function $f(z)$; instead, one often pieces together the Laurent series by combining known Taylor expansions. Because the Laurent expansion of a function is unique whenever it exists, any expression of this form that actually equals the given function $f(z)$ in some annulus must actually be the Laurent expansion of $f(z)$.

Convergent Laurent series

Laurent series with complex coefficients are an important tool in complex analysis, especially to investigate the behavior of functions near singularities.



$e^{-1/x2}$ and Laurent approximations: see text for key. As the negative degree of the Laurent series rises, it approaches the correct function.



$e^{-1/x2}$ and its Laurent approximations with the negative degree rising. The neighborhood around the zero singularity can never be approximated.

Consider for instance the function $f(x) = e^{-1/x^2}$ with $f(0) = 0$. As a real function, it is infinitely differentiable everywhere; as a complex function however it is not differentiable at $x = 0$. By replacing x by $-1/x^2$ in the power series for the exponential function, we obtain its Laurent series which converges and is equal to $f(x)$ for all complex numbers x except at the singularity $x = 0$. The graph opposite shows $e^{-1/x2}$ in black and its Laurent approximations

$$\sum_{n=0}^{N} (-1)^n \frac{x^{-2n}}{n!}$$

for $N = 1, 2, 3, 4, 5, 6, 7$ and 50. As $N \to \infty$, the approximation becomes exact for all (complex) numbers x except at the singularity $x = 0$.

More generally, Laurent series can be used to express holomorphic functions defined on an annulus, much as power series are used to express holomorphic functions defined on a disc.

Suppose

$$\sum_{n=-\infty}^{\infty} a_n (z - c)^n$$

is a given Laurent series with complex coefficients a_n and a complex center c. Then there exists a unique inner radius r and outer radius R such that:

- The Laurent series converges on the open annulus $A := \{z : r < |z - c| < R\}$. To say that the Laurent series converges, we mean that both the positive degree power series and the negative degree power series converge. Furthermore, this convergence will be uniform on compact sets. Finally, the convergent series defines a holomorphic function $f(z)$ on the open annulus.
- Outside the annulus, the Laurent series diverges. That is, at each point of the exterior of A, the positive degree power series or the negative degree power series diverges.
- On the boundary of the annulus, one cannot make a general statement, except to say that there is at least one point on the inner boundary and one point on the outer boundary such that $f(z)$ cannot be holomorphically continued to those points.

It is possible that r may be zero or R may be infinite; at the other extreme, it's not necessarily true that r is less than R. These radii can be computed as follows:

$$r = \limsup_{n \to \infty} |a_{-n}|^{1/n}$$

$$\frac{1}{R} = \limsup_{n\to\infty} |a_n|^{1/n}.$$

We take R to be infinite when this latter lim sup is zero.

Conversely, if we start with an annulus of the form $A = \{z : r < |z - c| < R\}$ and a holomorphic function $f(z)$ defined on A, then there always exists a unique Laurent series with center c which converges (at least) on A and represents the function $f(z)$.

As an example, let

$$f(z) = \frac{1}{(z-1)(z-2i)}.$$

This function has singularities at $z = 1$ and $z = 2i$, where the denominator of the expression is zero and the expression is therefore undefined. A Taylor series about $z = 0$ (which yields a power series) will only converge in a disc of radius 1, since it "hits" the singularity at 1.

However, there are three possible Laurent expansions about 0, depending on the region z is in:

- One is defined on the disc where $|z| < 1$; it is the same as the Taylor series,

$$f(z) = \frac{1+2i}{5} \sum_{k=0}^{\infty} \left(\frac{1}{(2i)^{k+1}} - 1 \right) z^k.$$

(The technique involves using partial fractions to split the original expression for f(z) into two simpler fractions and then exploiting the fact that 1/(1-z) is the formula for the sum of a geometric series with first term 1 and constant multiplier z.)

- Another one is defined on the annulus where $1 < |z| < 2$, caught between the two singularities,

$$f(z) = \frac{1+2i}{5} \left(\sum_{k=1}^{\infty} \frac{1}{z^k} + \sum_{k=0}^{\infty} \frac{1}{(2i)^{k+1}} z^k \right).$$

- The third one is defined on the infinite annulus where $2 < |z| < \infty$,

$$f(z) = \frac{1+2i}{5} \sum_{k=1}^{\infty} \frac{1-(2i)^{k-1}}{z^k}.$$

(The terms above can be derived through polynomial long division or using the sum of a geometric series trick again, this time using $\frac{1}{z}$ and $\frac{2i}{z}$ as the common ratios.)

The case $r = 0$, i.e. a holomorphic function $f(z)$ which may be undefined at a single point c, is especially important.

The coefficient a_{-1} of the Laurent expansion of such a function is called the residue of $f(z)$ at the singularity c; it plays a prominent role in the residue theorem.

For an example of this, consider

$$f(z) = \frac{e^z}{z} + e^{1/z}.$$

This function is holomorphic everywhere except at $z = 0$. To determine the Laurent expansion about $c = 0$, we use our knowledge of the Taylor series of the exponential function:

$$f(z) = \cdots + \left(\frac{1}{3!}\right) z^{-3} + \left(\frac{1}{2!}\right) z^{-2} + 2z^{-1} + 2 + \left(\frac{1}{2!}\right) z + \left(\frac{1}{3!}\right) z^2 + \left(\frac{1}{4!}\right) z^3 + \cdots$$

and we find that the residue is 2

Uniqueness

Suppose a function $f(z)$ holomorphic on the annulus $r < |z - c| < R$ has two Laurent series:

$$f(z) = \sum_{n=-\infty}^{\infty} a_n (z-c)^n = \sum_{n=-\infty}^{\infty} b_n (z-c)^n .$$

Multiply both sides with $(z-c)^{-k-1}$, where k is an arbitrary integer, and integrate on a path γ inside the annulus,

Laurent polynomials

A **Laurent polynomial** is a Laurent series in which only finitely many coefficients are non-zero. Laurent polynomials differ from ordinary polynomials in that they may have terms of negative degree

$$\oint_\gamma \sum_{n=-\infty}^{\infty} a_n (z-c)^{n-k-1} \, \mathrm{d}z = \oint_\gamma \sum_{n=-\infty}^{\infty} b_n (z-c)^{n-k-1} \, \mathrm{d}z.$$

The series converges uniformly on $r + \epsilon \leq |z - c| \leq R - \epsilon$, where ε is a positive number small enough for γ to be contained in the constricted closed annulus, so the integration and summation can be interchanged. Substituting the identity

$$\oint_\gamma (z-c)^{n-k-1} dz = 2\pi i \delta_{nk}$$

into the summation yields

$$a_k = b_k$$

Hence the Laurent series is unique.

Principal part

The **principal part** of a Laurent series is the series of terms with negative degree, that is

$$\sum_{k=-\infty}^{-1} a_k (z-c)^k .$$

If the principal part of *f* is a finite sum, then *f* has a pole at *c* of order equal to (negative) the degree of the highest term; on the other hand, if *f* has an essential singularity at *c*, the principal part is an infinite sum (meaning it has infinitely many non-zero terms).

If the inner radius of convergence of the Laurent series for *f* is 0, then this is if and only if: *f* has an essential singularity at *c* if and only if the principal part is an infinite sum, and has a pole otherwise.

If the inner radius of convergence is positive, *f* may have infinitely many negative terms but still be regular at *c*, as in the example above, in which case it is represented by a *different* Laurent series in a disk about *c*.

Laurent series with only finitely many negative terms are tame—they are a power series divided by z^k, and can be analyzed similarly—while Laurent series with infinitely many negative terms have complicated behavior on the inner circle of convergence.

References

1. Rodriguez, Rubi; Kra, Irwin; Gilman, Jane P. (2012), *Complex Analysis: In the Spirit of Lipman Bers*, Graduate Texts in Mathematics **245**, Springer, p. 12, ISBN 9781441973238

STUDIES OF FISH FAUNA OF DAL LAKE (KASHMIR REGION) WITH REFERENCE TO THE PHYSIOLOGICAL PARAMETERS

Veena[1], Shalini[2] and Neefiya[3]

[1,2]Baba Mastnath University, Asthal Bohar, Rohtak (124021), Haryana., Email: veena.gzb@gmail.com
[3]SGRR (PG) College, Dehradun.

Nature has been very kind to Kashmir in respect of fresh water resources and a great array of lakes and valleys. These aquatic habitats are inhabited by a number of endemic and emotive fish species such as Schizothorax and carps respectively.

The fish fauna of the valley is unique and having the top dominance of Schizothorax group has evolved a number of endemic species in the valley. Kashmir valley where temperature ranges between 10-18o c. It is delicate fish which loves cold water which is well oxygenated.

The present investigation are undertaken to study the fish fauna and physic-chemical parameters of fishes inhabiting in dal lake of Kashmir. The fishes inhabiting in Dal lake named as- Schizothorax niger, S. cunifrons, S, esocinus, Cyprinus carpio, Carassius carassius, Puntius conchonius, Crossochilns diplochilns etc. Fishes of the genus Puntius are found in South Asia and mainl and Southest Asia with a single species P.sunderi. The greatest species richness is in India. The maximum size for an adult of this genus is less than 25 cm, typically 7-15 cm and many species only achieve around 5 cm adult length. In appearance they may resemble miniature carp and are often brightly coloured or patterned.

These fishes are omnivorous, their diet includes small invertebrates and plant matter. Breeding is by egg scattering and takes place close to the bottom, near or within areas of dense plant growth. They do not show parental care, and adults may eat the young.

Schizothorax is a genus of cyprinid fish from central and East Asia. In India S.plagiostomusn is the most important food fish of the Himalayan region, including Kashmir, H.P. Uttarakhand and U.P. It also plays an important role in commercial fish production (Bahuguna Zoo)

According to Raizada (1985) S. plagiostomus weigh up to 2.5kg and reaches 60 cm in length. It is mature at 18-24cm length and spawns in natural and artificial environments in two seasons, Sept-Oct and March-April. It spawns naturally in clear water on a gravelly or fine pebbled bed at 10-30cm depth. Water current of 2.8-4 m/s, pH 7.5, dissolved Oxygen concentration of 10-15 mg/l.

The common carp (Cyprinus carpio) is a wide spread freshwater fish of eutrophic water in lakes and large rivers in Europe & Asia. Wild common carp are typically slimmer than domesticated forms, with body length about four times body height, red flesh and a forward protruding mouth. Their average growth rate by weight is about half the growth rate by weight is about half the growth rate of domesticated carp, which can grow to maximum length of 120cm, a maximum weight of over 40-80cm and 2-14 Kg.

The common carp prefer large bodies of slow or standing water and soft vegetative sediments. They naturally live in temperate climates in fresh or slightly brackish water with a pH of 6.5-9.0 and salinity up to about 0.5% and temperature of 3 to 30oc with spawning beginning at 17-18oc, they easily survive in winter in a frozen-over land, as long as some free water remains

below the ice. Common carp are omnivorous. They can eat a herbivorous diet of water plants, but prefer to scavenge the bottom for insects, crustaceans and benthic worms.

The crucian carp (Carssius carassius) is a medium-sized member of common carp family cyprinidae. The crucian is a medium-sized cyprinid typically 15 cm in body length, and rarely exceeds in weight over 1.5 Kg. But a maximum total length of 64.0 cm is reported for a male, and the heaviest weighed 3 Kg.

On the basis of investigations conducted during the course, found that the tubitily reported in during January month is OJTU, because in this month the temperature has been goes down and the water become too cold or freezed. The water temperature has been recorded 4oc.

Aquatic animals are sensitive to changes in water temperature. It has been changes during another season, fluctuation in temperature has been seen. The dissolved oxygen has been recorded as 8ppm. Variations may be possible, depended season or water quality. The pH value has been recorded 7-8. Most aquatic animal prefer a range of 6.5 to 8.4. They are adapted to a specific pH level and may die, stop reproducing or move away, if the pH of the water varies beyond.

The present day fish catch from Dal lake comprise more than 75% of the carp. The fish usually thrives in water which are rich in nutrients and organic matter. As compared to the carps which thrive even in pluted water, the Schizothorax fish species are now rarely available from the lake.

During the survey in the month of December and January, there are only 8 species has been found. Among there are 8 species, few species are rare in condition. This indicate that the number of species are declines or disappeared S. richardsonii, due to pollutants and unfavourable environmental conditions. The fish fauna of valley is unique and having the top dominance of Schiothorax fish species.

REFERENCES

1. Agarwal, N.K., N.Singh and H.R.Singh :Histological and histochemical study on the steroid synthesizing cellular sites in the testes of hill streams fish. Schizothorax plagiostomus. Acta. Ichthyol. et. Pisc.22: 113-118(1992)
2. Badola, S.P.: Ecological studies on the Ichthyo fauna of fresh water resources of Gahgwal. D, P. bil. Thesis, University of Garhwal, Srinagar (Garhwal),India(1979).
3. Joshi, C.B. and S. Sunder : Breeding and culture of snow-trout, Schizothorax richardsonii (Gray) is kumaon Himalayas. Uttar Pradesh J.Zool., 15(2):136-140(1995).
4. Sharma, R.C.: Qualitative and Quantitative seasonal variation in feeding of snow-trout Schizothorax plagiostomus (Heckel) of Garhwal Himalaya. Biol. Bulet Ind.6: 20-25 (1994).
5. Smarlt, Joseph (2007). A possible genetic basis for species replacement: preliminary results of interspecific hybridization between crucian carp carassius carassius(L) and introduced goldfish carassius auratus (L), aquativ Invasion 2(1) 59-62.

BASIC CONCEPTS OF DRUG TARGETING AND CARRIER SYSTEMS.

Pallavi Bhardwaj, S.P.Sharma and Monika Chahar

Baba Mastnath University Asthal Bohar Rohtak-124021, Haryana Email id: pallavi198277@gmail.com

ABSTRACT:
The most important chemical features and biological behavioral characteristics of the carrier molecules exploited for drug targeting purposes will be addressed. Furthermore, a selection of drug targeting preparations that are either in the stage of clinical testing or have been approved for application in the clinic is discussed. As the basis of drug development lies in the understanding of the molecular basis of diseases, selective interference with regulatory processes in health and disease by drug targeting will become a powerful technology. Drug targeting can, in this respect, serve both as a therapeutic approach and as a research tool in unravelling the functions of these processes in normal physiology and under patho-physiological conditions.

INTRODUCTION:

Target drug delivery system is a special form of drug delivery system where the pharmacologically active agent or medicament is selectively targeted or delivered only to its site of action or absorption and not to the non-target organs or tissues or cells. Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at pre identified (preselected) target in therapeutic concentration, while restricting its access to non-target normal cellular linings, thus minimizing toxic effects and maximizing therapeutic index. Targeting of drugs to special cells and tissues of the body without their becoming a part of systemic circulation is a very novel idea. If a drug can be administered in a form such that it reaches the receptor sites in sufficient concentration without disturbing in extraneous tissue cells. Such products are prepared by considering-Specific properties of target cells. Nature of markers or transport carriers or vehicles, which convey drug to specific receptors. Ligands and physically modulated components.

Advantages of drug targeting:

- Drug administration protocols may be simplified.
- Drug quantity may be greatly reduced as well as the cost of therapy.
- Drug concentration in the required sites can be sharply increased without negative effects on non-target compartments.

Disadvantages of drug targeting:

- Rapid clearance of targeted systems.
- Immune reactions against intravenous administered carrier systems.
- Insufficient localization of targeted systems into tumour cells.
- Diffusion and redistribution of released drugs.

IDEAL CHARACTERISTICS OF TARGETED DRUG DELIVERY SYSTEM:

- Targeted drug delivery system should be- biochemically inert (non-toxic), non-immunogenic.
- Both physically and chemically stable in vivo and in vitro.
- Restrict drug distribution to target cells or tissues or organs and should have uniform capillary distribution.
- Controllable and predictable rate of drug release.
- Drug release should not affect thedrug action.

- Therapeutic amount of drug release.
- Minimal drug leakage during transit.
- Carriers used must be bio-degradable or readily eliminated from the body without any problem.
- The preparation of the delivery systemshould be easy or reasonably simple, reproductive and cost effective.

TYPES OF DRUG TARGETING: An ideal targeted drug delivery approach would not only increase therapeutic efficacy of drugs but also decrease the toxicity associated with drug to allow lower doses of the drug to be used in therapy. Two approaches are used passive targeting and active targeting.

1. Passive targeting: Passive targeting refers to the accumulation of drug or drug-carrier system at a particular site due to physicochemical or pharmacological factors. Drug or drug carrier nanosystems can be passively targeted making use of the patho-physiological and anatomical opportunities.eg include targeting of anti-malarial drugs for treatment of leishmiansis, brucellosis, candiadsis

2. Active targeting : Active targeting employs specific modification of a drug/drug carrier nano systems with active? agents having selective affinity for recognizing and interacting with a specific cell, tissue or organ in the body . Direct coupling of drugs to targeting ligand, restricts the coupling capacity to a few drug molecules. In contrast, coupling of drug carrier nanosystems to ligands allows import of thousands of drug molecules by means of one receptor targeted ligand. Example of active targeting is use of monoclonal antibody the treatment of cancer.

This active targeting approach can be furth further classified into three different levels of targeting.

1. First order targeting it refers to restricted distribution of the drug carrier systems to the capillary bed of a predetermined target site, organ or tissue. Example includes compartmental targeting in lymphatics, peritoneal cavity, plural cavity, cerebral ventricles, eyes, joints, etc.

2. Second order targeting selective delivery of drugs to specific cell types such as tumour cells and not to the normal cells is referred as second order targeting .Eg include selective drug delivery to kupffer cells in the liver.

3. Third order targeting defined as drug delivery specifically to the intracellular site of targeted cells.eg include receptor based ligand mediated entry of a drug complex into a cell by endocytosis.

DRUG CARRIERS:

- Most important entity required for successful transportation of the loaded drug.
- Drug vectors which, transport and retain drug; deliver it within or in the vicinity of target.
- Do so through an inherent characteristic or acquired through structural modification.

Properties of an ideal drug carriers:

- It must be able to cross anatomical barriers and in case of tumour chemotherapy tumour vasculature.
- It must be recognized specifically andselectively by the target cells and must maintain the specificity of the surface ligands.
- The linkage of the drug and thedirecting unit (ligand) should bestable in plasma, interstitial andother biofluids.
- Carrier should be non-toxic, non-immunogenic and biodegradable particulate or macromolecule.

- After recognition and internalization, thecarrier system should release the drugmoiety inside the target organs, tissues orcells.
- The biomodules used as carrier shouldnot be ubiquitous (existing or being everywhere at the same time).

Type of drug carrier:

Liposomes
Monoclonal Antibodies and Fragments
Modified (Plasma) Proteins
Soluble Polymers
Lipoproteins
Microspheres and Nanoparticles
Polymeric Micelles
Cellular Carriers

Targeting Moieties:

- Antibodies
- Lectins and other proteins
- Lipoproteins
- Hormones
- Charged molecules
- Polysaccharides
- Low-molecular-weight ligands

Liposomes: Liposomes are small vesicles composed of unilamellar or multilamellar phospholipid bilayers surrounding one or several aqueous compartments. Charge, lipid composition and size (ranging from 20 to 10 000 nm) of liposomes can be varied and these variations strongly affect their behaviour *in vivo*. Many liposome formulations are rapidly taken up by macrophages.They are exploited either for macrophage-specific delivery of drugs or for passive drug targeting, allowing slow release of the drug over time from these cells into the general circulation. Cationic liposomes and lipoplexes have been extensively investigated for their application in non-viral vector mediated gene therapy. The use of molecules such as polyethylene glycol (PEG) to prevent liposome recognition by phagocytic cells led to the development of so called 'stealth' liposomes with longer circulation times and increased distribution to peripheral tissues in the body. Although liposomes do not easily extravasate from the systemic circulation into the tissues, enhanced vascular permeability during an inflammatory response or pro-angiogenic conditions in tumours can favour local accumulation.

Monoclonal Antibodies and Fragments: Development of monoclonal antibodies by Köhler and Milstein in 1975 passed the way to antibody therapy for disease. In the last 25 years, the number of pre-clinical and clinical studies with monoclonal antibodies and derivatives thereof have greatly increased.The majority of strategies based on antigen recognition by antibodies have been developed for cancer therapy. These strategies are mostly aimed at tumour associated antigens being present on normal cells but over- expressed by tumour cells. More recently, antibodies against other molecules have been developed for clinical application. Examples are anti-TNFα antibodies for treatment of chronic inflammatory diseases and anti-VEGF (vascular endothelial growth factor) antibodies which inhibit new blood vessel formation or angiogenesis. The advent of recombinant DNA technology led to the development of antibodies and fragments that are tailored for optimal behaviour *in vivo*. Humanized and chimeric antibodies can be

constructed to circumvent the human anti-mouse antibody response elicited by mouse antibody treatment of patients, which severely hampers the application of these powerful molecules.

Modified (Plasma) Proteins: Modified plasma proteins are attractive carriers for drug targeting as they are soluble molecules with a relatively small molecular weight. They can easily be modified by covalent attachment of peptides , sugars , and other ligands, as well as drugs of interest. Particularly in the case of liver cell targeting, quite extensive modifications of protein backbones such as albumins have been carried out.

Soluble Polymers: Soluble synthetic polymers have been widely employed as versatile drug carrier systems. Polymer chemistry allows the development of tailor made conjugates in which target moieties as well as drugs are introduced into the carrier molecule. In the case of enhanced permeability retention in e.g. tumour vasculature , the introduction of drugs into the polymer may suffice.As non-specific adherence to cells is an undesirable property, excessive charge or hydrophobicity should be avoided in the design of polymeric carriers. For cancer therapy, the well established N(-2-hydroxypropyl)methacrylamide (HMPA) polymers have been extensively studied.

Lipoproteins: Endogenous lipid particles such as LDL and HDL containing a lipid and apoprotein moiety can be seen as 'natural targeted liposomes'. The lipid core can be used to incorporate lipophilic drugs or lipophilic pro-drugs, covalent binding of the drug to the carrier is not necessary here.The apolipoprotein moiety of these particles can be glycosylated or modified with other (receptor) targeting ligands. Furthermore, modifications at the level of glycolipid incorporation can be employed to introduce targeting moieties. As with the liposomes, the size and charge of the particles determine their behaviour *in vivo*. Large particles will not easily pass the endothelial barrier of organs containing blood vessels with a continuous endothelial cell lining. The majority of the research on the use of LDL and HDL particles has been devoted to the targeting of drugs to the liver.

Microspheres and Nanoparticles: Microspheres and nanoparticles often consist of biocompatible polymers and belong either to the soluble or the particle type carriers. Besides the aforementioned HPMA polymeric backbone, carriers have also been prepared using dextrans, ficoll, sepharose or poly-L-lysine as the main carrier body. More recently alginate nanoparticles have been described for the targeting of antisense oligonucleotides . As with other polymeric carrier systems, the backbone can be modified with e.g. sugar molecules or antibody fragments to introduce cellular specificity. Nanoparticles are smaller (0.2–0.5 μm) than microspheres (30–200 μm) and may have a maller drug loading capacity than the soluble polymers. Formulation of drugs into the nanoparticles can occur at the surface of the particles and at the inner core, depending on the physicochemical characteristics of the drug. The site of drug incorporation significantly affects its release rate from the particle. After systemic administration they quickly distribute to and subsequently become internalized by the cells of the phagocytic system. Even coating of these carriers with PEG does not completely divert them from distribution to the phagocytes in liver and spleen. Consequently, intracellular infections in Kupffer cells and other macrophages are considered a useful target for these systems. Besides parenteral application of microspheres and nanoparticles for cell selective delivery of drugs, they have more recently been studied for their application in oral delivery of peptides and peptidomimetics.

Polymeric Micelles: Polymeric micelles are characterized by a core-shell structure. They have a di-block structure with a hydrophilic shell and a hydrophobic core. The hydrophobic core generally consists of a biodegradable polymer that serves as a reservoir for an insoluble drug. Non- or poorly biodegradable polymers can be used, as long as they are not toxic to cells and can

be renally secreted. If a water-soluble polymeric core is used, it is rendered hydrophobic by chemical conjugation with a hydrophobic drug. The viscosity of the micellar core may influence the physical stability of the micelles as well as drug release. The bio-distribution of the micelle is mainly dictated by the nature of the shell which is also responsible for micelle stabilization and interactions with plasma proteins and cell membranes. The micelles can contain functional groups at their surface for conjugation with a targeting moiety. Polymeric micelles are mostly small (10–100 nm) in size and drugs can be incorporated by chemical conjugation or physical entrapment. For efficient delivery activity, they should maintain their integrity for a sufficient amount of time after injection into the body. Most of the experience with polymeric micelles has been obtained in the field of passive targeting of anticancer drugs to tumours

Cellular Carriers: Cellular carriers may have the advantage of their natural biocompatibility. However, they will encounter endothelial barriers and can rather easily invoke an immunological response. Most of the approaches on cellular carriers have been applied to the field of cancer therapy. Antigen specific cytotoxic T lymphocytes have been studied as vehicles to deliver immunotoxins to cancer cells *in vivo*.

Conclusions: The development of drug targeting strategies for clinical application, especially for cancer therapy, have been identified, analysed and solved. Several drug targeting preparations have entered the phases of clinical testing and/or have now been marketed. However, these strategies should be subjected to continuous evaluation in the light of advances in the understanding of the numerous processes occuring in response to administration of the carriers and/or the drugs. New strategies under investigation will need to be optimized and extensively evaluated, taking advantage of the 'bench to bed-side' experience available today. Furthermore, in the coming years, combining expertise in the drug targeting field with the technological developments in molecular biology and molecular medicine will facilitate the elucidation of the cellular and molecular processes underlying disease.

REFERENCES:

- Drug Targeting Organ-Specific Strategies Edited by Grietje Molema and Dirk K. F. Meijer.
- Targeted and Controlled drug delivery (Novel carrier systems), S P Vyas and R K Khar,
- Progress in Controlled and Novel drug delivery systems by N K Jain, CBS publishers.
- Breimer DD, Adv. Drug Deliv. Rev. 1998, 33, 265–268.
- Mastrobattista E, Koning GA, Storm G, Adv. Drug Deliv. Rev. 1999, 40, 103–127.
- Duzgunes N, Nir S, Adv. Drug Deliv. Rev. 1999, 40, 3–18.
- Storm G, Crommelin DJA, PSTT 1998, 1, 19–31.
- Köhler G, Milstein C, Nature 1975, 256, 495–497.
- Farah RA, Clinchy B, Herrera L, Vitetta ES, Crit. Rev. Eukaryot. Gene Expr. 1998, 8, 321–356.
- Willuda J, Honegger A, Waibel R, Schubiger PA, Stahel R, Zangemeister-Wittke U, Pluckthun
- A, Cancer Res. 1999, 59, 5758–5767.
- Worn A, Pluckthun A, Biochemistry 1999, 38, 8739–8750.
- Charles P, Elliott MJ, Davis D, Potter A, Kalden JR, Antoni C, Breedveld FC, Smolen JS, Eberl

SYNTHESIS AND IR CHARACTERIZATION OF SILICA GEL BASED NANOCOMPOSITE MATERIALS

Monika Chahar[1*], Sushil Kumar[2], Pallavi Bhardwaj[1]

1. Baba Mastnath University, Asthal Bohar, Rohtak- 124 021, India.
2. Chaudhary Devi Lal University, Sirsa-125 055, India.

ABSTRACT

Nanocomposite materials based on silica gel have been prepared by using sol-gel chemistry. The mild condition associated with the sol-gel processing allow for the incorporation of dopant 2, 5-diphenyloxazol dye in the silica gel matrix to synthesize the composite material. In the present study, 2, 5-diphenyloxazol doped nanocomposite materials have been synthesized by taking tetraethylorthosilicate (TEOS) as precursor. The samples have doping of 2, 5-diphenyloxazol with different concentration such as 0.99×10^{-6}, 1.99×10^{-6}, 2.99×10^{-6}, 3.99×10^{-6}, 4.99×10^{-6} and 5.98×10^{-6} mol L^{-1} .The structural behaviour of prepared samples were characterized with the help of FTIR technique.

Keywords: Sol-gel process, nanocomposite materials, FTIR.

INTRODUCTION

Nanocomposite materials especially dye doped solid state laser materials and rare earth doped solid state laser materials attracted the research group due to their wide applications in the field of science and technology. Dye lasers are that type of laser material which uses an organic dye as the lasing or gain medium, usually as a liquid solution. The wide gain spectrum of available dyes allows these lasers to be highly tunable, or to produce very short-duration pulses (on the order of a few femtoseconds) [1]-[3]. The wide bandwidth makes them particularly suitable for tunable lasers and pulsed lasers. Incorporation of organic dye molecules in the silica gel matrix can explore new possibilities in the development of smart materials. Several research groups are engaged in the development and interpretation of these types of advanced materials. The solid state dye lasers based on LDS 698 doped in modified polymethylmethacrylate. Schultheiss Slike et al. have reported rhodamines in silica-zirconia materials, Scott J. Brian et al. have reported mesoporous and mesostructured materials for optical applications. Purificacion et al. have been reported photonic and nanobiophotonic properties of luminescent lanthanide-doped hybrid organic-inorganic materials Although recent work on laser performance of pyrromethene 567 dye in solid polymeric matrices with different cross-linking degrees, quenching of fluorescence for fluoro derivatives of the laser dye DCM in polar solutions and the comparison of spectroscopic and lasing properties of different types of sol-gel glass matrices containing Rh-6G has led to better understanding of this phenomenon[7]-[15]. The present research work involved the synthesis of dye laser material or composite material by taking silica gel as host matrix by using sol-gel method. The chemical doping of silica gel with organic laser dye such as 2,5-Diphenyloxazole [PPO] has been done and their spectroscopic characterization have been carried out to find their influence on structural properties.

2. EXPERIMENTAL SECTION

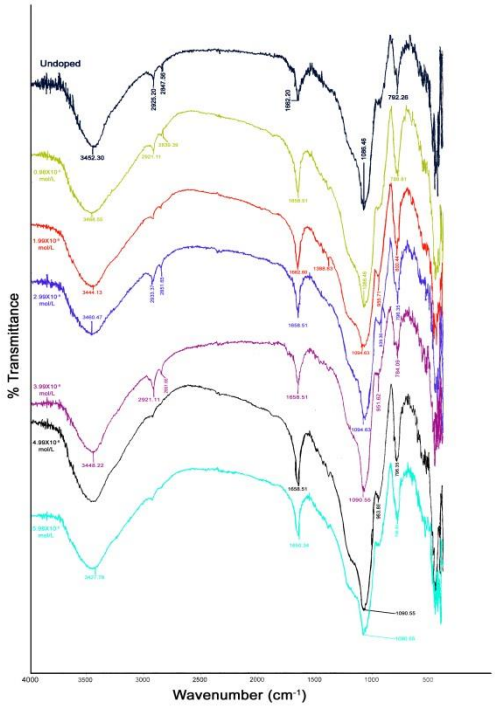
2.1 Chemicals

The following chemicals were used in the experimental work for the preparation of silica gel glass; tetraethylorthosilicate(TEOS)(HiMedia Laboratories Pvt.Ltd. Mumbai, India), 2,5-Diphenyloxazol (M.W; 221.25 and structural formula $C_{15}H_{11}NO$) (Sigma Aldrich, India) N,N-dimethylformamide(GC Grade, Spectrochem Pvt.Ltd. Mumbai, India), ethanol(AR Grade, Changshu Yangyuan Chemical China), hydrochloric acid (Qualigens fine chemicals, Glaxo Smith Kline Pharmaceuticals Limited Mumbai, India), ethylene glycol(AR Grade, Spectrochem

Pvt.Ltd. Mumbai, India), acetonitrile(Qualigens Fine Chemicals, Glaxo Smith Kline Pharmaceuticals Limited Mumbai, India).

2.2 Methodology

The materials in rod shaped have been fabricated by using the sol-gel method. The prepared reaction mixture is doped by 2, 5-Diphenyloxazol dye with different concentration such as 0.99 $\times 10^{-6}$, 1.99×10^{-6}, 2.99×10^{-6}, 3.99×10^{-6}, 4.99×10^{-6} and 5.98×10^{-6} mol L^{-1}. The reaction mixture doped with 2,5-Diphenyloxazol dye was casted into a flat, bottom glass tubes and put into oven at 42ºC for about 30 days . The gelling is started after two days at 42ºC The temperature variate slowly and slowly upto 80ºC for 72 h for final ageing to achieve good mechanical strength of prepared samples. Thus the samples with desired shaped and size have been achieved at low temperature.



3. RESULTS AND DISCUSSION

FTIR study

The spectra of pure silica gel and 2, 5-diphenyloxazol doped silica based material exhibit several absorption peaks as shown in Fig.a The concentration of dye varies as 0.99×10^{-6}, $1.99x10^{-6}$, $2.99x10^{-6}$, 3.99×10^{-6}, 4.99×10^{-6} and 5.98×10^{-6} mol/L. The absorption band in the region 4000-3000 cm^{-1} is mainly due to the combination of vibrations of Si-OH or water. The broad absorption band is generally composed of the stretching modes. The region of 3000-2800 cm^{-1} corresponds to symmetric and asymmetric stretching vibration of CH_2 and CH_3 groups of alkoxide and solvent residue. The main band in the region 1300-400 cm^{-1}, is associated with the combination of vibrations of silica network.

Fig.a FTIR spectra of undoped and 2, 5-diphenyloxazol dye doped silica based material

CONCLUSIONS

In the present work, 2, 5-diphenyloxazol dye doped silica based material has been prepared by sol-gel route using tetraethylorthosilicate as precursor. IR spectroscopy is employed to

understand structural changes, which occur at the surface and in the network of silica gel obtained and it has been observed from this study that the dye molecules/atoms are trapped in the pores of silica.

REFERENCES

1. F. J. Duarte and L. W. Hillman, Dye Laser Principles, Academic, New York, 1990.
2. T. W. Hansch, Appl. Opt., **11** (1972) 895.
3. I. Shoshan, N. N. Danon, and U. P. Oppenheim, J. Appl. Phys., **48** (1977) 4495.
4. M. G. Littman and H. J. Metcalf, Appl. Opt., **17**, (1978) 2224.
5. F. J. Duarte and J. A. Piper, Opt. Commun. , **35** (1980) 100.
6. F. J. Duarte and J. A. Piper, Appl. Opt., **20** (1981) 2113.
7. P. Zorabedian and F. J. Duarte, Tunable external cavity semiconductor lasers, in Tunable Lasers, Academic, New York, 1995.
8. F. J. Duarte and J. A. Piper, Opt. Commun., **43** (1982) 303.
9. 24. F. J. Duarte and L. W. Hillman, Dye Laser Principles, Academic, New York, 1990.
10. F. J. Duarte, High Power Dye Lasers, Springer-Verlag, Berlin, 1991.
11. M. A. Akerman, Dye laser isotope separation, in Dye Laser Principles, F. J. Duarte and L. W. Hillman (Eds.), Academic, New York, 1990.
12. W. Demtröder, Laser Spectroscopy, 3rd ed. Springer, 2003.
13. L. Goldman, Dye lasers in medicine, in Dye Laser Principles, F. J. Duarte and L. W. Hillman (Eds.), Academic, New York, 1990.
14. A. Costela et al., Medical applications of dye lasers, in Tunable Laser Applications, F. J. Duarte (Ed.), CRC, New York, 2009.
15. D. Klick, Industrial applications of dye lasers, in Dye Laser Principles, F. J. Duarte and L. W. Hillman (Eds.), Academic, New York, 1990.

NANOMATERIALS - REVIEW ARTICLE

Sanjay Kumar

Baba Mastnath University, Asthal Bohar, Rohtak-124001

ABSTRACT:
Nanotechnologies make use of very small objects. Nanomaterials are an increasingly important product of nanotechnologies. They contain nanoparticles, smaller than 100 nanometres in at least one dimension. Nanomaterials are coming into use in healthcare, electronics, cosmetics and other areas. Their physical and chemical properties often differ from those of bulk materials, so they call for specialised risk assessment. This needs to cover health risks to workers and consumers, and potential risks to the environment. This is currently done on a case by case basis, but risk assessment methods need to be kept up to date as the use of nanomaterials expands, especially as they find their way into consumer products.
Keywords: Nanomaterials, electronics, physical properties, chemical properties.

INTRODUCTION

Materials of which a single unit is sized at least one dimension i.e., between 1 and 1000 nanometers (10 to the power of 9 meter) but it is usually 1-100 nm. Two types of nanomaterials are there they are Natural nanomaterials and Synthetic nanomaterials. Synthetic nanomaterials are again 2 types: Fullerenes and Nanoparticles. Nanomaterials research takes a materials science-based approach to nanotechnology. Nanoscale materials are too small and we cant see with our naked eyes and even with microscopes and those nanomaterials are called as engineered nanomaterials and they have unique optical, electronic, or mechanical properties. Review articles are the summary of current state of understanding on a particular research topic. They analyze or discuss research previously published by scientist and academicians rather than reporting novel research results. Review article comes in the form of systematic reviews and literature reviews and are a form of secondary literature. Systematic reviews determine an objective list of criteria, and find all previously published original research papers that meet the criteria. They then compare the results presented in these papers. Literature reviews, by contrast, provide a summary of what the authors believe are the best and most relevant prior publications. The concept of review article is separate from the concept of peer-reviewed literature. It is possible for a review to be peer-reviewed, and it is possible for a review to be non-peer-reviewed. The open access articles published in this scholarly journal are reviewed by at least two reviewers of the associated fields. The journal publishes original research articles, reviews, case reports, short communications, etc and emphasizes theoretical and experimental work. To ensure high quality articles, both editors and reviewers actively participate in the peer review process and help in completing the review process within 21 days. As an important educational platform the journal provides scientists and researchers access to the newest trends and research outlooks. Please browse through the list of peer-reviewed journals to find the scientific publication of your interest. OMICS Group is a scientific organization and online publishing house that drives the progress of research through freely available open access journals and international conferences. With 350 top peer-reviewed journals in its list and many expert reviewers and scientists in its editorial board OMICS Group is among the best open access publishers of the world. Also, OMICS Group organizes more than 100 international scientific conferences annually and provides eBooks, and additional services such as Scholars Central. OMICS Group has got

support of more than 150 scientific associations, 30,000 editorial board members and 3.5 million readers[1-5].

Materials engineered to such a small scale are often referred to as engineered nanomaterials (ENMs), which can take on unique optical, magnetic, electrical, and other properties. These emergent properties have the potential for great impacts in electronics, medicine, and other fields. For example,

1. Nanotechnology can be used to design pharmaceuticals that can target specific organs or cells in the body such as cancer cells, and enhance the effectiveness of therapy.
2. Nanomaterials can also be added to cement, cloth and other materials to make them stronger and yet lighter.
3. Their size makes them extremely useful in electronics, and they can also be used in environmental remediation or clean-up to bind with and neutralize toxins.

However, while engineered nanomaterials provide great benefits, we know very little about the potential effects on human health and the environment. Even well-known materials, such as silver for example, may pose a hazard when engineered to nano size.

Nano-sized particles can enter the human body through inhalation and ingestion and through the skin.

Some nanomaterials can occur naturally, such as blood borne proteins essential for life and lipids found in the blood and body fat. Scientists, however, are particularly interested in engineered nanomaterials (ENMs), which are designed for use in many commercial materials, devices and structures. Already, thousands of common products including sunscreens, cosmetics, sporting goods, stain-resistant clothing, tires, and electronics are manufactured using ENMs. They are also in medical diagnosis, imaging and drug delivery and in environmental remediation [5-10].

There are three main take-home points:

- Currently, very little is known about nanoscale materials and how they affect human health and the environment. The NIEHS is committed to supporting the development of nanotechnologies that can be used to improve products and solve global problems in areas such as energy, water, medicine and environmental remediation, while also investigating the potential risks these materials pose to human health and the environment. NIEHS researchers are committed to prevention through design, a phrase which embodies the effort to avoid any potential hazards in the production, use, or disposal of nanoscale products and devices by anticipating them in advance.
- **There is no single type of nanomaterial.** Nanoscale materials can in theory be engineered from minerals and nearly any chemical substance, and they can differ with respect to composition, primary particle size, shape, surface coatings and strength of particle bonds. A few of the many examples include nanocrystals, which are composed of a quantum

dot surrounded by semiconductor materials, nano-scale silver, dendrimers, which are repetitively branched molecules, and fullerenes, which are carbon molecules in the form of a hollow sphere, ellipsoid or tube.

- **The small size makes the material both promising and challenging.** To researchers, nanomaterials are often seen as a "two-edged sword." The properties that make nanomaterials potentially beneficial in product development and drug delivery, such as their size, shape, high reactivity and other unique characteristics, are the same properties that cause concern about the nature of their interaction with biological systems and potential effects in the environment. For example, nanotechnology can enable sensors to detect very small amounts of chemical vapors, yet often there are no means to detect levels of nanoparticles in the air—a particular concern in workplaces where nanomaterials are being used.
- **Research focused on the potential health effects of manufactured nano-scale materials is being developed, but much is not known yet.** NIEHS is committed to developing novel applications within the environmental health sciences, while also investigating the potential risks of these materials to human health.[10-15]

CONCLUSION

Nanotechnology is a field of applied science, focused on the design, synthesis, characterization and application of materials and devices on the nano scale. This branch of knowledge is a sub-classification of technology in physics, biology, chemistry, other scientific fields and involves the study of phenomenon and manipulation of materials in the nano scale. This results in materials and systems that exhibit significantly changing chemical, physical and biological properties due to their structure and size . Nano materials posses a large fraction of surface atoms per unit volume which open new possibilities in surface- based sciences . The behavior of nano materials is not necessarily predictable from what we know at macro scale. At the nano scale, high desirable, properties are created due to dominance of interfacial phenomenon, size confinement, nanoparticles and other related nanotechnologies lead to improved catalysts, tunable photo activity, increased strength and other interesting characteristics.

REFERENCES

1. E. Russell, Nanotechnologies and the shrinking world of textiles, Textile Horizons, 9/10 (2002) 7-9.
2. C. N. R. Rao, A. Muller, and A. K. Cheetham, Chemistry of Nanomaterials, Wiley-VCH, Weinheim (2004).
3. R.P. Feynmann, Miniaturization, Reinhold, New York (1961).
4. K.Y. Chumbimuni-Torres, Z. Dai, N. Rubinova, Y. Xiang, E. Pretsch, J. Wang and E. Bakker, J. Am. Chem. Soc. 128 (2006) 13676.
5. N.T.K. Thanh and Z. Rosenzweig, Anal. Chem.74 (2002) 1624.
6. M. Bruchez, M. Moronne, P. Gin, S. Weiss and A.P. Alivisatos, Science 281(1998) 2013.
7. A.L. Efros and A. L. Efros, Fizikai Tekhnika Poluprovodnikov 16 (1982)1209.
8. W .C. W. Chan and S. M. Nie, Science 281 (1998) 2016.
9. National Nanotechnology Initiative: the Initiative and its Implementation Plan; NSTC/NSET report, Washington D.C., March (2001).
10. G. A. Mansoori, United Nations Tech. Monitor, Special Issue 53 (2002)
11. W.X. Zhang and T. Masciangioli, Environ. Sci. Technol.102A (2003) 37.
12. G. A. Mansoori, G. R. Vakili- Nezhaad, and A.R. Ashrafi, Inter. J. Pure and Applied Math. Sci. 2 (2005)
13. E. Katz, I. Willner and Angew. Chem. Inter. Ed., 43 (2004) 6042.
14. G. A. Mansoori, Proceed. NanoSci. Tech. Workshop, Kashan Unversity, May (2003).
15. G. A. Mansoori, The 4th Int'l Conf. Fluids and Thermal Energy Conversion 7 (2003).

DEPARTMENT OF PHARMACEUTICAL SCIENCES

MICROSPHERES AS DRUG CARRIER: A REVIEW

Minakshi Gupta, Anusha Rohilla, Monika Kaushik

Deptt of Pharm Sciences, Baba Mast Nath University, Asthal Bohar (Rohtak) Haryanae-mail: minakshi.sbmnipsr@gmail.com

ABSTRACT: *Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.*

KEYWORDS: Microspheres, controlled release, target site, specificity, therapeutic efficacy, novel drug delivery.

INTRODUCTION

The development of new delivery systems for the controlled release of drugs is one of the most interesting fields of research in pharmaceutical sciences. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. The process of targeting and site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposome, bioerodible polymer, implants, monoclonal antibodies and various particulate. One such approach is using microspheres as carriers for drugs. Microsphere can be used for the controlled release of drugs, vaccines, antibiotics, and hormones. For example, by taking advantage of the characteristics of microspheres, beyond the basic benefits, the microspheres could provide a larger surface area and possess an easier estimation of diffusion and mass transfer behavior. Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). Microspheres are sometimes referred to as microparticles. Biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin, the synthetic polymer include poly lactic acid and polyglycolic acid. The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubility and stabilities, process safety and economic considerations (1-2)

Polymers used: The polymers (4) used to prepare microspheres are classified into two types:

1. Synthetic Polymers
2. Natural Polymers

Synthetic polymers are divided into two types.

i. Non-biodegradable polymers

- Poly methyl methacrylate (PMMA)
- Acrolein
- Glycidyl methacrylate
- Epoxy polymers

ii. Biodegradable polymers (3-4)

- Lactides, Glycolides & their co polymers
- Poly alkyl cyano Acrylates
- Poly anhydrides

Natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates (5-9)

A] Proteins:

- Albumin
- Gelatin
- Collagen

B] Carbohydrates:

- Agarose
- Carrageenan
- Chitosan
- Starch

C] Chemically modified carbohydrates:

- Poly dextran
- Poly starch.

Advantages (10):

1. Microspheres provide constant and prolonged therapeutic effect. Reduces the dosing frequency and thereby improve the patient compliance.
2. They could be injected into the body due to the spherical shape and smaller size.
3. Microsphere morphology all ows a controllable variability in degradation and drug release.

PHARMACEUTICAL APPLICATIONS:

Ophthalmic Drug Delivery: Polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Due to their elastic properties, polymer hydro gels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments, ophthalmic chitosan gels improve adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow (11).

Gene Delivery: Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems. Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets. However, when used in vivo they cause immune responses and oncogenic effects. To overcome the limitations of viral vectors, non-viral delivery systems are considered for gene therapy. Non-viral delivery system has advantages such as ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale reproducible production. Polymer has been used as a carrier of DNA for gene delivery applications (12).

Oral Drug Delivery: The potential of polymer films containing diazepam as an oral drug delivery was investigated in rabbits. The results indicated that a film composed of a 1:0.5 drug-polymer mixture might be an effective dosage form that is equivalent to the commercial tablet dosage forms. The ability of polymer to form films may permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make polymer a unique polymer for oral drug delivery applications (13).

Nasal Drug Delivery: The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. Polymer based drug delivery systems, such as micro spheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Various polymer salts such as chitosan lactate, chitosan aspartate, chitosan glutamate and chitosan hydrochloride are good candidates for nasal sustained release of vancomycin hydrochloride (14).

Gastrointestinal Drug Delivery: Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug prednisolone. Floating hollow microcapsules of melatonin showed gastroretentive controlled release delivery system. Release of the drug from these microcapsules is greatly retarded with release lasting for 1.75 to 6.7 hours in simulated gastric fluid. Most of the mucoadhesive microcapsules are retained in the stomach for more than 10 hours e.g., Metoclopramide and glipizide loaded chitosan microspheres (15).

Vaginal Drug Delivery: Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer, embeds clotrimazole, an imidazole derivative, is widely used for the treatment of mycotic infections of the genitourinary tract (16).

Transdermal Drug Delivery: Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Chitosan-alginate polyelectrolyte complex has been prepared in-situ in beads and microspheres for potential applications in packaging, controlled release systems and wound dressings (17).

Colonic Drug Delivery: Polymer has been used for the specific delivery of insulin to the colon. The chitosan capsules were coated with enteric coating (Hydroxyl propyl methyl cellulose phthalate) and contained, apart from insulin, various additional absorption enhancer and enzyme inhibitor. It was found that capsules specifically disintegrated in the colonic region. It was suggested that this disintegration was due to either the lower pH in the ascending colon as compared to the terminal ileum or to the presence bacterial enzyme, which can degrade the polymer (18).

CONCLUSION:

It has been observed that microspheres are better choice of drug delivery system than many other types of drug delivery system because it is having the advantage of target specificity and better patient compliance. Its applications are enormous as they are not only used for delivering drugs but also for imaging tumors, detecting bimolecular interaction etc. In future by combining various other strategies, microspheres will find the central place in novel drug delivery.

REFERENCES

1. Chein YW. Oral Drug Delivery Systems: In Novel drug delivery systems. Vol.50, Marcel Dekker,Inc., New York. 139- 177(1992).
2. Jain NK. Controlled and Novel drug delivery, 4th Edition, CBS Publishers New Delhi, India; 236-237.
3. K. Lalla and K. Sapna, Biodegradable microspheres of poly(dl-lactic acid) containing piroxicam as a model drug for controlled release via the parenteral route. J. Microencapsul, 10(4): 449–460, (1993).

4. P.M. Dandagi, VS. Mastiholimath, M.B. Patil, M.K. Gupta, Biodegradable microparticulate system of captopril. International Journal of Pharmaceutics, 307: 83-88, (2006).
5. Rana mazumder, lila K. Nath, Anwarul, Haque, Tarasankar Maity, Prasant K. Choudhary, Bhupendra Shreshta, Formulation and in vitro evaluation of natural polymers based microsphere for colonic drug delivery, International journal of pharmacy and pharmaceutical sciences, 2(1): 211-219, (2010).
6. Kavitha K, Chintagunta Pavanveena, Anil Kumar S. N., Tamizh Mani T, Formulation and evaluation of trimetazine hydrochloride loaded gelatin microsphere. International Journal of Pharmacy and Pharmaceutical Sciences, 2(3):67-70, (2010).
7. Lorenzo-Lamosa ML. Design of microencapsulated chitosan microspheres for colon drug delivery. J Control Release , 52(1- 2): 109-118, (1998).
8. Sudha Mani T and Naveen Kumar K, At preparation and evaluation of ethyl cellulose microspheres of ibuprofen for sustained drug delivery. International Journal Of Pharma Research And Development, 2(8):120-121, (2010).
9. Bunty Chanu Irom, K. Kavitha, M. Rupeshkumar1, SD. Jagadeesh Singh, Natural Polymeric Microsphere for Drug Delivery: A Review. International Journal Of Pharmaceutical Research And Development, 4(07):31-37, (2012).
10. Vyas SP, Khar RK. Targeted and Controlled drug delivery., 7th Edition; Vallabh Prakashan, New Delhi India , 420-445.
11. Andreas Zimmer, J&g Kreuter, Microspheres and nanoparticles used in ocular delivery systems. Advanced Drug Delivery Reviews, 16:61-73, (1995).
12. Yun YH, Goetz DJ, Yellen P, Chen W., Hyaluronan microspheres for sustained gene delivery and site-specific targeting. Biomaterials, 25(1):147-57, (2004)
13. Lamprecht, Hiromitsu Yamamoto, Hirofumi Takeuchi, Yoshiaki Kawashima, pH-sensitive microsphere delivery increases oral bioavailability of calcitonin. Journal of Controlled Release, 98:1-9, (2004).
14. Ilium L, Farraj NF, Critechley H, Davis SS, Nasal administration of gentamicin using a Novel microsphere delivery system. Int J Pharm, 46:261-265, (1998).
15. Ma N, Xu L, Wang Q, Zhang X, Zhang W, Li Y, Jin L, Li S. Development and evaluation of new sustained-release floating microspheres. Int J Pharm, 358(1-2):82-90, (2008).
16. N. Dobaria, R. Mashru, N.H. Vadia, Vaginal Drug delivery systems: A review of Current syatus. East and cemtral African journal of pharmaceutical sciences, 10:3-13, (2007).
17. Lee S, McAuliffe DJ, Kollias N, Flotte TJ, Doukas AG. Photomechanical delivery of 100-nm microspheres through the stratum corneum: implications for transdermal drug delivery. Lasers Surg Med, 31(3):207-210, (2002).
18. M.L. Lorenzo-Lamosa, C. Remun˜a´n-Lo´pez, J.L. Vila-Jato, M.J. Alonso, Design of microencapsulated chitosan microspheres for colonic drug delivery. Journal of Controlled Release, 52:109-118, (1998).

BLOOD BRAIN BARRIER – VITAL BRIDGE FOR SUCCESS OF THERAPY

Balvinder Singh, Anuradha Pannu, Pawan Jalwal, Rajiv Kumar Arora

Deptt. of Pharma. Sciences, Baba Mastnath University, Asthalbohar (Rohtak) Haryana.E-mail-balvindersinghpharmaco@gmail.com

ABSTRACT:

In human body, the Blood Brain Barrier (BBB) is one of the complicated barriers in-vivo and its role is to maintain homeostasis of the brain. Tight junctions (TJs) are structures that form a narrow and continuous seal. These structures, together with the brain endothelial cells, make an almost impermeable barrier for drugs administered through the peripheral circulation. The Blood Cerebrospinal Fluid Barrier (B-CSF-B) is formed by the choroid plexus epithelial cells and the TJs which link these cells. P-glycoprotein (P-gp) efficiently prevent entry of drug molecules into CNS. Recent reports have identified Multidrug resistance Associated Proteins (MRPs) in the brain capillary endothelium and human brain microvessels.

KEYWORDS: Blood Brain Barrier (BBB), Tight junctions (TJs), Blood Cerebrospinal Fluid Barrier (B-CSF-B), P-glycoprotein (P-gp), Multidrug resistance Associated Proteins (MRPs).

1. INTRODUCTION

The **Blood Brain Barrier (BBB)** is one of the complicated barriers in-vivo and its role is to maintain homeostasis of the brain. The BBB, formed by the brain capillary endothelium (1), is an interface between the bloodstream and the brain parenchyma, controlling the passage of endogenous and exogenous substances into and out of the CNS(2). Brain capillaries, differently from the peripheral capillaries, present no fenestrae, a low amount of pinocytosis vesicles and particular tight junctions also known as zonula occludens (3). Tight junctions (TJs) are structures that form a narrow and continuous seal surrounding each endothelial and epithelial cell at the apical border and are aimed at strictly regulating the movement of molecules through the paracellular pathway (4). The BBB endothelial TJs show some differences in morphology, composition, and complexity features from those of both the epithelia and peripheral endothelia (5). These structures, together with the brain endothelial cells, make an almost impermeable barrier for drugs administered through the peripheral circulation. A further contribution to the peculiar BBB functions is given by the periendothelial accessory structures represented by astrocytes, (6) pericytes, and the basal membrane. Astrocytes, generally classified into fibrous and protoplasmic, represent the major component (~90%) of the brain mass. Fibrous astrocytes have a star-like morphology and often present many long processes, known as "end-feet", that end on the basal membrane of the BBB. These cells have a multitude of functions important for the brain homeostasis (maintenance of K^+levels, inactivation of neurotransmitters, regulation and production of growth factors and cytokines), many of which are related to the production of apolipoprotein E (7).

Pericytes are spherical cells holding a prominent nucleus and many primary and secondary lysosomes in the cytoplasm and seem to be virtually involved in the BBB formation, differentiation processes (8). The surface area of brain capillaries is approximately 100cm^2/g tissue (9). There are, however, highly porous and leaky capillaries lacking endothelial tight junctions around the ventricles of the brain called "circumventricular organs" (CVOs) where the B-CSF-B is located. The main CVOs are the choroid plexus, a source of the CSF. The other CVOs include pituitary gland, pineal gland and part of the hypothalamus. The total surface area of the BBB has been estimated to be approximately 5000-fold greater than one of the CVOs,

implying that entry into CSF may not be an efficient way of delivering substance from systemic circulation to the brain tissue (10).

In a brain capillary, a single endothelial cell forms a tubular shape and the circular extensions are held together by tight junctions. Thus, the BBB is a thin, membranous barrier that separates the brain from systemic blood circulation to protect the brain from the changing components in the blood stream and prevent the escape of neurotransmitters and other active components from the CNS(10).However it is evident that hormones and plasma proteins, in addition to substances such as amino acids, nucleosides, glucose and some electrolytes, cross the BBB through receptor-mediated endocytosis and/or membrane influx/efflux transporter (11).

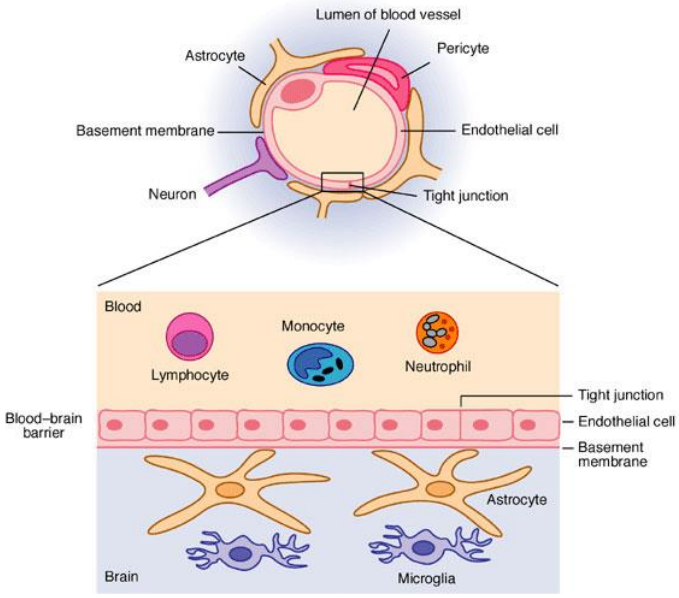


Figure 1: A representative cross-section of a cerebral capillary of the BBB.

2. Blood Cerebrospinal Fluid Barrier (B-CSF-B)

The choroid plexus epithelial cells and the TJs which link these cells forms the B-CSF-B . These epithelial cells have a well-developed apical brush border and basolateral inter-digitations, as well as numerous mitochondria, all of which may be important in fluid and solute transport (12).

3. Efflux transporter's distribution and their role

The large family of transmembrane proteins are represented by the ATP-binding cassette genes. These proteins bind ATP and use the energy to derive the transport of various molecules across cell membranes (13). ABC transporter proteins are classified based on the sequence and organization of their ATP binding domain(s), are known as nucleotide-binding folds. There are seven sub families of ABC transporter classified as ABC A, ABC B, ABC C, ABC D, ABC E, ABC F, and ABC G. ABC pumps are mostly unidirectional. ABC proteins are present in all living species with a relatively conserved structure which contains a combination of ABC and transmembrane domains. Various efflux transporters are also expressed in brain capillary endothelium. Many drugs are substrate for efflux transporters, which has been implicated in reducing the brain uptake of these drugs (14). There are also efflux transporters which have several hydrophilic substrates such as metabolites of cerebral neurotransmitters. Since hydrophilic metabolites are transported very slowly across the BBB by passive diffusion, these transporters may play a role in the detoxification of the CNS (15).

4. P-glycoprotein (P-gp)

The primary structure of human P-gp consist of 1280 amino acids, 2 homologous parts of approximately equal length, 2 ATP binding domains and 12 transmembrane domains (16). P-gp is a 170kD phosphorylated and glycosylated plasma membrane protein belonging to ABC super family of transporter proteins. Many studies support that drug transporting P-gp forms an important part of BBB.

Immunostaining analysis of isolated brain capillaries suggested that the luminal membrane of the brain capillary endothelial cells is a primary site of P-gp localization, and P-gp is functionally

active in transporting drug from brain (or basolateral) side to the blood (or luminal) side of these cells (17,18). It is the primary active drug efflux pump that binds and translocates molecules against a concentration gradient at the expense of ATP hydrolysis. Some researchers believes that a P-gp has a common drug binding site and the efflux of unrelated substrate can be explained by substrate-induced fit by utilizing residues from transmembrane domain 4-6 and 9-12 (19). P-gp expression has been documented in a wide range of normal tissues like kidney, adrenal glands, liver, small intestine, colon, lung, prostate, skin, spleen, placenta, heart, skeletal muscle, stomach, BBB, and ovary (20).

4.1. Role of P-gp in distribution of drug across BBB

The entry of many therapeutic agents into the brain are restricted by BBB and B-CSF-B. Tight junctions prevent free diffusion of small polar molecules across BBB. However, entry of large lipid soluble molecules is also limited across BBB by the presence of several ABC efflux transporters i.e., P-gp which efficiently prevent entry of drug molecules into CNS.

5. Multidrug resistance Associated Proteins (MRPs)

ABC protein superfamily has Multidrug resistance Associated Proteins (MRPs). MRP family contains at least nine members: MRP1, MRP2, MRP3, MRP4, MRP5, MRP6, MRP7, MRP8 and MRP9. These membrane proteins mediate ATP-dependent unidirectional efflux of glutathione, glucuronate, or sulfate conjugates of lipophilic drug. In addition to many anionic conjugates, a number of unconjugated amphiphilic anions can also serve as substrates for MRPs.

Recent reports have identified MRP in the brain capillary endothelium and human brain microvessels. Of the nine MRP isoforms currently known, a recent report identified MRP homologues MRP1, MRP4, MRP5 and MRP6 in both primary cultured bovine brain endothelial cells and capillary-enriched bovine brain homogenates. MRP7 has been identified in brain homogenate, but its exact localization has not yet been determined. MRP2 has been identified in the apical (luminal) membrane of rat brain capillary endothelium (21).

CONCLUSION

The Blood Brain Barrier is still a mystery to be solved. The more details we get, the more challenges we face in tackling the crossing of this barrier. Today's major challenge is the inability of drugs to attain sufficient concentration in CNS resulting in Sub therapeutic concentration of drugs in brain which lead to the drug resistance. P-gp has also been shown to efflux wide variety of drug across BBB thus limiting the adequate CNS drug concentration for therapeutic effect.

REFERENCES:

1. Pardridge WM. Peptide drug delivery to the brain. New York: Raven Press, Ltd; 1991.
2. Yousif S, Marie-Claire C, Roux F, Scherrmann JM, Decleves X. Expression of drug transporter at the blood-brain barrier using an optimized isolated rat brain microvessel strategy. Brain Res 2007; 1134(1):1-11.
3. Lapierre LA. The molecular structure of the tight junction. Adv Drug Deliv Rev 2000; 41:255-64.
4. Wolburg H, Lippoldt A. Tight junctions of the blood-brain barrier: development, composition and regulation. Vasc Pharmacol 2002; 38:323-37.
5. Kniesel U, Wolburg H. Tight junctions of the blood-brain barrier. Cell Mol Neurobiol 2000; 20:57-76.
6. Abbott NJ. Astrocyte–endothelial interactions and blood-brain barrier permeability. J anat 2002; 200:629–38.
7. Gee JR, Keller JN. Astrocytes: regulation of brain homeostasis via apolipoprotein E. Int J Biochem Cell Biol 2005; 37:1145-50.
8.. Balabanov R, Dore-Duffy P. Role of the CNS microvascular pericyte in the bloodbrain barrier. J Neurosci Res 1998; 53:637-44.
9. Pardridge WM, Triguero D, Yang J, Cancilla PA. Comparison of in vitro and in vivo model of drug transcytosis through the blood brain barrier. J Pharmacol ExpTher 1990; 253:884-91.
10. Pardridge WM. Peptide drug delivery to the brain. New York: Raven Press, Ltd; 1991.

11. Abbott NJ, Romero IA. Transporting therapeutics across the blood-brain barrier. Mol Med Today 1996; 3:106-13.
12. Smith DE, Johanson CE, Keep RF. Peptide and peptide analog transport systems at the blood-CSF barrier. Adv Drug Deliv Rev 2004; 56:1765-91.
13. Higgins CF. ABC transporters: from micro-organisms to man. Annu Rev Cell Biol 1992; 8:67-113.
14. Schlosshauer B. The Blood Brain Barrier: morphology, molecules, and neurothelin. Bioassays 1993; 15:341-6.
15. Kusuhara H, Sekine T, Utsunomiya-Tate N, Tsuda M, Kojima R, Cha SH, et al. Molecular cloning and characterization of a new multispecific organic anion transporter from rat brain. J Biol Chem 1999; 274:13675-80.
16. Chen CJ. Internal duplication and homology with bacterial transport proteins in the MDR 1 (P-glycoprotein) gene from multidrug resistant human cells. Cell 1986; 47:381-9.
17. Thiebaut F, Tsuruo T, Hamada H, Gottesman MM, Pastan I, Willingham MC. Immunohistochemical localization in normal tissue of different epitopes in the multidrug transport protein P170: evidence for localization in brain capillaries and crossreactivity of one antibody with a muscle protein. J Histochem Cytochem 1989; 37:159-64.
18. Beaulieu E, Demeule M, Ghitescu L, Beliveau R. P-glycoproteins is strongly expressed in luminal membranes of the endothelium of blood vessels in the brain. Biochem J 1997; 326:539-44.
19. Loo TW, Clarke DM. Location of the rhodamine binding site in the human multidrug resistance P-glycoprotein. J Biol Chem 2002; 277:44332-8.
20. Ambudkar SV. P-glycoprotein: from genomics to mechanism. Oncogene 2003; 22:7468-85.
21. Miller DS. Xenobiotic transport across isolated brain microvessels studied by confocal microscope. Mol Pharmacol 2000; 58:1357-67.

COMPUTER AIDED DRUG DESIGN (CADD): A NOVEL TOOL IN DRUG DISCOVERY & DEVELOPMENT

Arun Kumar, Dr. Rajiv Tonk, Pawan Jalwal

Faculty of Pharmaceutical Sciences, Baba Mastnath University, Asthal Bohar, Rohtak-124021

ABSTRACT

Computers are an essential tool in the modern medicinal chemistry and are important in both drug discovery and development. Strategies for CADD vary depending on the extent of structural and other information available regarding the target (enzyme/receptor) and the ligands. Computer-aided drug design (CADD) is an exciting and diverse discipline where various aspects of applied and basic research merge and stimulate each other. In the early stage of a drug discovery process, researchers may be faced with little or no structure activity relationship (SAR) information. The process by which a new drug is brought to market stage is referred to by a number of names most commonly as the development chain or "pipeline" and consists of a number of distinct stages. To design a rational drug, we must firstly find out which proteins can be the drug targets in pathogenesis. In present review we reported a brief history of CADD, DNA as target, receptor theory, structure optimization, structure-based drug design, virtual high-throughput screening (vHTS), graph machines.

1. INTRODUCTION

All the world's major pharmaceutical and biotechnology companies use computational design tools. At their lowest level the contributions represent the replacement of crude mechanical models by displays of structure which are a much more accurate reflection of molecular reality capa-ble of demonstrating motion and solvent effects [1-3]. Beyond this, theoretical calculations permit the computa-tion of binding free energies and other relevant molecular properties. The theoretical tools include empirical mo-lecular mechanics, quantum mechanics and, more re-cently, statistical mechanics. This latest advance has permitted explicit solvent effects to be incorporated. Un-derpinning all this work is the availability of high quality computer graphics, largely supported on workstations [1-4].

Two distinct categories of research are clearly distin- guishable:

1) Crystallography, NMR or homology modelling. A detailed molecular structure of the target macromolecule, the drug receptor, is known from x-ray.

2) Variable activity of otherwise similar molecules.

The target receptor binding site has properties which can only be inferred from a knowledge of the both these types of approach will now be considered and illustrated with some recent examples.

2. A BRIEF HISTORY OF CADD [9]

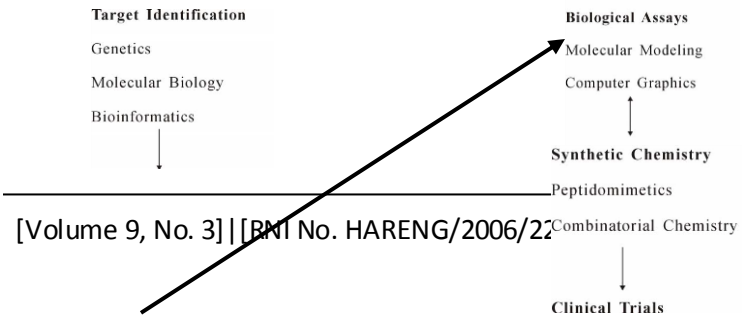
1900: The receptor and lock-and-key concepts P. Eh- rich (1909) and E. Fisher (1894);

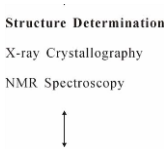
1970s: Quantitative structure-activity relationships (QS- AR), Limitations: 2-Dimensional, retrospective analy- sis;

1980s: Beginning of CADD Molecular Biology, X-ray crystallography, multi-dimensional NMR Molecular mo- deling, computer graphics;

1990s: Human genome Bioinformatics, Combinatorial chemistry, High-throughput screening.

2.1. HOW DOES CADD WORK? [13]





2.2. Molecular Modeling: Molecular modeling is a general term that covers a wide range of molecular mechanics and computational chemistry techniques used to build, display, manipulate, simulate and analyze molecular structure and to calculate properties of those structures. Molecular modeling techniques can be divided into molecular graphics and computation chemistry

Molecular Graphics: It is the core of modeling system, providing for the visualization of molecular structure and its properties. In molecular modeling the data produced are converted into visual image on the computer screen by graphic packages. These images can be displayed in a variety of styles like space fill, stick, ball and stick etc. Ribbon presentation is used for large large molecules like nucleic acid and protein.

Molecular Mechanics: In this technique the energy of structure is calculated. The equation used in molecular mechanics follow the law of classical physics and applies to the molecular nuclei without consideration of the electrons. It assumes that the total potential energy in a molecule is given by the sum of all the energies of the attractive and repulsive forces between the atoms in the structure.

E total= Σ Estretching + Σ Ebend + Σ Etorsion + Σ Evdw + Σ Ecoulombic

Molecular Dynamics: Molecular dynamics programs allow the modular to show the dynamic nature of the molecule by simulating the natural motion of the atom in a structure. The velocities of the atoms are related directly to temperature. Higher temperature stimulations are used to search conformational shape Molecular dynamics can also be used to find minimal energy structure and conformational analysis

Quantum Sechanics: It is based on the realization that electrons and all material particles exhibit wave like properties. H Ψ= E Ψ y E Ψ represents the total potential and kinetic energy of all the particles in the structure. H is the Hamiltonium operator acting on the wave function. Quantum mechanical methods are suitable for calculating the following 1. Heat of formation 2. Dipole moments 3. Electrostatic potentials 4. Bond dissociation energies 5. Transition stage geometries and energies.

2.3. SOFTWARE FOR MOLECULAR MODELING

General purpose molecular modeling (large & small mole- cules): molecular mechanics, dynamics and multifunctional programs; Quantum Chemistry calculations (small molecules): molecular orbital or quantum mechanical calcula- tion; Database of molecular structures (large & small molecules): software for storage and retrieval of molecular struc- ture data; Molecular graphics (large & small molecules): programs to visualize molecules QSAR (small molecules).

2.4. Optimization [14]

The second step of drug discovery involves the modifica- tion of the hits in order to improve the biological proper- ties of the compound by changing its pharmacophore. Using QSAR to modify lead compounds would be less tedious then having to physically synthesize the com- pounds. Moreover, such *in silico* methods could theo- retically help to modify the compounds to exhibit the most potency, most selectivity, best pharmacokinetics and least toxicity. QSAR involves mainly physical che- mistry and molecular docking tools that lead to tabu- lated data and first and second order equations. There are many theories, being the most relevant Hansch's analysis that involves Hammett electronic parameters, Esteric para- meters and logP parameters [15].

2.5. Receptor Theory

A receptor [16], in the biochemistry context, is a/are protein molecule(s), found in either the plasma mem- brane or the cytoplasm of a cell, to which one or more specific kinds of signaling molecules may attach. A molecule which attaches to a receptor is called a ligand, and may be a peptide or other small molecule, such as a neurotransmitter, a hormone, a pharmaceutical drug, or a toxin. Each kind of receptor can bind only certain ligand shapes. Each cell typically has many receptors, of many different kinds.

An agonist is a drug that binds to a receptor of a cell and triggers a response by the cell. An agonist often mimics the action of a naturally occurring substance. An agonist produces an action. An antagonist blocks an action of an agonist. Endogenous (such as hormones and neurotransmitters) or exogenous (such as drugs) agonists and antagonists, either stimulate or inhibit a biological response in receptors [17].

3. CADD STRATEGIES IN THE DRUG DISCOVERY PROCESS

Strategies for CADD vary depending on the extent of structural and other information available regarding the target (enzyme/receptor) and the ligands. "Direct" and "indirect" design are the two major modeling strategies currently used in the drug design process. In the indirect approach the design is based on comparative analysis of the structural features of known active and inactive com- pounds. In the direct design the three-dimensional fea-tures of the target (enzyme/receptor) are directly con- sidered.

3.1. CADD in Lead Generation

3D Structure of the Protein Unknown

In the early stage of a drug discovery process, research- ers may be faced with little or no structure activity rela- tionship (SAR) information. At this point, assay devel- opment and screening should be undertaken immediately by the high-throughput screening (HTS) group [18], and chemists should immediately follow up on any screening leads or other sources of initial information. The com- pounds screened could be commercially available, natu- ral products, collections of in-house synthesized com- pounds or emerge from combinatorial libraries. Compu- tational chemists can, however, help in the choice of the compounds to be selected for HTS.

Instead of performing random screening, a set of compounds presenting diversity in their physicochemical properties can be selected to find leads. The aim of these analyses is to select and test fewer compounds, whilst gaining as much information as possible about the data- set [19]. Any reduction of the number of compounds to be tested, while only reducing the amount of redundancy within a database without introducing any voids, should have an important impact on research efficiency and the costs associated [20]. Recently, the use of rational design to maximize the structural diversity of database, for lead findings and refinements, was investigated. Hierarchical clustering and maximum dissimilarity methods were compared to a random approach in order to study their efficiency for the diversity enhancement of three-dimen- sion databases. The investigations were done using two- dimensional fingerprints as a validated molecular descrip-tor and the performance of rational selection methods vs. random approach has been compared [18,19,21-23].

The first step to derive a new lead, also called second- dary lead, will be to study the stereoelectronic properties of the selected primary leads. The primary leads should be selected among a set of compounds showing a large variety in chemical structures, and interact with the same target via the same binding mechanism. By com- parison of the stereoelectronic properties

of primary leads, a pharmacophore is defined. A pharmacophore model is a spatial arrangement of atoms or functional groups believed to be responsible for biological activity [24]. In this model the rest of the molecule acts as a skeleton to hold the groups in the right place. Typically, the derived pharmacophores consist, generally, of 3 - 5 features, and the distances between them (angles and other geometric measures are sometimes used).

3.2. Structure-Based Drug Design

Within many of the rational drug design projects in the group, computer-aided methods, such as virtual screen- ing and de novo design techniques, play an important role. NMR spectroscopy in conjunction with molecular modeling and other spectroscopic methods allows invest- tigations to be made into molecular mechanisms of ligand-target recognition at the atomic level [25]. This information is a necessary component in the design of novel therapeutics and in prediction of interactions of drugs with the targets. Also over the years, the group hasstudied details of binding of ligands to the minor groove of DNA, such as Hoechst 33,258, or to tRNA [26]. NMR methods are also used by the group to study inter- actions of proteins with ligands. There is 300 MHz in- strumentation in the school, and the group has shared usage of 500 MHz high-field instruments housed in the Department of Chemistry. The group collaborates exten- sively with Professor Gareth Morris, inventor and pio- neer of many modern NMR techniques, thereby bringing novel techniques to bear on red biological problems [27].

3.3. Bioinformatics in Computer-Aided Drug Design

A few years ago, the National Institutes of Health (NIH) created the Biomedical Information Science and Tech- nology Initiative (BISTI) to examine the current state of bioinformatics in the United States. BISTI's working definition of bioinformatics included its use in biomedi- cal research, in particular for drug discovery and devel- opment programs. Bioinformatics was seen as an emer- gin how drugs are found, brought to clinical trials and eventually released to the marketplace [28]. Computer-Aided Drug Design (CADD) is a special- ized discipline that uses computational methods to simu- late drug-receptor interactions.

3.4. Virtual High-Throughput Screening (vHTS)

Pharmaceutical companies are always searching for new leads to develop into drug compounds. One search method is virtual high-throughput screening. In vHTS, protein targets are screened against databases of small molecule compounds to see which molecules bind strongly to the target. If there is a "hit" with a particular compound, it can be extracted from the database for fur- ther testing. With today's computational resources, sev- eral million compounds can be screened in a few days on sufficiently large clustered computers. Pursuing a hand- ful of promising leads for further development can save researchers considerable time and expense. ZINC is a good example of a vHTS compound library [30].

4. CONCLUSION

The successful stories of CADD application in drug dis- covery in recent years have demonstrated the potential value of CADD in drug development. CADD approaches can provide valuable information for target identification and validation, lead selection, small-molecular screening and optimization. In particular, those sub disciplines of CADD have demonstrated promising application for de- sign of drug. The latest technological advances (QSAR/ QSPR, structure-based design, combinatorial library de-sign, chemoinformatics & bioinformatics); the growing number of chemical and biological databases; and an explosion in currently available software tools are pro-viding a much improved basis for the design of ligands and inhibitors with desired specificity. In future our re-view will helpful for design of drug with minimal side effect and high potency.

REFERENCES

1. W. G. Richards, "Computer-Aided Drug Design," *Pure and Applied Chemistry*, Vol. 66, No. 8, 1994, pp. 1589- 1596. doi:10.1351/pac199466081589
2. S. Haworth, C. Burt, F. Gago, C. A. Reynolds and W. G. Richards, "A Prototype Bioreductive DNA Groove Binding Ligand," *Anticancer Drug Design*, Vol. 6, No. 1, 1991, pp. 59-61.
3. S. Haworth, A. H. Elcock, A. Rodger and W. G. Rich-ards, "Sequence Selective Binding to the DNA Major Groove: Tris (1,lO-phenanhline) Metal Complexes Bind-ing to Poly(dG-dC) and Poly(dA-dT)," *Journal of Bio-molecular Structure and Dynamics*, Vol. 9, No. 1, 1991, pp. 23-29. doi:10.1080/07391102.1991.10507891
4. S. Haworth, A. H. Elcock, A. Rodger and W. G. Rich-ards, "A Binding Mode of A-[tris(l,lO-phenanthrohe)ru-thenium(II)]2+ Exhibiting Preference for Purine-3',5'-Pyri- midine Sites of DNA," *Journal of Biomolecular Structure and Dynamics*, Vol. 9, No. 1, 1991, pp. 553-569. doi:10.1080/07391102.1991.10507936
5. M. Jayakanthan, G. Wadhwa, T. M. Mohan, L. Arul, P. Balasubramanian and D. Sundar, "Computer-Aided Drug Design for Cancer-Causing H-Ras p21 Mutant Protein," *Letters in Drug Design and Discovery*, Vol. 6, No. 1, 2009, pp. 14-20. doi:10.2174/157018009787158526
6. D. A. Spandidos and N. M. Wilkie, "Malignant Transfor- mation of Early Passage Rodent Cells by a Single Mu-tated Human Oncogene," *Nature*, Vol. 310, 1984, pp. 469- 475.
7. Valencia, P. Chardin, A. Wittinghofer and C. Sander, "The Ras Protein Family: Evolutionary Tree and Role of Conserved Amino Acids," *Biochemistry*, Vol. 30, No. 19, 1991, pp. 4637-4648. doi:10.1021/bi00233a001
8. M. Barbacid, "Ras Genes," *Annual Review of Biochemis-try*, Vol. 56, 1987, pp. 779-827. doi:10.1146/annurev.bi.56.070187.004023
9. R. Khosravi-Far and C. J. Der, "The Ras Signal Trans-duction Pathway," *Cancer and Metastasis Reviews*, Vol. 13, No. 1, 1994, pp. 67-89. doi:10.1007/BF00690419
10. Russo, V. Bazan, V. Agnese, V. Rodolico and N. Geb- bia, "Prognostic and Predictive Factors in Colorectal Cancer: Kirsten Ras in CRC (RASCAL) and TP53CRC Collaborative Studies," *Annals of Oncology*, Vol. 4, Suppl 4, 2005, pp. 44-49.
11. G. Oxford and D. Theodorescu, "The Role of Ras Super-family Proteins in Bladder Cancer Progression," *Journal of Urology*, Vol. 170, No. 5, 2003, pp. 1987-1993. doi:10.1097/01.ju.0000088670.02905.78
12. J. John, M. Frech and A. Wittinghofer, "Biochemical Pro- perties of Haras Encoded p21 Mutants and Mechanism of the Autophosphorylation Reaction," *The Journal of Bio-logical Chemistry*, Vol. 263, 1988, pp. 11792-11799.
13. H. Kiaris and D. A. Spandidos, "Mutations of Ras Genes in Human Tumors," *International Journal of Oncology*, Vol. 7, No. 3, 1995, pp. 413-421.
14. L. George and J. H. Ching, "VPython Application To The Computer-Aided Drug Design Problem," *The Python Papers Monograph*, Vol. 2, 2010, pp. 1-5.
15. D. G. Sprous, J. Zhang, L. Zhang, Z. Wang and M. A. Tepper, "Kinase Inhibitor Recognition by Use of a Mul-tivariable QSAR Model," *Journal of Molecular Graphics and Modelling*, Vol. 24, No. 4, 2006, pp. 278-295. doi:10.1016/j.jmgm.2005.09.004
16. D. Selassie, "Burger's Medicinal Chemistry, Drug Discovery and Development," 6th Edition, John Wiley & Sons, Inc., New York, 2003.
17. Structure-Activity Relationships (QSAR), "A Review, Combinatorial Chemistry & High Throughput Screen-ing," Vol. 9, 2006, pp. 213-228.
18. K. R. Oldenburg, "Annual Report in Medicinal Chemis-try," J. A. Bristol, Ed., Academic Press, London, Vol. 33, 1998, pp. 301-307.
19. W. H. Moos, G. D. Green and M. R. Pavia, "Chapter 33. Recent Advances in the Generation of Molecular Diver-sity," *Annual Reports in Medicinal Chemistry*, Vol. 28, 1993, pp. 315-324. doi:10.1016/S0065-7743(08)60903-3
20. F. Ooms, "Molecular Modeling and Computer Aided Drug Design. Examples of their Applications in Medici-nal Chemistry," *Current Medicinal Chemistry*, Vol. 7, No. 2, 2000, pp. 141-158. doi:10.2174/0929867003375317
21. J. Kuhlman, *International Journal of Clinical Pharma-cology and Therapeutics*, Vol. 35, 1997, pp. 541-552.
22. R. G. Halliday, S. R. Walker and C. E. Lumley, *Journal of Pharmaceutical Medicine*, Vol. 2, 1992, pp. 139-154.

23. K. Ghose and J. J. Wendoloski, "Perspective in Drug Discovery and Design," Kluwer/Escom, Vol. 9-11, 1998, pp. 253-271.
24. J. Abraham and G. E. Kellogg, "3D-QSAR in Drug Design," H. Kubinyi, Ed., Escom, Leiden, Vol. 1, 1993, pp. 506-522.
25. Scherer, P. Dubois and B. Sherwood, "VPython: 3D Interactive Scientific Graphics for Students," *Computing in Science and Engineering*, Vol. 2, No. 5, 2000, pp. 56-62.
26. J. Irwin, D. M. Lorber, S. L. McGovern, B. Wei and B. K. Shoichet, "Docking and Drug Discovery," *Computational Nanoscience and Nanotechnology*, Vol. 2, 2002, pp. 50-51.
27. Taft, V. B. da Silva and C. H. T de P. da Silva, "Current Topics in Computer-Aided Drug Design," *Journal of Pharmaceutical Sciences*, Vol. 97, No. 3, 2008, pp. 1089-1098. doi:10.1002/jps.21293
28. Bernard, A. Coop and A. D. MacKerell Jr., "Com-puter-Aided Drug Design: Structure-Activity Relationships of Delta Opioid Ligands," *Drug Design Reviews*, Vol. 2, No. 4, 2005, pp. 277-291. doi:10.2174/1567269054087596
29. W. G. Richards, "Computer-Aided Drug Design," *Pure and Applied Chemistry*, Vol. 66, No. 8, 1994, pp. 1589- 1598. doi:10.1351/pac199466081589
30. S. Park, J. M. Kim, Y. B. Lee and C. H. Ahn, "QSID Tool: A New Three-Dimensional QSAR Environmental Tool," *Journal of Computer-Aided Drug Design*, Vol. 22, No. 12, 2008, pp. 873-883.
31. H. Kubinyi, "Chance Favors the Prepared Mind—From Serendipity to Rational Drug Design," *Journal of Recep-tor and Signal Transduction Research*, Vol. 19, No. 1-4, 1999, pp. 15-39. doi:10.3109/10799899909036635
32. M. von Itzstein, W. Y. Wu, G. B. Kok, M. S. Pegg, J. C. Dyason, B. Jin, T. V. Phan, M. L. Smythe, H. F. White, S. W. Oliver, P. M. Colman, J. N. Varghese, D. M. Ryan, J. M. Woods, R. C. Bethell, V. J. Hotham, J. M. Cameron and C. R. Penn, "Rational Design of Potent Sialidase- Based Inhibitors of Influenza Virus Replication," *Nature*, Vol. 363, No. 6428, 1993, pp. 418-423. doi:10.1038/363418a0
33. J. Greer, J. W. Erickson, J. J. Baldwin and M. D. Varney, "Application of the Three-Dimensional Structures of Pro-tein Target Molecules in Structure-Based Drug Design," *Journal of Medicinal Chemistry*, Vol. 37, No. 8, 1994, pp. 1035-1054. doi:10.1021/jm00034a001
34. J. P. Vacca and J. H. Condra, "Clinically Effective HIV-1 Protease Inhibitors," *Drug Discovery Today*, Vol. 2, No. 1, 1997, pp. 6-18. doi:10.1016/S1359-6446(97)01053-2
35. P. C. Sternweis and A. G. Gilman, "Aluminum: A Require- ment for Activation of the Regulatory Component of Adenylate Cyclase by Fluoride," *Proceedings of the Na-tional Academy of Sciences USA*, Vol. 79, No. 16, 1982, pp. 4888-4891. doi:10.1073/pnas.79.16.4888
36. J. Sondek, D. G. Lambright, J. P. Noel, H. E. Hamm and P. B. Sigler, "GTPase Mechanism of Gproteins from the 1.7-Å Crystal Structure of Transducin α.GDP.AlF4-," *Na- ture*, Vol. 372, 1994, pp. 276-279. doi:10.1038/372276a0

FLAVOURING AGENTS AND TASTE MASKING IN PHARMACEUTICAL FORMULATIONS

Upma[1], Shilpi Arora[1]

Department of Pharmaceutical Sciences and research, Baba Mastnath University, Asthal bohar,Rohtak

Flavour refers to a mixed sensation of taste, touch, smell, sight and sound, all of which involve a combination of physio-chemical and physiological actions that influence the perception of substances. With the expansion of technology in the flavour industry, many artificial or imitation flavours have been created. Cough syrups, laxatives, sedatives antihistamines, antibiotics, vitamins and pediatric and geriatric formulations now are available in a variety of flavours which successfully mask unpleasant tastes without affecting physical and chemical stability. The suitable flavours are selected through the results of elaborate taste – panel studies. Formulators have found that unpleasant taste masking problem can best be resolved by use of blends of distinctive flavours. Now since many flavours are odorous, the brain receives some additional impulses from the oil factory receptors in the nose which coordinate with the gustatory stimuli to produce the mingled sensation that is recognized as the flavour of a substance. The specific therapeutic agents and associated flavours with unique names individuals certain formulations.. For example, an orange-mint flavour is especially effective in disguising diphenhydramine in an expectorant formulation. The use of a spice vanilla flavour for phenylephrine and chloropheniramine maleate preparation has been proposed. Strawberry is well suited to tranquilliser formulations. Maple combined with butterscotch is well suited to improve the taste of adsorbents such as kaolin and pectin. Also this same flavour is recommended for aminophylline and theophylline. Mint is preferred in antacid preparation.

The taste buds are sensitive to a number of basic tastes i.e. sweet, sour, bitter, salt and possibly, metallic and alkaline, but their response is modified by some additional factors such as temperature, physical nature and some special characteristics like astringency and pungency of he flavoured material. Flavour acceptance is also affected by age. In general, children like fruit flavoured syrup, adults prefer a more acid taste, while many old people find mint or wine flavours more agreeable. Response to the flavour may not be the same in health and disease while a flavour acceptable for a short time may become objectionable if the treatment is prolonged.

THE TYPES OF FLAVOURING AGENT USED IN THE PREPARATION ARE:

1. Sweetening agents: These include sucrose, invert syrup, treacle (used in chlorodyne i.e. chloroform and morphine tincture BPC), sorbitol , saccharine sodium etc.

2. Flavoured syrup: These include fruit flavoured syrup, syrups with weak therapeutic activity for example the pleasantly aromatic odour and pungent taste of Ginger syrup make it a satisfactory flavour for laxative mixtures containing rhubarb while its carminative action (ability in relieve flatulence) is helpful in this type of preparation, and cocoa syrup.

3. Aromatic Oils: Like caraway, clove, dill, lemon, orange, pepper-mint etc.

4. Synthetic flavours: These include synthetic sweeteners, chloroform, vanillin, benzaldehyde etc. and variety of organic compounds like alcohols, aldehydes, esters, ketones, fatty acids and lectones are use alone or combined with essential oils.

Taste is an important parameter in administering drugs orally. Undesirable taste is one of the important formulation problems that are encountered with many drugs. Administration of bitter drugs orally with acceptable level of palatability is a key issue for health care providers. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of oral pharmaceuticals. [1] Several oral pharmaceuticals, numerous food and beverage products, and bulking agents have unpleasant, bitter-tasting components.The methods most commonly involved for achieving taste masking include various chemical and physical methods that prevent the drug substance from interaction with taste buds.

TASTE MASKING TECHNOLOGIES:

Various methods are available to physically mask the undesirable taste of drugs, some of which are described below:

1. Taste masking with flavors, sweeteners, and amino acids
2. Polymer coating of drug:
3. Formation of inclusion complexes:
4. Ion exchange resin complexes:
5. Solid dispersion
6. Microencapsulation
7. Mass extrusion
8. Multiple Emulsions
9. Development of Liposome
10. Prodrug concept
11. Taste masking by spraydrying technique
12. Taste masking by adsorption
13. Taste Masking with Lipophilic Vehicles like lipids and lecithins

EVALUATION OF FLAVOURS:

For the assessment of flavours volunteers are used and they are subjected to taste tests. Each volunteer tastes three samples, two of which are the same while the other is slightly different. An acceptable volunteer must detect the odd one. Only few samples should be examined are each session because repeated testing numbs the taste buds and so raises the taste threshold. The full dose of the preparations must be taken and the experiment should be designed to minimize the effects of personal variation and other factors such as temperature, age, environment and time of the day.

Finally, the stability test must be performed for the flavours used in the preparation. It should be confirmed that the flavour used is stable in the preparation and is unaffected by the container. Deterioration of flavours may be accelerated by certain factors like,

i) alkaline pH (except cinnamon oil)
ii) hydrolysis except esters
iii) oxidation except citrus oils

CONCLUSION:

Taste masking of bitter drugs has been a challenge to the scientist. We have made an attempt to describe various methods, which could be suitable for taste masking of bitter drugs. There are number of technologies available which effectively mask the objectionable taste of drugs but require skill ful application which does not affect the bioavailability of drug.With application of these techniques and proper evaluation of taste masking effect one can improve product preference to a large extent. Moreover, the development of taste masking methodology requires great technical skill, and the need for massive experimentation.

REFERENCE:

1. Remington's Practice of Pharmacy 16th edition, Mack Publishing Co., Easton Penn, U.S.A. (1980).
2.Kuchekar BS, Badhan AC and Mahajan HS: Mouth Dissolving Tablets: A Novel Drug Delivery System. *Pharma Times* 2003; 35: 7-9.
3. Sharma V, Chopra H: Role of Taste And Taste Masking of Bitter Drugs In Pharmaceutical Industries: An overview. *International Journal of Pharmacy and Pharmaceutical Sciences* 2010; Vol 2 (4):12-18.
4. Mendes WR, Anaebonam AO and Daruwala JB: In Lachman L, Liberman HA and Kanig JL: Theory and Practice of Industrial Pharmacy, Third Edition, 1976, 346.
5Vijay A. Agrawal, Aditya P: Taste Abatement Techniques To Inprove Palatability Of Oral Pharmaceuticals: A Review. International Journal of Pharmaceutical Research And Development 2008; Vol 2: 22-30.
6. Borodkin S: Polycarboxylic acid Ion exchane resin absorbates for taste coverage in chewable tablets. *Journal of Pharmaceutical Science* 1971; 60(10): 1523-1527.
7Pokharkar VB, Kshirsagar SJ and Fatima L: Taste masking of Pharmaceuticals. *Pharmainfo*2006*;* 7-11.
8Sharma S, Lewis S: Taste Masking Technologies: A Review. *International Journal of Pharmacy and Pharmaceutical Sciences* 2010; Vol 2, Issue 2:25-33

NANOEMULSION ENHANCE THE BIOAVAILABILITY OF THE BCS CLASS 2 AND LIPOPHILIC DRUS: A COMPREHENSIVE REVIEW

Pawan Jalwal, Balvinder Singh, Arun Kumar

Faculty of Pharmaceutical Sciences, Baba Mastnath University, Email: pawan_jalwal@rediffmail.com

ABSTRACT:

It is estimated that 40% of new chemical entities discovered by the pharmaceutical industry today are poorly water soluble and suffers from low bioavailability. Nanoemulsions are known to extend the drug response time. Nanoemulsions are submicron sized emulsion that is under extensive investigation as drug carriers for improving the delivery of therapeutic agents. Nanoemulsion droplet size typically lies in the range of 10-200 nm. Nanoemulsions are isotropic system composed of one immiscible liquid (oil) dispersed in another liquid (aqueous media) and stabilized by surfactant molecules. Nanoemulsion act by entrapment of active ingredients in the core of the nanoemulsion droplets. They have wide applications in cosmetic, diagonostics, drug therapies, and cancer and transdermal delivery system also.

Keywords: BCS, Nanoemulsion, poor water soluble etc.

INTRODUCTION

Nanoemulsion has been identified as a promising delivery system for various drugs. Nano size droplets lead to transparent emulsions so that product appearance may not be altered by the addition of an oil phase. Retention time of drug can be increased in the body with the help of nanoemulsion so less amount of drug is required for the therapeutic action. Nanoemulsion droplets have greater surface area per volume and because of extremely low surface tension of whole system it increases the poorly water-soluble drug uptake in the gastrointestinal tract (GIT) and thereby enhancing the oral bioavailability. When nanoemulsion containing lipophilic drug have reached the systemic circulation on oral administration, the pharmacokinetic and biodistribution pattern of the compound can be determined by the physicochemical properties like droplet size of the nanoemulsion formulations rather than chemical properties of drug molecule. Oil in water (o/w) nanoemulsions is more often used for the formulations and water in oil (w/o) has been less described. Both the types of nanoemulsions are experiencing a very active development and have various advantages as pharmaceuticals and in cosmetics science as well. According to biopharmaceutical classification system (BCS) drugs are divided into four classes based on their solubility and permeation profile, BCS class 2 drugs are poorly soluble.

Table 1: List of reported nanoemulsion formulation of BCS class 2 drugs

Drugs	Category
Dapsone	antibacterial
Ezetimibe	Cholestrol lowering
Coltrimazole	Antifungal
Itraconazole	Antifungal
Candesartan Cilexetil	Antihypertensive

ADVANTAGES AND DISADVANTAGES

Advantages

- Increase the bioavailability
- Helps in solubilizing lipophilic drug
- Increase the rate of absorption

- Rapid and efficient penetration of drug moiety.
- Used for various routes like oral, intravenous and topical

Disadvantages

- Stability is influenced by environmental parameters
- Limited solubilizing capacity for high melting substance.
- Large concentration of surfactant and co-surfactant are needed for stabilizing the nanodroplets
- Components used formulation must be non toxic for pharmaceutical application.

Differences between Emulsion, Nanoemulsion and Microemulsion

Emulsion	Nanoemulsion	Microemulsion
Cloudy appearance	Clear or translucent	Clear
Preparation requires large energy	No requirement	No requirement
Thermodynamically unstable	Thermodynamically stable	Thermodynamically stable
Phase separation occur	No phase separation	No phase separation

Theory of formation of Nanoemulsion

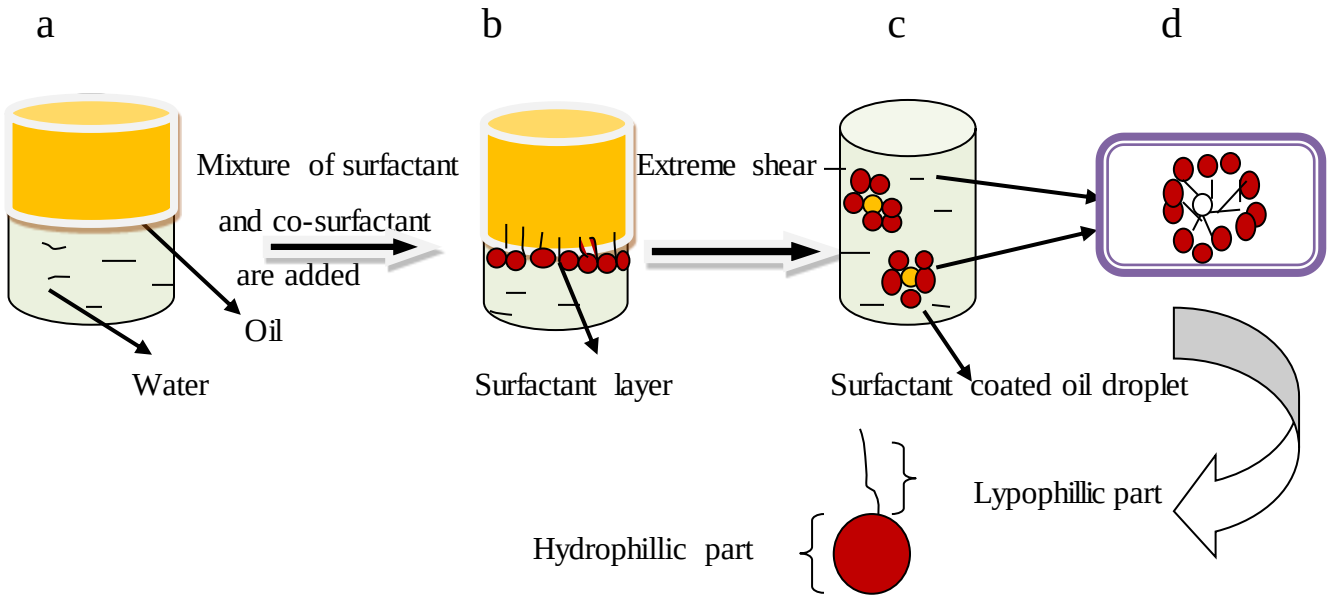
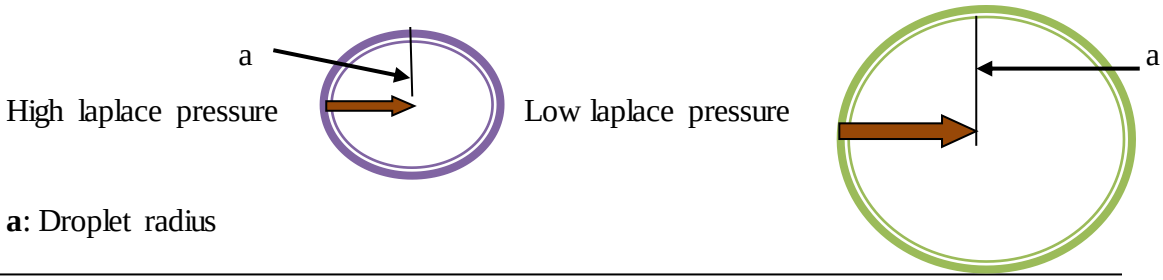


Figure 1: a) Oil and water are exits as two different layers.
b) Addition of surfactant remains at the interface.
c) On applying shear, oil droplets break down and surfactant layer remains on oil droplets and forms a stable emulsion.



a: Droplet radius

(a) (b)

Figure 2: Relation between droplet radius and Laplace pressure

Nanoemulsion is a multiphase colloidal dispersion which is generally characterized by its stability and clarity. There is a marginal difference between the Nanoemulsion and Microemulsion. Nanoemulsion requires external shear for rupturing the droplets to nanoscale, while Microemulsion generally forms through thermodynamic self assembled equation phase in which the surface tension does not play a significant role.

The molecules of two liquid phases exhibit the different attractive interactions since an interfacial tension (ϭ) exists between the two liquids in their contact point **(Figure1a).** The energy is required to create an interfacial area (A) between the two liquid phases is ϭA. The liquid phase having low density always remains in the upper side, as oil phase remains in the upper side and water phase in the lower side. Hence the system is under thermodynamic equillibrium in the absence of any surfactants. So to reduce the interfacial tension at the interface surfactant is added **(Figure1b).** If oil -water interface is coated with surfactants that brought in close to each other and then a thin film of water will remain at the interface .Hence the interface repels each other due to the like charges of surfactants **(Figure1c).** At a less fraction of dispersed phase (Φ), droplets remains spherical with a radius (a), the curved interface exerts a pressure on the molecule inside the droplet called Laplace pressure.

Laplace pressure $\prod_L = 2\sigma/a$ **....(1)**

ϭ : Interfacial tension

a : Droplet radius

Since Laplace pressure is inversely proportional to the radius, the larger droplets experience a lesser laplace pressure than the smaller ones and vice versa **(Figure2a** and **Figure2b).** So to deform a droplet, the applied shear must overcome Laplace pressure. Hence, a larger shear stress (τ) is to be applied to rupture the droplets into smaller size.

Shear stress $\tau = \eta_c\gamma$ **....(2)**

η_c : Viscosity of continuous phase

γ : Shear rate.

τ : Shear stress

According to Taylor in last century, droplet size is inversely proportional to the shear stress. He developed a relation how applied shear stress ruptured the isolated droplet to the smaller size. Here radius (a) is directly proportional to the interfacial tension (ϭ) and inversely proportional to the shear stress (τ).

$a \propto \sigma/\tau$

$a = \sigma/\eta_c\gamma$ ....(3)

Components of Nanoemulsion

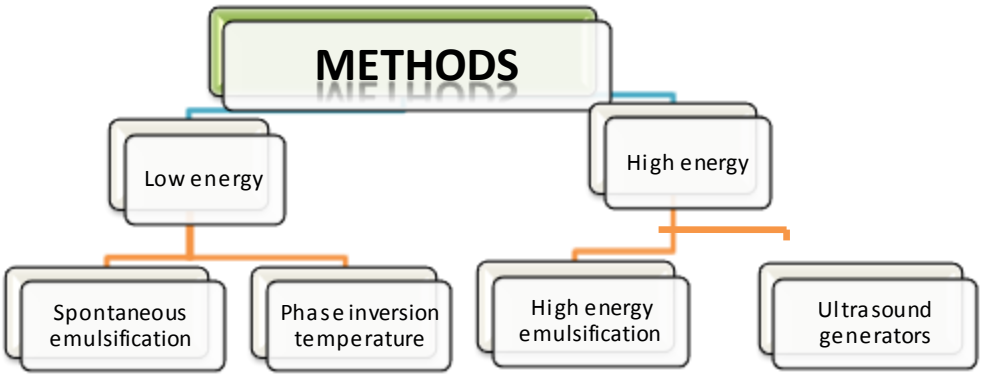
Oil	They increase the transportation of lipophilic drug and is essential to the formulation
Surfactant	They decrease the interfacial tension to a very low value to aid in dispersion
Aqueous phase	Aqueous phase plays a wide role in o/w nanoemulsion formulation

Table 2: Enlist various oils, surfactant and co surfactant used for Nanoemulsion formulation

Oils	Surfactant	Co-surfactant
Isopropyl myristate	Tween 80	Ethylene glycol
Olive oil	Tween 20	Propylene glycol
Captex 355	Poloxamer 188	Transcutol P
Myritol 318	Cremophor RH 40	ethanol
Castor oil	Lauroglycol 90	propanol

Preparation Method

Bioavailability of lipophillic drugs can be enhanced by reducing the size of drug in formulation by using any of the following methods



Spontaneous emulsification:

Homogeneous organic solution (oil and a lipophilic surfactant) was injected under magnetic stirring for 30 min to the aqueous phase. Then the diffusion of the organic solvent in the external under reduced pressure water miscible solvent was removed forming the o/w nanoemulsion aqueous phase has occurred. Then 45 min under reduced pressure water miscible solvent was removed forming the o/w nanoemulsion.

Phase inversion method:

Phase transition occurs by the chemical energy resulting in fine dispersion. The phase transitions are produced by changing the composition at constant temperature or by changing the temperature at constant composition. Phase inversion temperature (PIT) method was introduced by shinoda et al. based on principle of the changes of solubility of polyoxyethylene type surfactant with temperature.

High pressure homogenisation

As the name suggests it involves the use of high pressure homogenizer to produce nanoemulsion of extremely small particle size. In this the dispersion of two liquids is achieved by forcing their mixtures through a small inlet orifice at a very high pressure (500 to 5000psi). Primaquine nanoemulsion was prepared by using high pressure homogenization.

To obtain the optimized formulation following process variables should be investigated

- **Effect of Homogenization Pressure:** To obtain the optimized formulation the homogenizing pressure ranges from 100-150 bars. The higher is the size the lower is the particle size obtained.

- **No. of Homogenization cycles:** The higher the homogenization cycles the smaller is the particle size obtained. The cycles are carried out in 3, 4 or 10 cycles. Polydispersity index of the drug after each cycle helps in analyzing the number of cycle.

Sonication method

This is the best method for the nanoemulsion formulation. Basically sonication mechanism is used for the particle size reduction. Only the small batches can be prepared by this method. NEs are produced by ultrasonic agitation of a premixed emulsion of microscale droplets. Ultrasonic frequencies of about 20 kHz or larger is used to vibrate the solid surface which agitates the premixed emulsion to break the microscale droplets to the nanoscale. Aspirin nanoemulsion was prepared by ultrasonic cavitation method using cremophor EL.

Microfluidization

Aqueous phase and oily phase are mixed to form coarse emulsion or homogenizer which further forms stable nanoemulsion of desired particle size which is filtered under nitrogen to remove large droplets to form nanoemulsion**.** Microfluidizer utilizes a high pressure positive displacement pump (500-20000psi), which forces the product through microchannels.

Construction of Phase Diagram: Pseudo-ternary phase diagrams of oil, water, and co-surfactant/surfactants mixtures are constructed at fixed cosurfactant/ surfactant weight ratios. Phase diagrams are obtained by mixing of the ingredients using aqueous titration method. If monophasic (clear and transparent) system is formed after stirring; the samples shall be marked as points in the phase diagram. The area covered by these points is considered as the Nanoemulsion region of existence.

Table 3: Comparison of different methods of preparation of Nanoemulsion

Method	Pros	Cons
High-pressure Homogenization	High-volume throughput of nano-scale droplets and low polydispersibility	Recirculation is necessary for uniform size distribution. High-energy consumption and increase in temperature of emulsion during Processing
Ultrasonic agitation	Very efficient in reducing droplet sizes	Recirculation is necessary for Uniform size distribution. Appropriate for small batches only
Solvent displacement method	Can yield nanoemulsions at room temperature and require simple stirring for the fabrication	Use of organic solvents which requires additional inputs for their removal from nanoemulsion. A high ratio of solvent to oil is required to obtain a nanoemulsion with a desirable droplet size
Phase inversion temperature	Economical and no need of sophisticated equipment	Coalescence rate is very fast if the cooling and heating process is not fast
Microfluidization	Low droplet size, Minimum Coalescence. More Stability	Sophisticated instrument required. High pressure required

Table 4: Enlist various marketed formulations of Nanoemulsion

Drug	Brand name	Market Therapeutic indication
Flurbiprofen axetil	Ropion	Non steroidal analgesic
Alprostadil Palmitate	Liple	Vasodilator Platelet Inhibitor
Propofol	Troypofol	Anesthetic
Dexamethasone	Limethason	Steroid

Characterization of Nanoemulsion

X-Ray diffraction (XRD)

XRD is most widely used for the identification of crystalline compounds by their diffraction pattern. *Mulik et al*. showed that the diffraction pattern of curcumin is significantly different from the diffraction pattern of solid lipid nanoparticles loaded with curcumin.

Uses: Determination of the crystal structure, Identification and structural analysis of samples, Recognition of amorphous materials in partially crystalline mixtures, etc.

Atomic force microscopy (AFM)

This is a new technique with high resolution (±0.1nm) and has been used to directly view the single atoms or molecules. AFM plays a major role in imaging of almost any type of surface, including polymers, ceramics, composites, glass, and biological samples. AFM allows biomolecules to be imaged not only under physiological conditions but also during biological processes.

Phase analysis

Phase of nanoemulsion (O/W or W/O) can be measured by electrical conductivity using conductometer.

Transmission electron microscopy (TEM

TEM is technique used to study morphology and structure of nanoparticles. Bouchemal et al. studied the morphology and structure of the nanoemulsions using TEM. The combination of bright field imaging at increasing magnification and of diffraction modes were used to reveal the form and size of the emulsions.

Table 5: Enlist various techniques for characterization of Nanoemulsion

Characterization	Technique	Working
Particle size	Photon Correlation Spectroscopy (PCS) (range nm-mm) Dynamic Light Scattering (DLS) (sub-mm) Atomic Force Microscopy (AFM) (nm) Laser Diffraction (LD) (range nm to lower mm)	Analyzes fluctuation in light scattering due to brownian movement Measures particle size distribution
Structure/ Morphology	Electron Microscopy (i) Scanning Electron Microscopy(SEM) (ii) Transmission Electron Microscopy(TEM	Measures the structure/ Morphology by using Holey film grid
Surface charge measurement (Zeta potential	Electrophoresis; Electroosmosis; Streaming potential; Sedimentation Potential	Surface zeta potential of NEs measured by mini electrode to predict surface properties

-41 to -60mv)		
Thermal stability	Differential scanning colorimetry (DSC)	Thermal behaviour is analyzed
Viscosity	Brook field type rotary viscometer	Viscosity measured at different shear rates at different temperatures
Thermodynamic stability studies	Centrifugation study Heating- cooling cycle Freeze thaw cycle	Performed at 5000rpm for 30 min . Involved six cycles between4ºC and 40ºC and stored at each temperature for 48h. Involved three cycles between -21ºC and +25ºC for 48h.

Applications of Nanoemulsion

Table 6: Applications of Nanoemulsion

Antimicrobial	Nanoemulsions are active against bacteria, fungi and spores and thermodynamically driven to fuse with lipid organisms
Mucosal vaccine	Nanoemulsions causes proteins applied to the mucosal surface to be adjuvant and it facilitates uptake by antigen -presenting cells. Influenza vaccine ,HIV vaccine and hepatitis vaccine are the examples of vaccine which can be prepared in Nanoemulsion form.
Non-toxic Disinfectant Cleaner	Nanospheres of oil droplets carry surface charge that efficiently penetrate the surface charges on microorganisms .Parachlormetaxylenol containing Nanoemulsion acts by targeting in cell walls .
Cell culture technology	Nanoemulsions acts by better uptake of oil -soluble supplements in cell cultures which improve growth and vitality of cultured cells.
Treatment of other diseases	Topical Nanoemulsion of Diclofenac - Oesteoarthritis Oral Nanoemulsion of Primaquine - Antimalarial.
As a vehicle for enhancement of skin permeation	Reported Nanoemulsions whose skin permeation was enhanced Aclofenac Trandermal NE Carvediol Transdermal NE Celecoxib Transdermal NE
Improved oral delivery of poorly soluble drugs	Reported Oral Nanoemulsions of poorly soluble drugs Paclitaxel NE Coenzyme Q_{10} (ubiquinone)
Parenteral Delivery	Fats ,carbohydrates ,vitamins are delivered via parenteral NE
Ocular delivery	Topical NE of pilocarpin

CONCLUSION

Nanoemulsion is a technique which can be widely used for the poorly soluble drugs. For the nanoemulsion formulation the two basic needs are lipophilicity and drug must be of BCS class 2 or class 4. Log P value 5 is generally regarded as the upper limit of lipophillicity. Nanoemulsion can be prepared by any technique and bioavailability is increased easily.

REFERENCES:

1. Sharma Nitin ,Bansal Mayank .Nanoemulsion :A new concept of delivery system.Chronicles of Young Scientists ,1(2):(2010); 2-6.
2. Tang Ying Siah , Manickam Sivakumar. Formulation development and optimization of novel Cremophor EL based nanoemulsion using ultrasound cavitation . Ultrasonics Sonochemistry, 19 :(2012); 330-345.

3. Viniciues Raphael de Almeida,Borges.Nanoemulsion containing dapsone for topical administeration :A study in vitro release and epidermal permeation .International Journal of Nanomedicine ,8:(2013);535-544.
4. Bali Vikas ,Ali Mushir .Study of surfactant combinations and development of a novel nanoemulsion for minimising variations in bioavailability of ezetimibe.Colloids and Surfaces :Biointerfaces ,76:(2010);410-420.
5. Borhade Vivek,Pathak Sulabha.Clotrimazole nanoemulsion for malaria chemotherapy part 1:Preformulation studies ,formulation design and physicochemical evaluation .International journal of pharmaceutics,431:(2012);138-148.
6. Burapapadh Kanak poran,Takeuchi Hirofumi. Novel pectin based nanoparticles prepared from nanoemulsion templates for improving in vitro dissolution and in vivo absorption of poorly water soluble drug.European journal of pharmaceutics and biopharmaceutics.82:(2012);250-261.
7. Gao Fang,Znang Znineen. Nanoemulsion improves the oral absorption of candesartan cilexetil in rats;Preformance and mechanism .Journal of controlled release ,149:(2011);168-174.
8. Devarajan V , Ravichandran V. Nanoemulsion as modified drug delivery tool.DevarajanV,pharmacie globale (IJCP), 4:(2011);01.
9. Singh Vishal,Kumar hari Sl .Nanoemulsification-A novel targeted drug delivery tool.Journal of drug delivery and therapeutics ,2(4):(2012);40-45.
10. Kotta Sabna,Khan Wadood Abdul.Exploring oral nanoemulsions for bioavailability enhancement of poorly water soluble drugs.Informa health ISSN,(2012);1742-5247.
11. Patel P Ronak ,Joshi R Jay,An overview on nanoemulsion:A novel approach .IJPSR,3(12):(2012);4640-4650.
12. Myers D Surfaces.Interfaces and colloids.Wiley ;New york ,2nd edition,(1999).
13. Meleson K ,Graves S. Formulation of concentrated nanoemulsions by extreme shear,Soft matter ,2(2,3):(2004);109-23.
14. Mason TG .New fundamentals concepts in emulsion rheology.Current opinion colloid Interface Science ,4:(1999);3231-8.
15. Taylor GI .The formulation of emulsion in definable fields of flow .Proc R Soc A 146 :(1934);501.
16. KH Hussan R. Nanoemulsion as a novel transdermal drug delivery system .Interantional journal of pharmaceutics sciences and research 2(8):(2011);1938-1946.
17. Jain Mahavir ,Limbachiya Hardik. Nanoemulsion :A review .International journal of allied and applied sciences.1:(2012);1.
18. Singh K Kamalinder ,Vingkar k. Formulation ,antimalarial activity and biodistribution of oral lipid nanoemulsion of primaquine.International journal of pharmaceutics,347:(2008);136-143.
19. Vitale SA ,Katz JL. Liquid droplet dispersion formed by homogeneous liquid -liquid nucleation:"The Ouzo effect" ,Langmuir.19:(2003);104-10.
20. Taylor P.Ostwald ripening in emulsion :estimation of solution thermodynamics of the disperse phase.Colloid Interface Science,106:(2003);261-85.
21. Tadros Th.F,Izquierdo P.Formulation and stability of nanoemulsions.Adv Colloid Interface Science,108-109:(2004);303-18.
22. T Lusty T,Safron SA.Microemulsion networks: The onset of biocontinuity .J Phys Condens Matter ,12:(2000);A 253-62.
23. Bouchemal K ,Briancon S.Nanoemulsion formulation using spontaneous emulsification:solvent ,oil and surfactant optimisation.International J Pharm ,280(1-2):(2004);241-51.
24. Bali V,Ali M. Nanocarrier for the enhanced bioavailability of cardiovascular agent :in vitro,pharmacodynamic ,pharmacokinetic and stability assessment .International J Pharm ,403(1):(2011);246-56.
25. Shafiq S ,Shakeel F.Design and development of oral oil in water ramipril nanoemulsion :in vitro and in vivo assessment .J Biomed Nanotechnol,3(1):(2007);28-44.
26. Abolmaali Sadat Samira,Tamaddon Mohammad Ali.Pharmaceutical nanoemulsion and their potential topical and transdermal application. Iranian journal of pharmaceutical sciences,7(3):(2011);139-150.
27. Bhatt Aarti ,Bisht Punit .Novel Drug delivery system nanoemulsion : A recent review . Journal of drug discovery and tharapeutics,1(3):(2013);27-35.
28. Chaudhary Hema ,Samita. Solid Lipid Nanoparticles:An innovative Nano-vehicle for drug delivery.Nanosciences and Nanotechnology -Asia,3:(2013);000
29. Mukherjee S Ray. Solid Lipid Nanoparticles: A modern formulation approach in drug delivery system.Indian J.Pharm.Sci, 71(4):(2009);349-358.
30. Al-Haj N, Rusede A .Solid lipid Nanoparticles preparation and characterisation .Int.J.Pharm ,5:(2009);90-93.

31. Gadha A,Rania Hf .Diazepam loaded solid lipid nanoparticles:Design and characterisation.AAPS Pharm.Sci.Tech,10(1):(2009);211-219.
32. Swarupananda M ,Subha Drata R.Design and evaluation of Itraconazole loaded Solid lipid nanoparticulate system for improving the antifungal therapy.Pak.J.Pharm,Sci,22(2):(2009);131-138.
33. Bandi R,Ganesh ns.Nanoparticulate drug delivery systems:An overview.J.Pharm Res,4(6):(2011);1688-1690.
34. Jie .L,Wen H. Isotretinoin Loaded solid lipid nanoparticles with skin targetting for topical delivery.Int.J.Pharm, 328:(2007);191-195.
35. Branko S,Draen K. Measurement and application of zeta potential.Rdarsko-geolo-naftni zbornik.4:(1992);147-151.
36. Dianruiz, Tianwei T .Preparation of ordonin loaded solid lipid nanoparticles and studied on them in vitro and in vivo.Nanotech,17:(2006);5821-5828.
37. Chouksey RK,Pandey HK. Nanoemulsion :A review .Inventi rapid ,Pharm Tech 2:(2011).
38. Singh KK,Vingkar Sk .Formulation ,antimalarial activity and biodistribution of oral lipid nanoemulsion of primaquine.Int J.Pharm ,347:(2008);136-43.
39. Shakeel F,baboota S.Nanoemulsion as vehicles for transdermal delivery of acelofenac.AAPS Pharm.Sci.Tech, 8:(2007);E104.
40. Dixit N,kohli K.Nanoemulsion system for the transdermal delivery of a poorly soluble cardiovascular drug .J Pharm.Sci.Technol, 62:(2008);46-45.
41. Shakeel F,Baboota S.Skin permeation mechanism and bioavailability enhancement of celecoxib from transdermally applied nanoemulsion. J Nanobiotechnol, 6:(2008);8.
42. Rosano HL,Cavello JL.Mechanism of formation of six microemulsion systems.In:Rosana HL,Clausse M,eds.Microemulsion systems,New York,NY:(1987);259-257.
43. Belal F,Zaogi AL. A stability Indicating LC method for the simultaneous determination of ramipril and hydrochloride in dosage forms.J Pharm Biomed Anal .24:(2001);335-342.
44. Vaccine Adjuvants ;Derek t.O' Hagan;Humana Press ,214.

DRUG DELIVERY AND NANOPARTICLES

Rajiv Kumar Arora, Monika Kaushik, Balvinder Singh

Faculty of Pharm. Sciences, Baba Mastnath University, Asthal Bohar, Rohtak

INTRODUCTION

Recent years have witnessed unprecedented growth of research and applications in the area of nanoscience and nanotechnology. There is increasing optimism that nanotechnology, as applied to medicine, will bring significant advances in the diagnosis and treatment of disease. Anticipated applications in medicine include drug delivery, both in vitro and in vivo diagnostics, nutraceuticals and production of improved biocompatible materials. Engineered nanoparticles are an important tool to realize a number of these applications. It has to be recognized that not all particles used for medical purposes comply to the recently proposed and now generally accepted definition of a size ≤100 nm. However, this does not necessarily has an impact on their functionality in medical applications. The reason why these nanoparticles (NPs) are attractive for medical purposes is based on their important and unique features, such as their surface to mass ratio that is much larger than that of other particles, their quantum properties and their ability to adsorb and carry other compounds.

NPs have a relatively large (functional) surface which is able to bind, adsorb and carry other compounds such as drugs, probes and proteins. However, many challenges must be overcome if the application of nanotechnology is to realize the anticipated improved understanding of the patho-physiological basis of disease, bring more sophisticated diagnostic opportunities, and yield improved therapies. Although the definition identifies nanoparticles as having dimensions below 0.1 μm or 100 nm, especially in the area of drug delivery relatively large (size >100 nm) nanoparticles may be needed for loading a sufficient amount of drug onto the particles. In addition, for drug delivery not only engineered particles may be used as carrier, but also the drug itself may be formulated at a nanoscale, and then function as its own "carrier". The composition of the engineered nanoparticles may vary. Source materials may be of biological origin like phospholipids, lipids, lactic acid, dextran, chitosan, or have more "chemical" characteristics like various polymers, carbon, silica, and metals. The interaction with cells for some of the biological components like phospholipids will be quite different compared to the non biological components such as metals like iron or cadmium. Especially in the area of engineered nanoparticles of polymer origin there is a vast area of possibilities for the chemical composition.

Although solid NPs may be used for drug targeting, when reaching the intended diseased site in the body the drug carried needs to be released. So, for drug delivery biodegradable nanoparticle formulations are needed as it is the intention to transport and release the drug in order to be effective. However, model studies to the behavior of nanoparticles have largely been conducted with non-degradable particles. Most data concerning the biological behavior and toxicity of particles comes from studies on inhaled nanoparticles as part of the unintended release of ultrafine or nanoparticles by combustion derived processes such as diesel exhaust particles. Research has demonstrated that exposure to these combustion derived ultrafine particles/nanoparticles is associated with a wide variety of effects including pulmonary inflammation, immune adjuvant effects and systemic effects including blood coagulation and cardiovascular effects. Since the cut-off size for both ultrafine and nanoparticles (100 nm) is the same, now both terms are used as equivalent. Based on the adverse effects of ultrafine particles as part of environmental pollution, engineered nanoparticles may be suspected of having similar

adverse effects. It is the purpose of this review to use this database on combustion derived nanpoarticles (CDNP) obtained by inhalation toxicology and epidemiology and bridge the gap to engineered nanoparticles.

NANOPARTICLES AND DRUG DELIVERY

Drug delivery and related pharmaceutical development in the context of nanomedicine should be viewed as science and technology of nanometer scale complex systems (10–1000 nm), consisting of at least two components, one of which is a pharmaceutically active ingredient, although nanoparticle formulations of the drug itself are also possible. The whole system leads to a special function related to treating, preventing or diagnosing diseases sometimes called smart-drugs or theragnostics. The primary goals for research of nano-bio-technologies in drug delivery include:

- More specific drug targeting and delivery,
- Reduction in toxicity while maintaining therapeutic effects,
- Greater safety and biocompatibility, and
- Faster development of new safe medicines.

The main issues in the search for appropriate carriers as drug delivery systems pertain to the following topics that are basic prerequisites for design of new materials. They comprise knowledge on (i) drug incorporation and release, (ii) formulation stability and shelf life (iii) biocompatibility, (iv) biodistribution and targeting and (v) functionality. In addition, when used solely as carrier the possible adverse effects of residual material after the drug delivery should be considered as well. In this respect biodegradable nanoparticles with a limited life span as long as therapeutically needed would be optimal.

Overview of nanoparticles and their applications in Life Sciences

The aims for nanoparticle entrapment of drugs are either enhanced delivery to, or uptake by, target cells and/or a reduction in the toxicity of the free drug to non-target organs. Both situations will result in an increase of therapeutic index, the margin between the doses resulting in a therapeutic efficacy (eg, tumor cell death) and toxicity to other organ systems. For these aims, creation of long-lived and target-specific nanoparticles is needed. Most of the compounds are biodegradable polymers resulting in drug release after degradation. One of the problems in the use of particulate drug carriers including nanomaterials is the entrapment in the mononuclear phagocytic system as present in the liver and spleen. However, liver targeting of nanoparticles may be favorable when treating liver diseases like tumor metastasis or hepatitis. Surface modification with polyethylene glycol (PEG) resulted in prolonged presence in the circulation by inhibiting recognition and phagocytosis by the mononuclear phagocytic system. In addition to altering the distribution the PEG modification also reduced in vitro toxicity when gold nanorods were modified using PEG. Coating of NP may also be needed to prevent agglomeration. Several coatings can be used to prevent agglomeration and keeping the particles in colloidal suspension including various polymers like polyethylene glycol (PEG), poly(vinylpyrrolidone) (PVP) etc, natural polymers like dextran, chitosan, pullulan etc, and surfactants like sodium oleate, dodecylamine etc.

Chemicals under investigation for drug delivery

NP size can influence the NP distribution as was demonstrated for lipid vesicles for which a lower liver uptake was found for the smaller vesicles (200/300 nm versus 25/50 nm) (Seki et al 2004). Even small size differences may be of influence for the actual distribution and thus bioavailability. For liposomes with sizes >100 nm the clearance rate by the mononuclear phagocytic system increased with increasing size, while for sizes below 100 nm charge was more important. However, not all particles with sizes below 100 nm will behave similarly and

composition will be important as well. Analogous to earlier findings on asbestiform and mineral fibers, the actual size and shape of nanomaterials will be of importance.

Besides degradation physical means such as heating and light may be used to provoke the therapeutic effect (cell death) or for local drug release, respectively. Thermosensitive nanoparticles may be used for selective release of the content after specific localization. An example of this principle is presented in Figure 1. For doxorubicin an enhanced cytotoxicity was observed in vitro at 42 °C compared to 37 °C using copolymers of polyethylene glycol (PEG) and poly-L-lactide. In addition, the release of photosensitizers from nanoformulations by light, so called photodynamic therapy, was able to induce cytotoxicity as demonstrated for PLGA nanoparticles containing zinc(II) phthalocyanine and indocyanine green.

USE OF NP FORMULATIONS IN DRUG DELIVERY

One of the major challenges in drug delivery is to get the drug at the place it is needed in the body thereby avoiding potential side effects to non diseased organs. This is especially challenging in cancer treatment where the tumor may be localized as distinct metastases in various organs. The non restricted cytotoxicity of chemotherapeutics thus limits the full use of their therapeutic potential. Local drug delivery or drug targeting results in increased local drug concentrations and provides strategies for more specific therapy. Nanoparticles have specific particles as tools to enable these strategies. These include benefits such as their small size which allows penetration of cell membranes, binding and stabilization of proteins, and lysosomal escape after endocytosis.

The entrapment of chemotherapeutics in nanosized formulations like liposomes has been already subject of study for considerable time. Liposomes as nanosized phospholipid "fatty" structures have the advantage of being small, flexible and biocompatible thus being able to pass along the smallest arterioles and endothelial fenestrations without causing clotting. Now also other materials, including various (co-)polymers and dendrimers at the nanosize range have become available to alter the distribution of encapsulated or attached drugs.

One of the therapeutics under intensive study is paclitaxel (taxol). For paclitaxel the nanoparticle formulation resulted in enhanced cytotoxicity for tumor cells in vitro, and at the same time an increased sustainable therapeutic efficacy in an in vivo animal model. The paclitaxel was encapsulated in vitamin E TPGS-emulsified poly (D,L-lactic-co-glycolic acid) (PLGA) nanoparticles, and this system resulted in a higher and prolonged level above the effective concentration in vivo, reflected in an increased area under the curve (AUC)

Apart from size the surface chemistry of particles is of crucial importance in particle uptake, distribution and effects. This was shown extensively with acute and chronic models of surface modified micro quartzes. Quartz which was coated with PVNO-polymer was taken up by macrophages without toxicity and showed no genotoxicity in epithelial cells or acute and chronic inflammation. On the other hand naïve quartz caused these effects to a large extent. An altered body distribution was demonstrated for two types of polymer particles. Only PMMA (about 1.4 μm and about 6.4 μm) particles but not PS (about 1.2 μm, 5.2 μm and 12.5 μm) particles could be recovered form the spleen after intraperitoneal administration. Whether a similar situation exists for nanoparticles is unknown, but studies with surface modified polystyrene particles do suggest different effects on blood coagulation, mitochondrial ROS formation and cellular oxidative burst. In addition, as mentioned above the coating of nanoparticles with polyethylene glycol (PEG) increases the time in circulation for the nanoparticles.

The aims for nanoparticle entrapment of drugs are either enhanced delivery to, or uptake by, target cells and/or a reduction in the toxicity of the free drug to non-target organs. For these

aims, creation of long-lived and target-specific nanoparticles is needed. One of the problems is the entrapment of nanoparticles in the mononuclear phagocytic system as present in the liver and spleen. However, liver targeting of nanoparticles may be favorable when treating liver diseases like tumor metastasis or hepatitis. Also oligonucleotides for modification of gene expression were demonstrated to migrate into the liver when bound to biodegradable polyalkylcyanoacrylate nanoparticles. Surface modification with PEG resulted in prolonged presence in the circulation by inhibiting recognition and phagocytosis by the mononuclear phagocytic system. Besides reduction of therapeutic efficacy, liver entrapment may also have an adverse effect on liver function. For cyanoacrylate and polystyrene nanoparticles (about 214 nm and about 128 nm, respectively) transient liver alterations were observed after acute and chronic intravenous administration. Inflammatory responses were characterized by secretion of acute phase protein α1-acid glycoprotein by hepatocytes. In addition, antioxidant defenses of hepatocytes were depleted probably as a result of local release of oxidative species.

Although nanoformulation is aimed at enhancing drug delivery without loss of drug activity, in a study comparing insulin-chitosan nanoparticles to chitosan solution and chitosan powder formulations the insulin-chitosan nanoparticles were less effective in terms of bioavailability and lowering blood glucose level in both a rat and sheep model.

A REVIEW ON OCULAR DRUG DELIVERY SYSTEM

Rishi Pal,

SBMNIPS&R, Baba Mastnath University, Asthal Bohar , Rohtak Haryana(INDIA). E-mail ID: rishi2105@gmail.com

INTRODUCTION

Ocular drug delivery is one of the most appealing and arduous endeavors facing by the pharmaceutical scientist. The primitive ophthalmic solutions, suspensions and ointment dosage forms are unquestionably no longer satisfactory to combat some current virulent diseases. Conventional drug delivery systems; which include solutions, suspensions, gels, ointments and inserts, suffer with the problems or disadvantages as well as advantages. It leads to development of advanced techniques for ocular therapy those include particulate delivery system which improves the pharmacokinetic and pharmacodynamic properties of various types of drug molecules and novel controlled drug delivery systems such as dendrimers, microemulsions, muco-adhesive polymers, hydrogels, iontophoresis, collagenshelid, prodrug approaches.

In spite of the constraints of swift elimination from the precorneal cavity of eye, ocular formulations in the form of solutions are still granted highest precedence by formulators because they are comparatively uncomplicated to prepare, refine and disinfect. Other advanced approaches for the treatment of macular degeneration include intravitreal small interfering RNA (siRNA) and inherited retinal degenerations involve gene therapy. This system provides many advantages over conventional systems as they increase the efficiency of drug delivery by improving the release profile and also reduces drug toxicity. The rapid progress of the biosciences opens new possibilities to meet the needs of the posterior segment treatments. The examples include the antisense and aptamer drugs for the treatment of cytomegalovirus (CMV) retinitis and age-related macular degeneration, respectively, and the monoclonal antibodies for the treatment of the age-related macular degeneration.

OPHTHALMIC DISORDERS:

According to location of diseases, ocular disorders are grouped as

1. Periocular 2. Intraocular.

1. Periocular disorders:

a) Blepharitis: An infection of lid structures (usually by staphylococcus aureus) with concomitant seborrhoea, rosacea, a dry eye and abnormalities in lipid secretions

b) Conjunctivitis: The condition in which redness of eye and presence of a foreign body sensation are evident. There are many causes of conjunctivitis but the great majority results are of acute infection or allergy.

c) Kertitis: The condition in which patient have a decreased vision ,ocular pain, red eye, and often a cloud / opaque cornea .It is mainly caused by bacteria ,viruses, fungi etc.

d) Trachoma: This is caused by the organism chalmydia trachoma is; it is the most common cause of blindness in North Africa and Middle East.

2. Intraocular disorders: These conditions are difficult to manage and include intraocular infections: i.e. infections in the inner eye, including the aqueous humour, iris, vitreous humour and retina.

Glaucoma:

Glaucoma is a group of disease of the eye characterized by damage to the ganglion cells and the optic nerve. If left untreated, these effects may lead to various degrees of loss of vision and blindness. Increased intraocular pressure (IOP) remains the most important risk factor for the development of glaucoma.

TYPES OF GLAUCOMA:

Glaucoma may be classified in a variety of ways, which describe causative factors, when known. Based upon the mechanism of obstruction of outflow of aqueous humor:

a. Glaucoma angle closure: Usually a more acute form of disease and is seen in 5 to 10% of all patients.

b. Open angle glaucoma: Occurs in 80% to 90% of cases .It can be further described as either high tension or normal tension (also known as low tension) glaucoma

c. Congenital glaucoma: This results from developmental ocular abnormalities and occurs in less than 2% of patients. Finally, glaucoma may be secondary to other ocular disorders, systemic disorders, or trauma, or may be seen with medication usage, or after intraocular surgery.

The following characteristics are required to optimize ocular drug delivery systems.

- A good corneal penetration.
- A prolonged contact time of drug with corneal tissue.
- Simplicity of installation and removal for the patient.
- A non-irritative and at ease form (the viscous solution should not irritate lachrymation and reflex flashing).
- Appropriate rheological properties and concentration of viscolyzer

ADVANTAGES OF OCULAR DRUG DELIVERY SYSTEMS

1. Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.
2. To provide sustained and controlled drug delivery.
3. To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
4. To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
5. To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
6. To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
7. To provide better housing of delivery system.

MECHANISM OF DRUG RELEASE :

The mechanism of controlled drug release into the eye is as follows:

A. Diffusion,

B. Osmosis,

C. Bio-erosion

ROUTES OF OCULAR DRUG DELIVERY

There are several possible routes of drug delivery into the ocular tissues. The selection of the route of administration depends primarily on the target tissue. Traditionally topical ocular and sub conjunctival administrations are used for anterior targets and intra-vitreal administration for posterior targets. Design of the dosage form can have big influence on the resulting drug concentration and on the duration of drug action.

Topical ocular: Typically topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design (e.g. gels, gelifying formulations, ointments, and inserts) [10]. During the short contact of drug on the corneal surface it partitions to the epithelium and in the case of lipophilic compounds it remains in the epithelium and is slowly released to the corneal stroma and further to the anterior chamber

Sub-conjunctival administration: Traditionally subconjunctival injections have been used to deliver drugs at increased levels to the uvea. Currently this mode of drug delivery has gained new momentum for various reasons. After subconjunctival injection drug must penetrate across sclera which is

more permeable than the cornea. Interestingly the scleral permeability is not dependent on drug lipophilicity . In this respect it clearly differs from the cornea and conjunctiva.

Intravitreal administration: Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina. It should be noted, however, that delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE barrier. Small molecules are able to diffuse rapidly in the vitreous but the mobility of large molecules, particularly positively charged, is restricted. Large molecular weight and water-solubility tends to prolong the half-life in the vitreous. Drugs can be administered to the vitreous also in controlled release formulations (liposomes, microspheres, implants) to prolong the drug activity

RECENT ADVANCES AND CHALLENGES IN OCULAR DRUG DELIVERY SYSTEM

Recent advances in topical drug delivery have been made that improve ocular drug contact time and drug delivery, including the development of ointments, gels, liposome formulations and various sustained and controlled-release substrates, such as the Ocusert, collagen shields and hydro-gel lenses. The development of newer topical delivery systems using polymeric gels, colloidal systems and cyclodextrins will provide exciting new topical drug therapeutics. The delivery of therapeutic doses of drugs to the tissues in the posterior segment of the eye, however, remains a significant challenge.

DEVELOPMENTS AND CHALLENGES

Solutions and suspensions: Solutions are the pharmaceutical forms most widely used to administer drugs that must be active on the eye surface or in the eye after passage through the cornea or the conjunctiva. Solutions also have disadvantages: the very short time the solution stays at the eye surface, its poor bioavailability (a major portion, i.e., 75% is lost via nasolacrimal drainage), the instability of the dissolved drug and the necessity of using preservatives.

Sol to gel systems: The new concept of producing a gel in situ (e.g., in the cul-de-sac of the eye) was suggested for the first time in the early 1980s. It is widely accepted that increasing the viscosity of a drug formulation in the precorneal region leads to an increased bioavailability, due to slower drainage from the cornea. The formulation gave better release of drug over a long period of time in the rabbit's eye as compared to conventional eye drops.

Sprays: Although not commonly used, some practitioners use mydriatics or cycloplegics alone or in combination in the form of eye spray. These sprays are used in the eye for dilating the pupil or for cycloplegics examination.

Contact lenses: Contact lenses can absorb water-soluble drugs when soaked in drug solutions. These drugsaturated contact lenses are placed in the eye for releasing the drug for a long period of time. The hydrophilic contact lenses can be used to prolong the ocular residence time of the drugs. In humans, the Bionite lens which was made from hydrophilic polymer (2-hydroxy ethyl methacrylate) has been shown to produce a greater penetration of fluorescein.

Artificial tear inserts: A rod shaped pellet of hydroxy propyl cellulose without preservative is commercially available (Lacrisert). This device is designed as a sustained release artificial tear for the treatment of dry eye disorders. It was developed by Merck, Sharp and Dohme in 1981.

Filter paper strips: Sodium fluorescein and rose Bengal dyes are commercially available as drug-impregnated filter paper strips. These dyes are used diagnostically to disclose corneal injuries and infections such as herpes simplex and dry eye disorders.

Microemulsion: Due to their intrinsic properties and specific structures, microemulsions are a promising dosage form for the natural defense of the eye. Indeed, because they are prepared by inexpensive processes through auto emulsification or supply of energy and can be easily sterilized, they are stable and have a high capacity of dissolving the drugs. The in vivo results and preliminary studies on healthy volunteers have shown a delayed effect and an increase in the bioavailability of the drug.

Ocular inserts: Ocular inserts are solid dosage forms and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The ocular inserts maintain an effective drug concentration in the target tissues. Limited popularity of ocular inserts has been attributed to psychological factors, such as reluctance of patients to abandon the traditional liquid and semisolid medications and to occasional therapeutic failures (e.g., unnoticed expulsions from the eye,

membrane rupture, etc.). A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, nonerodible and hydrogel inserts

Collagen shield: Collagen is regarded as one of the most useful biomaterials. The excellent biocompatibility and safety due to its biological characteristics such as biodegradability and weak antigenecity made collagen the primary resource in medical applications. Collasomes show promise among drug delivery systems to the human eye. They are first fabricated from porcine scleral tissue, which bears a collagen composition similar to that of the human cornea. The shields are hydrated before they are placed on the eye, having been stored in a dehydrated state. Typically the drug is loaded into the drug solution for a period of time prior to application.

Ocular iontophoresis: Iontophoresis is the process in which direct current drives ions into cells or tissues. When iontophoresis is used for drug delivery, the ions of importance are charged molecules of the drug. If the drug molecules carry a positive charge, they are driven into the tissues at the anode; if negatively charged, at the cathode. Ocular iontophoresis offers a drug delivery system that is fast, painless and safe; and in most cases, it results in the delivery of a high concentration of the drug to a specific site.

Liposomes: Liposomes are phospholipid-lipid vesicles for targeting drugs to the specific sites in the body. They provide controlled and selective drug delivery and improved bioavailability and their potential in ocular drug delivery appears greater for lipophilic than hydrophilic compounds.

Niosomes: In order to circumvent the limitations of liposomes, such as chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids, niosomes have been developed as they are chemically stable compared to liposomes and can entrap both hydrophilic and hydrophobic drugs. They are nontoxic.

Mucoadhesive dosage forms: The successful development of newer mucoadhesive dosage forms for ocular delivery still poses numerable challenges.

Nanoparticles and microparticles: Particulate polymeric drug delivery systems include micro and nanoparticles. The upper size limit for microparticles for ophthalmic administration is about 5-10 mm. Above this size, a scratching feeling in the eye can result after ocular application.

CONCLUSION:

A few new products have been commercialized as a result of the research into ophthalmic drug delivery. The performance of these new products, however, is still far from being perfect. An ideal system should be able to achieve an effective drug concentration at the target tissue for an extended period of time, while minimizing systemic exposure. In addition, the system should be both comfortable and easy to use. Patient acceptance will continue to be emphasized in the design of future ophthalmic drug delivery systems. Major improvements are required in each of the technologies discussed in this review. Some approaches are relatively easy to manufacture, but are limited in their ability to provide sustained drug release.

REFERENCES:

1. Lang J C. Ocualar drug delivery conventional ocular formulation. Advanced drug delivery review 1995;16:39-43.
2. K Basavaraj, Nanjawade, Manvi FV and Manjappa AS: In situ-forming hydrogels for sustained ophthalmic drug delivery. Journal of Controlled Release 2007; 122: 119–134.
3. Sahoo KS, fahima SAD, kumar K: Nanotechnology in ocular drug delivery, Drug delivery today 2008; 13: 144-151.
4. Greaves JL and Wilson CG: Treatment of diseases of the eye with mucoadhesive delivery systems. Advance Drug Delivery Review 1993; 11: 349– 383.
5. Ahmed L, Gokhale RD, Shah MV and Paton TF: Phytochemical determinants of drug difussion across the conjunctiva, sclera and cornea. Journal of Pharmaceutical Science 1987: 76 : 583-587.
6. Ahmed I. The noncorneal route in ocular drug delivery. In: Mitra AK (ed). Ophthalmic drug delivery systems. 2nd ed. New York: Marcel Dekker; 2003: 335-363.
7. Ahmed I, Patton TF. Importance of the noncorneal absorption route in topical ophthalmic drug delivery. Invest Ophthalmol Vis Sci 1985;26:584-587.
8. M F Saettone (1995), "Effect of different vehicles on ocular kinetics/distribution", Ocular Toxicology, (Eds. I Weisse, O Hockwin, K Green and R C Tripathi), Plenum Press, New York and London, pp. 109–12.

9. Benedetto DA, Shah DO, Kaufman HE. The instilled fluid dynamics and surface chemistry of polymers in the precorneal tear film. Invest Ophthalmol 1975;14:887-902.

10. Hosaka S, Ozawa H, Tanzawa H. Controlled release of drug from hydrogel matrices. J Appl Polym Sci 1979;23:2089.

11. Rootman DS, Jantzen JA, Gonzalez JR, Fischer MJ, Beuerman R, Hill JM. Pharmacokinetics and safety of transcorneal iontophoresis of tobramycin in the rabbit. Invest Ophthalmol Vis Sci 1988;29:1397-401.

12. Hetoni P, Di Cilo G, Grandi M, Morroli M, Saettone MF, Darougar S. Silicon rubber/Hydrogel composite ophthalmic inserts preparation and preliminary in-vitro/in-vivo evaluation. Eur J Pharma Biopharmacetics 1995;46:125-32.

13. Mitra AK. Opthalmic drug delivery system. Marcel Dekker. 2nd ed. In: Ocular Penetration Enhancers 2003;130:281-307.

14. Kanai A, Alba RM, Takano T, Kobayashi C, Nakajima A, Kurihara K, et al. The effect on the cornea of alpha cyclodextrin vehicle for cyclosporin eye-drops. Transplant Proc 1989;21:3150-2.

15. Heller J. Controlled release of biologically active compounds from bioerodible polymers. Biomaterials 1980;1:51-7.

16. Bawa R. Ocular inserts. In: Mitra AK, editor. Ophthalmic Drug Delivery Systems. New York: Marcel Dekker; 1993. p. 223-59.

17. K Basavaraj, Nanjawade, Manvi FV and Manjappa AS: In situ-forming hydrogels for sustained ophthalmic drug delivery. Journal of Controlled Release 2007; 122: 119–134.

18. Andrews GP, Laverty TP and Jones DS: Mucoadhesive polymeric platforms for controlled drug delivery Review article. European Journal of Pharmaceutics and Biopharmaceutics 2009; 71: 505–518.

A REVIEW ON STABILITY OF SUSPENSION

Gaurav Khurana*

Department of Pharmaceutics SBMNIPSR, Rohtak, **Email:** gaurav.khurana786@gmail.com

INTRODUCTION:

SUSPENSION

A pharmaceutical suspension is a course dispersion in which insoluble solid particles are dispersed in a liquid medium. Suspensions are heterogenous system consisting of 2 phases.

The particles have diameters for the most part greater than 0.1 micron and some of the particles are observed under the microscope to exhibit Brownian movement if the dispersion has a low viscosity. A Pharmaceutical suspension is a coarse dispersion in which internal phase is dispersed uniformly throughout the external phase.

Stability: Some drugs are not stable in solution form. In such cases it is necessary to prepare an insoluble form of that drug. Therefore drugs are administered in the form of suspension. e.g. Procaine Penicillin G.

Choice of solvent: If the drug is not soluble in water and solvents other than water are not acceptable, suspension is the only choice. e.g. Parenteral corticosteroid.

Mask the taste; In some cases drugs are made insoluble and dispensed in the form of suspension to mask the objectionable taste. e.g. Chloramphenicol base is very bitter in taste, hence the insoluble chloramphenicol palmitate is used which does not have the bitter taste

Prolonged action: Suspension has a sustaining effect, because, before absorption the solid particles should be dissolved. This takes some time. e.g. Protamine Zinc Insulin and procaine penicillin G.

Bioavailability: Drugs in suspension exhibit a higher bioavailability compared to other dosage forms (except solution) due to its large surface area, higher dissolution rate. e.g. Antacid suspensions provides immediate relief from hyperacidity than its tablet chewable tablet form.

Classification

a) Flocculated suspension

b) Deflocculated suspension

TABLE: Comparison between Deflocculated and Flocculated System

Deflocculated System	**Flocculated System**
<!-i) Pleasant appearance, because of uniform dispersion of particles.	<!-i) Somewhat unsightly sediment.
<!-ii) Supernatant remains cloudy.	<!-ii) Supernatant is clear
<!iii) Particles exist as separate entities	<!-iii) Particles form loose aggregates.
<!-iv) Rate of sedimentation is slow, as the size of particles are small.	<!-iv) Rate is high, as flocs are the collection of smaller particles having a larger size.
<!-v) Particles settle independently and separately	<!--v) Particles settle as flocs.
<!-vi) The sedimentation is closely packed and form a hard cake.	<!-vi) Sediment is a loosely packed network and hard cake cannot form.
<!-vii) The hard cake cannot be redispersed.	<!-vii) The sediment is easy to redisperse.
<!-viii)Bioavailability is higher due to large	<!-viii)Bioavailability is comparatively less due to small specific surface area.

specific surface area.	

Advantage

 Suspension have better bioavailability than tablet, capsule, powder dosage form.
 Easy to manufacture and cost effective

Suspended insoluble medicaments are easy to swallow.

Disadvantage

 Preparation must be shaken prior to measuring a dose.
 Accuracy of dosage is less reliable than with solution.
 Crystal formation.
 Breaking of suspension.

Pharmaceutical suspensions

1. Antacid oral suspensions
2. Antibacterial oral suspension
3. Dry powders for oral suspension (antibiotic)
4. Analgesic oral suspension
5. Anthelmentic oral suspension
6. Anticonvulsant oral suspension
7. Antifungal oral suspension

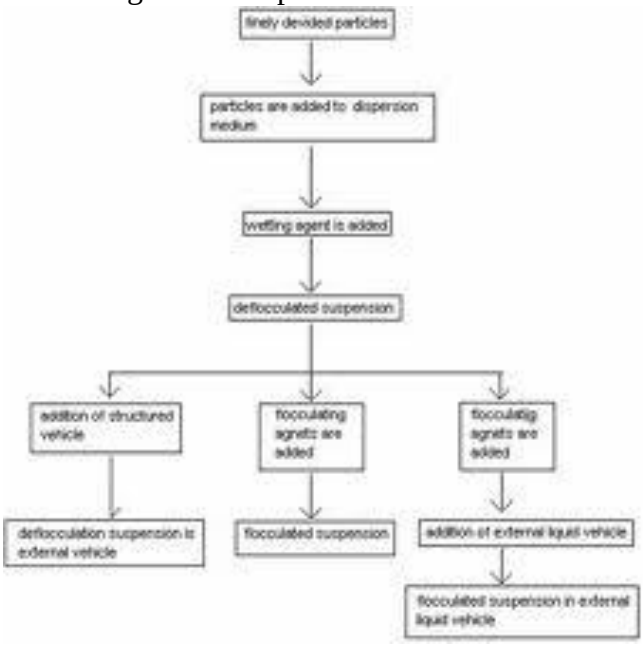


Fig. Preparation of suspension

Colloidal suspensions(< 1 micron)

-Suspensions having particle sizes of suspended solid less than about 1micron in size are called as colloidal suspensions.

Coarse suspensions (>1 micron)

Suspensions having particle sizes of greater than about 1micron in diameter are called as coarse suspensions.

Nanosuspensions (10 ng)

Suspensions are the biphasic colloidal dispersions of nanosized drug particles stabilized by surfactants.
Size of the drug particles is less than 1mm.

USES

Suspension is usually applicable for drug which **is insoluble**
(or) poorly soluble.

E.g. Prednisolone suspension

To prevent **degradation** of drug or to **improve stability of drug.**

E.g. Oxy tetracycline suspension

To mask the taste **of bitter of unpleasant drug**.E.g. Chloramphenicol palmitate suspension
Suspension of drug can be formulated for **topical application**

EVALUATION TEST OF SUSPENSION

Sedimentation volume

Since redispersibility is one of the major considerations in assessing the acceptability of a suspension, and since the sediment formed should be easily dispersed by moderate shaking to

yield a homogeneous system, measurement of the sedimentation volume and its ease of redispersion are the two common evaluative procedures.

The sedimentation volume, F, is defined as the ratio of the final, or ultimate volume of the sediment (Vu), to the original volume of the suspension (Vo), before settling. Thus

$$F = Vu / Vo$$

The sedimentation volume can have values less than 1 to greater than 1. If the volume of sediment in a flocculated system equals the original volume of suspension, then F = 1. Such a product is said to be in 'flocculation equilibrium'.

The suspension is taken in a measuring cylinder upto a certain height and left undisturbed. The particles will settle gradually. The value of F is determined from the ratio of the volume of the sediment at that instant of time (Vu) and the original volume of the suspension (Vo). The value of F is plotted against time (t). The plot will, will start at 1.0. at time zero. The curve will either run horizontally or gradually sloping downward to the right as time goes on.

One can compare different formulations and choose the best by observing the line, the better formulation obviously producing lines that are more horizontal and/or less steep.

If the suspension is highly concentrated then the suspension is diluted with the continuous medium (liquid phase) and then the sedimentation volume is determined.

Degree of flocculation (β)

It is the ratio of the sedimentation volume of the flocculated suspension ,F , to the sedimentation volume of the deflocculated suspension, F∞

$$ß = F / F\infty$$

$$ß = \frac{(Vu/Vo)\ \text{flocculated}}{(Vu/Vo)\ \text{deflocculated}}$$

The minimum value of ß is 1,when flocculated suspension sedimentation volume is equal to the sedimentation volume of deflocculated suspension

Redispersibility

The evaluation of redispersibility is also important. To quantitate this parameter to some extent, a mechanical shaking device may be used. It simulates human arm motion during the shaking process and can give reproducible result when used under controlled conditions.

CANCER: A CONCEPTUALIZE APPROACH

Jyoti dahiya[1], Priti Mehndiratta[1]

[1]Department of Pharmaceutical Sciences, Baba Mastnath University, Rohtak (124001), India.Email: jyotidahiya.2710@gmail.com, pritimehndiratta88@gmail.com

INTRODUCTION TO CANCER

Cancer is a devastating disease and Celsus, a Roman encyclopedist translated the term "*carcinos"* described by Greek Physician Hippocrates, the father of Medicine into a Latin term "*cancer*" (1). Cancer has troubled mankind throughout medical history and is not considered a novel disease. The historical origin of cancer dates back to 1500 B.C in ancient Egypt, where evidence reveals the emergence of cancer into Egyptian culture (2). Scribed in ancient Egyptian medical textbooks and current physical examinations, fossil tumors of soft tissues and bones were discovered in mummified human carcasses. These bone remnants suggest possible bone cancer, known as osteosarcoma. During Egyptian times, cancer was broadly defined to encompass a spectrum of various swellings and inflammations. As a result, the history of cancer was heavily buried under a less severe medical discovery, noted strictly as inflammation (2). This fatal disease known as cancer has become increasing visible in the 19th century under the influence of numerous factors.

Scientists from the 19th century had the ability to understand the complex nature of cancer, compared to previous decades; however, the immense progress in medical science did not produce any favourable cure, halting the knowledge of cancer etiology (2). The lack of a cure and the increased mortality rate prompted greater concern about the disease at this time.

The term cancer refers to a group of diseases which share similar characteristics. Cancer can affect all living cells in the body, at all ages and in both genders. Diagnostic work-up, treatment methods and outcome of treatment are not uniform for all cancers. Advanced technology is required in many situations and ongoing research initiatives might lead to better understanding of the disease and its control (3). In cancer, even with limited resources, an impact can be achieved if the right priorities and strategies are established and implemented.

Treatment of malignant diseases with drugs is a rather recent development, started after 1940 when nitrogen mustard was used, but progress has been rapid, both in revealing pathobiology of the diseases and discovery of new drugs. In addition, attempts have been made to define optimal combinations, treatment strategies and patient support measures. Nearly 85% of reported cancers relate to solid tumors, which lead to approximately half of deaths from these patients (4). According to the United State (U.S.) National Cancer Institute, treatment for cancers, in general, include standard or conventional therapies:

- Chemotherapy
- Radiation therapy, and/or Surgery;
- Angiogenesis inhibitors
- Biological therapy
- Gene therapy
- Bone marrow transplantation
- Peripheral blood stem cell transplantation
- Hyperthermia
- Laser therapy
- Photodynamic therapy

- Targeted cancer therapies etc.

Cancer chemotherapy is now of established value and a highly specialized field. Although many effective medicines have been discovered and are available in the market for treatment of cancer. Rate and possibilities of cure have also improved during the last two decades; the positive diagnosis of this disease continues to be traumatic for the patient and his near and dear ones. Cancer has been on the rise since the average human lifespan has increased so dramatically over the last century (5).

Cancer is a disease of uncontrolled cell division, invasion and metastasis. It is generally considered to be due to the Clonal expansion of a single Neoplastic cell. Cancer is the uncontrolled growth of abnormal cells in the body and these cells are also called malignant cells. Cancer grows out of normal cells in the body. Cancer appears to occur when the growth of cells in the body is out of control and cells divide too quickly. It can also occur when cells forget how to die. The abnormal overgrowth of cancer cells can create a mass of excess tissue called a tumor as shown in figure 1.(6)

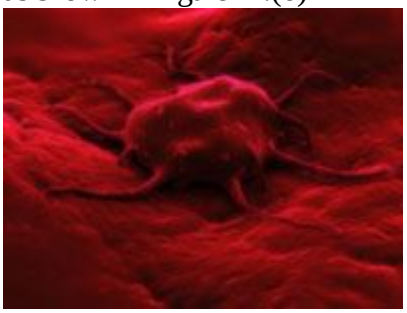


Figure 1: Pictorial representation of cancer cell.

CARCINOGENESIS

Carcinogenesis, the process of cancer development, is complex and can be categorized into five main stages: initiation, promotion, progression, invasion and metastases as given in figure 2. The first stage of initiation involves accumulation of genetic changes or hits in a single cell as suggested by Knudson (7) and Nowell (8). Tumor promotion is the second stage of carcinogenesis, during which a single initiatied cell with genetic changes expands clonally and is dependent on the favourable conditions for cellular growth such as interactions between tumor cells and stroma, growth factor availability, vascularization, O2 partial pressure and many other factors (9).

The third stage of carcinogenesis is tumor progression and a classical example of this stage was described by Vogelstein and his colleagues in colorectal carcinogenesis which involves successive waves of clonal selection (10).

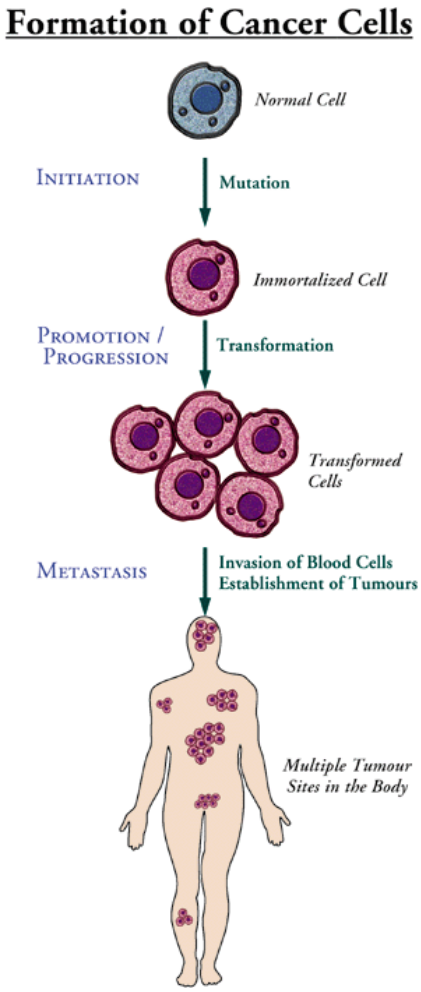


Fig2:Schematic representation of carcinogenesis

Invasion is the fourth stage of carcinogenesis and involves progression of neoplastic cells to malignant cells; and this is associated with additional gentic and epigenetic changes in the tumors and more aggressive characteristics with time.

The invasion and metastases phenotype of tumor cells is characterized by the ability of these cells to attach to host cells and this may involve extracellular matrix (ECM) factors (11, 12).

STAGES OF CANCER

Most types of cancer have four stages, as shown in figure 3. A brief summary of cancer stages have been given in the following text:

Stage I usually means a cancer is relatively small and contained within the organ it started in.

StageII usually means the cancer has not started to spread into surrounding tissue, but the tumour is larger than in stage 1. Sometimes stage 2 means that cancer cells have spread into lymph nodes close to the tumour. This depends on the particular type of cancer.

StageIII usually means the cancer is larger. It may have started to spread into surrounding tissues and there are cancer cells in the lymph nodes in the area.

Stage IV means the cancer has spread from where it started to another body organ. This is also called secondary or metastatic cancer (13).

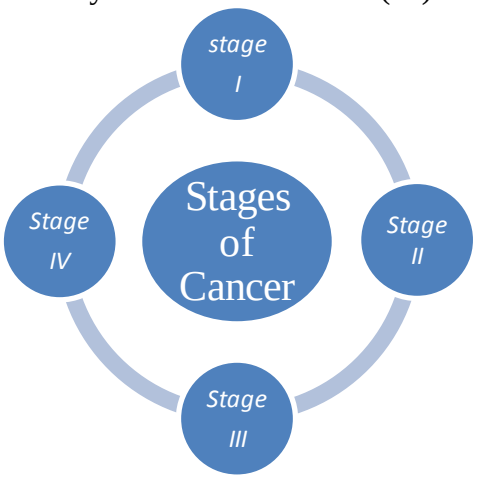


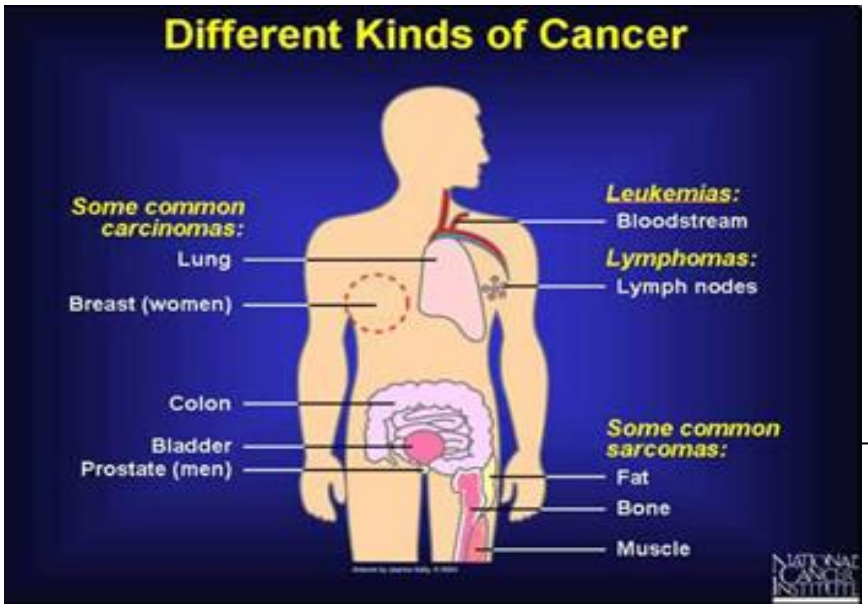
Figure3: Schematic diagram of stages of cancer

TYPES OF CANCER

Cancers are classified on the basis of type of cell that the tumor resembles and is therefore presumed to be the origin of the tumor. These types include:

Carcinoma: Cancers derived from epithelial cells. This group includes most of the common cancers, particularly in the aged, and includes nearly all those developing in the breast, prostate, lung, pancreas and colon.

Sarcoma: Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which develop from cells originating in mesenchymal cells outside the bone marrow.



Lymphoma and Leukemia: These two classes of cancer arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively.

Germ cell tumor: Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgermi noma), respectively.

Blastoma: Cancers derived from immature "precursor" cells or embryonic tissue. These are also most common in child (14).

Figure4: Types of cancer.

CANCER TREATMENTS

The treatment for cancer is usually designed by a team of doctors or by the patient's oncologist and is based on the type of cancer and the stage of the cancer. Most treatments are designed specifically for each individual. Although patients may obtain a unique treatment protocol for their cancer, most treatments have one or more of the following components: surgery, chemotherapy, radiation, or combination treatments (a combination of two or all three treatments).

Chemotherapy has been used for cancer therapy since the late 1940's (2). In cancer chemotherapy, chemicals are administered orally, or by intravenous, intraperitoneal, or intraarterial injection to systemically destroy cancer cells. The actions of chemotherapeutic agents relate to the cell cycle in the body (2,16). Chemotherapy is the initial treatment of choice. The main side effect of chemotherapy includes nausea, vomiting, hair loss, anaemia, diarrhea, constipation, low blood count, and fertility changes etc. The typical routes of administration of anticancer drugs are oral (tablets and capsules) and parenteral route as intramuscular and intravenous (i.v.).

ANTICANCER DRUGS

Anticancer, or Antineoplastic, drugs are used to treat malignancies or cancerous growths. The Anticancer drugs either kill cancer cells or modify their growth. In addition to their prominent role in Leukemia's and lymphomas, drugs are used in conjunction with surgery, radiotherapy and immunotherapy in the Combined Modality Approach for many of the solid tumors, especially metastatic. Antineoplastic drugs may be divided into two classes: cycle specific and non-cycle specific. Cycle specific drugs act only at specific points of the cell's duplication cycle, such as anaphase or metaphase, while non-cycle specific drugs may act at any point in the cell cycle. In malignant diseases, drugs are used:

- To cure or prolonged remission.
- Palliation: Gratifying results are obtained (shrinkage of evident tumour, Alleviation of symptoms) and life is prolonged.
- Adjuvant chemotherapy: Drugs are used to mop up any residual malignant cells (micro metastases) after surgery or radiotherapy. This is routinely employed now.

Anticancer drugs may interact with a number of other medicines. When this happens, the effects of one or both of the drugs may change or the risk of side effects may be greater (17,18,19).

ANTICANCER DRUGS USED FOR TREATMENT OF DIFFERENT CANCERS

Various Anticancer drugs are employed for the treatment of different cancers either in single use or in combination with other drugs. Some major drugs with their marketed formulation are briefly discussed below in table 1.1 (20):

Table 1.1: Drugs effective in different types of cancer

Drugs	Cancer Types	Marketed Formulation
Gemcitabine	Ovarian cancer, Breast cancer, Lung cancer, Pancreatic cancer.	Gemzar, Stada
Azacitidine	Myelodysplastic syndrome.	Vidaza
Irinotecan	Metastatic carcinoma of Colon or Rectum.	Camptosar

Melphalan	Multiple myeloma, Epithelial carcinoma.	Alkeran
Pemetrexed	Lung cancer, Mesothelioma.	Alimta
Topotecan	Lung cancer, Ovary cancer.	Hycamtin
Docetaxel	Breast cancer, Lung cancer, Prostate cancer, Head and Neck cancer, Gastric adeno carcinoma.	Toxotere
Paclitaxel	Ovary cancer.	Taxol
Busulfan	Chronic Myelogenous leukemia.	Busulfex
Valrubicin	BCG refractory carcinoma.	Valstar
Bendamustine	Chroni lymphocytic leukemia, Non Hodgkin's lymphoma.	Treanda
Imatinib	Chronic myeloid leukemia, Myelodysplastic.	Gleevec

REFERENCES

1. Cancer facts & figures 2008. American cancer society [Internet]. 2008. [cited 2012 Mar 25]. Available from: http://www.cancer.org/docroot/STT_1x_Cancer_Facts_and_Figures_2008.asp
2. Sandoval MA, Sloat BR, Cui Z. Supeior anti-tumour activity exhibited from a Gemcitabine prodrug incorporated into Lecithin based Nanoparticles [Baccalaureate of Science in BioResource Research, Toxicology option thesis]. Oregon State University; 2009.
3. Nair MK, Cherian V, Swaminathan R. Cancer: Current scenario, intervention strategies and projections for 2015 [Internet]. [cited 2012 Mar 27]. Available from: http://www.whoindia.org/linkfiles/cancer_resource_commision_on_macroeconomic_and_health_bg_p2_cancers_current_scenario.pdf
4. Jain RK. Transport of molecules, particles, and cells in solid tumours. Annu. Rev. Biomed. Eng. 1999; 01:241-263.
5. National cancer control programmes Policies and managerial guidelines. World health organization [Internet]. 2002. [cited 2012 May 10]. Available from: http://whqlibdoc.who.int/hq/2002/9241545577.pdf
6. Goodman LS, Gilman A, Brunton LL, Lazo JS, Parker KL. Goodman and Gilman's The pharmacological basis of therapeutics. 11th ed. McGraw-Hill Prof Med/Tech; 2006.
7. Knudson AG. Genetics of human cancer. Genet. 1975; 79 Suppl:305-16.
8. Nowell PC. The clonal evolution of tumor cell populations. Sci. 1976; 194:23-28.
9. Sarasin A. An overview of the mechanisms of mutagenesis and carcinogenesis. Mutat.Res. 2003; 544:99-106.
10. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990; 61:759-67.
11. Nicolson GL. Tumor cell instability, diversification, and progression to the metastatic phenotype: from oncogene to oncofetal expression. Cancer Res. 1987; 47:1473-87.
12. Kerbel RS, Viloria-Petit A, Okada F, Rak J. Establishing a link between oncogenes and tumor angiogenesis. Mol.Med. 1998; 4:286-95.
13. Stages of cancer. Cancer research UK [Internet]. [cited 2012 Jan 16]. Available from: http://cancerhelp.cancerresearchuk.org/about-cancer/cancer-questions/how-many-stages-of-cancer-are-there
14. Moscow JA , Cowan KH. Biology of cancer. 23rd ed. Philadelphia Elsevier; 2007.

15. Thun MJ. Epidemiology of cancer. 23rd ed. Philadelphia Elsevier; 2007.
16. Collins K, Jacks T, Pavletich NP. The cell cycle and cancer. Proc. Natl. Acad. Sci. USA 1997; 94: 2776-2778.
17. Tripathi KD. Essential of medical pharmacology. 6th ed. JPBMP; 2008.
18. Griffiths W. American journal of hospital pharmacy. Europe; 1993.
19. Satoskar RS, Bhandarkar SD. Pharmacology and pharmacotherapeutics. 18th ed. Mumbai: Popular prakashan; 1994.
20. Sweetman SC. Martindale: The Complete Drug Reference. 36th ed. Pharmaceutical press; 2009.

TEA AND CARDIOVASCULAR SYSTEM

Shilpi Arora, Upma,

Baba Mastnath University,Faculty of Pharmacy,Rohtak, Haryana.

INTRODUCTION

Tea is an ancient beverage steeped in history and romance and loved by many. In fact, tea is the most commonly consumed beverage in the world after water. There are various legends about how tea was discovered, but the most famous is the story of Shen Nung, the ancient Emperor of China, who, in 2737 BC, was boiling his drinking water when leaves from a nearby tea bush tree blew into the cauldron. After drinking the brew, the emperor was pleasantly surprised by its flavor and restorative properties. Thus, tea was born. It quickly became the favorite beverage in China and spread to Europe and the Americas.

Throughout history, tea has been believed to help "purify the body" and "preserve the mind." Over the past several decades, thousands of published studies in leading medical journals have provided the proof to support tea's ancient health claims.

HOW TEA WORKS IN THE BODY

Tea contains hundreds, if not thousands, of bioactive compounds, including amino acids, caffeine, lignins, proteins, xanthines and flavonoids. Tea flavonoids and the related polyphenols account for more than one-third of the weight of tea leaves; the health benefits of tea are most often attributed to tea flavonoids.

Tea flavonoids are bioactive compounds that have specific cellular targets that are related to the cardiovascular, chemopreventive, metabolic, neuroprotective and other health benefits. Recent research has explored the potential health attributes of tea through human clinical trials, population-based studies, and *in vitro* laboratory research.

Additional research suggests tea flavonoids and related bioactive compounds in tea may play important roles in various areas of health and may operate through a number of different mechanisms still being explored.

GREEN TEA AND BLACK TEA

Leaves from the *Camellia sinensis* plant are used to make both green tea and black tea. To obtain green tea, leaves are steamed for 1 minute and then allowed to dry.Black tea, however, is obtained by leaving the leaves at room temperature for 16 to 20 hours before drying them. The steaming process inactivates polyphenol oxidase in the green tea leaves, leaving them rich in polyphenols, especially catechins. The primary catechins found in green tea are epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate.5 The fermentation process of black tea leaves results in the conversion of catechins to theaflavins, such as theaflavin, theaflavin-3-gallate, theaflavin-3,3'-digallate, and thearubigin polymers.5 It has been shown that the antioxidant capabilities of catechins in green tea and thearubigins in black tea are

comparable, suggesting that the differences in processing the leaves have little effect on the health benefits of the bioflavonoids.

Effect of Tea on cardiovascular function

The findings of epidemiological studies concerning tea consumption and cardiovascular health have been perplexing. Some studies suggest a cardiovascular benefit from drinking tea; others suggest adverse effects from tea consumption, and some suggest no effect on cardiovascular health.8 In an attempt to evaluate the contradictory information from a number of epidemiological studies concerning tea and cardiovascular health, Peters et al. conducted a meta-analysis of tea consumption in relation to stroke, myocardial infarction, and all coronary heart disease of 10 cohort studies and 7 case-controlled studies. Their meta-analysis found an 11% decrease in the incidence of myocardial infarction with an increase of 3 cups of tea consumption daily. In addition, they concluded that elevated tea consumption increased the risk of stroke in Australia and heightened risk for coronary disease in the United Kingdom, but decreased the incidence of both in other regions. Arts et al. suggested that the inconsistencies seen in epidemiological studies might be due to the lack of control for catechin intake from other dietary sources. In their Zutphen Elderly Study, catechin consumption from all sources was controlled in a cohort of 806 men. The data suggested that increasing the daily intake of catechin by 7.5 mg from dietary sources other than tea resulted in a 20% decrease in the risk of ischemic heart disease. These data suggest that in future studies, the amount of bioflavonoids consumed from all sources should be tightly controlled.

Antioxidant Mechanism

Nitric Oxide (NO) plays a significant role in vasculature integrity. The vasculature modulates vasomotor tone, platelet activity, leukocyte adhesion, and vascular smooth muscle cell proliferation. Increased oxidative stress canresult in a loss of NO activity and compromised vascular integrity. In situations of oxidative stress, lipids in arterialwall cells, including macrophages, are exposed to oxidation. An increase in antioxidant concentrations can restore nitric-oxide-dependent responses. Even though bioflavonoids possess potent antioxidant capabilities to restore nitric-oxide-dependent responses in the vasculature, the antioxidant properties of tea bioflavonoids must survive the processes of digestion and absorption and eventually end up in plasma. Langley-Evans investigated plasma antioxidant potential after consumption of tea and found that consuming black tea increased plasma antioxidant capabilities in humans by 50 to 70%. Likewise, Duffey etl examined the flow-mediated dilation of the brachial artery of patients with coronary artery disease 2 hours after they consumed 450 ml of black tea, and after they consumed 900 ml of black tea daily for 4 weeks. Both shortterm and long-term tea consumption resulted in vasomotor function values comparable to those from healthy individuals.

These data suggest that antioxidants from tea can be found in plasma and can exert both short-term and longterm vascular benefits. The oxidative modification hypothesis of atherosclerosis suggests that LDL oxidation plays a causative role in early atherogenesis. Supporting this hypothesis, oxidized LDL has been identified in atherosclerotic lesions. It has also been shown that 'oxidized macrophages' can readily oxidize LDL and potentiate atherosclerosis.

Flavonoids inhibit LDL oxidation in several ways. They can act as scavengers of free radicals. In addition, they can chelate transition metal ions, thereby reducing the metal's potential to generate free radicals. That action protects vitamin

E and carotenoids in the LDL particle. Flavonoids have been shown to protect against low density lipoprotein (LDL) oxidation both in vitro and in vivo. Oxidation of LDL was inhibited in vivo after dietary consumption of several
nutrients rich in flavonoids, including tea polyphenols.

CONCLUSION

A growing body of evidence indicates that bioflavonoids from tea maintain levels of antioxidant capabilities in the plasma that exert beneficial effects on the cardiovascular system. It has also been shown that the antioxidant capabilities of bioflavonoids act in a number of ways to restore vasculature integrity and inhibit atherogenesis. However, continued investigation is required to identify which bioflavonoids or combinations of bioflavonoids are necessary to optimally reduce cardiovascular disease.

REFERENCES

1. Balentine DA, Wiseman SA, Bouwens LCM. The chemistry oftea flavonoids. *Crit Rev Food Sci Nutr*. 1997;37:693-704.
2. Wiseman SA, Balentine DA, Frei B. Antioxidants in tea. *CritRev Food Sci Nutr*. 1997;37:705-718.
3. Tijburg LBM, *et al*. Tea flavonoids and cardiovascular diseases:a review. *Crit Rev Food Sci Nutr*. 1997;37:771-785
4. Peters U, Poole C, Arab L. Does tea affect cardiovascular disease?A meta-analysis. *Am J Epidemiol*. 2001;154:495-503.
5. Miura Y, Chiba T, Miura S, Tomita I, Umegaki K, Ikeda M, Tomita T. Green tea polyphenols (flavan-3-ols) prevent oxidative modification of low density lipoproteins: an ex vivo study in humans. *J Nutr Biochem*. 2000;11:216–22.
6. Kris-Etherton PM, Keen CL. Evidence that antioxidants flavonoids in tea and cocoa are beneficial for cardiovascular health. Curr Opin Lipidol. 2002;13:41–9.
7. Yang GY, Liao J, Li C, Chung J, Yurkow EJ, Ho CT, Yang CS. Effect of black and green tea polyphenols on c-jun phosphorylation and H_2O_2 production in transformed and non-transformed human bronchial cell lines: possible mechanisms of cell growth inhibition and apoptosis induction. Carcinogenesis. 2000;21:2035–9.
8. Dreosti IE. Antioxidant polyphenols in tea, cocoa, and wine. Nutrition. 2000;16:692–4.

SOLID DISPERSIONS: AN APPROACH TO ENHANCE THE BIOAVAILABILITY OF POORLY WATER-SOLUBLE DRUGS

PritiMehndiratta, JyotiDahiya

Department of Pharmaceutical Sciences & Research, BMU

INTRODUCTION

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Therefore, pharmaceutical researchers' focuses on two areas for improving the oral bioavailability of drugs include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble. Unfortunately, many of these potential drugs are abandoned in the early stages of development due to the solubility problems. It is therefore important to realize the solubility problems of these drugs and methods for overcoming the solubility limitations are identified and applied commercially so that potential therapeutic benefits of these active molecules can be realized.

ADVANTAGES OF SOLID DISPERSIONS

There are various reasons for the improvement of solubility of poorly water-soluble drug using solid dispersion technology. The reasons for solid dispersion or advantages of solid dispersions are as follows:

Particles with reduced particle size : Molecular dispersions, as solid dispersion, represent the last state on particle size reduction, and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium . A high surface area is formed which results an increased dissolution rate and further improved the bioavailability of the poorly watersoluble drug .

Particles with improved wettability: The solubility enhancement of the drug is related to the drug wettability improvement verified in solid dispersion.

Particles with higher porosity: Particles in solid dispersions have been found to have a higher degree of porosity and the increase in porosity also depends on the properties of the carrier. When polymers having linear structure are utilized it produces larger and more porous particle as compared with SDs that prepared with reticular polymers. More porous nature of the particle results higher dissolution rate.

Drugs in amorphous state: Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher degree of solubility. Drug in its amorphous state shows higher drug release because no energy is required to break up the crystal lattice during the dissolution process.

DISADVANTAGES OF SOLID DISPERSIONS

The major disadvantages of SDs are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate on ageing. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which leads to the reduction of drug solubility. Moisture and temperature have more of deteriorating effect on solid dispersions than on physical mixtures. Sometimes it is difficult to handle because of tackiness.

LIMITATIONS OF SOLID DISPERSIONS

Although a great research interest in solid dispersion in the past four decades, the commercial utilization is very limited. Problems of solid dispersion involve (i) the physical and chemical stability of drugs and vehicles, (ii) method of preparation, (iii) reproducibility of its physicochemical properties, (iv) formulation of solid dispersion into dosage forms, and (v) scale-up of manufacturing processes .

PREPARATION OF SOLID DISPERSIONS

The fusion (melt), solvent evaporation, spray drying, lyophilization (freeze drying), hot-melt extrusion, electrostatic spinning method, coating on sugar beads using fluidized bed-coating system, supercritical fluid technology, are the methods reported for the preparation of solid dispersions and these methods are discussed below.

Fusion Method:

The fusion method is sometimes called melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term "fusion method" is preferred. Fusion or Melting method was first introduced by Sekiguchi et al. in 1961 where the drug was melted in a carrier and after cooling the dry mass obtained was pulverized and sieved to obtain powder. They prepared the SDs of Sulfathiazole in different carriers (e.g. ascorbic acid, acetamide, nicotinamide, nicotinic acid, succinimide and urea) by the formation of melt of different drug carrier mixtures. Cooling of the drug-carrier melt was done on ice bath with continuous stirring until the dry mass was obtained. Dua et al. in 2010, prepared solid dispersions of aceclofenac with various hydrophilic carriers (urea, mannitol, PVP and PVP/VA-64) in different ratios such as 1:0.5, 1:1 and 1:2 by weight basis using melting or fusion method) with an aim to improve the extent and rate of dissolution. A particular advantage of these carriers for the formation of SDs is having its good solubility in different organic solvents. Additional attractive features of such carriers include improved compound wettability. This study clearly shows that additions of various hydrophillic carriers like urea, mannitol, PVP and PVP/VA-64 to aceclofenac improves its dissolution rate. Further, all the solid dispersions performed better than the corresponding physical mixtures. The present study also showed that urea, mannitol and PVP/VA-64 yielded solid dispersions with a less improved dissolution rate than PVP as carrier. The melting point of a binary system is dependent upon its composition, i.e., the weight fraction of drug and the carrier present in the system. By proper selection and control, the melting point of a binary system may be much lower than the melting points of its two components. Under such conditions, this melting method can be used to prepare solid dispersions, even if the pure drug may undergo decomposition at or near its melting point . The main advantages of this method are its simplicity and economy. In addition melting under vacuum or blanket of an inert gas such as nitrogen may be used to prevent oxidation of drug or carrier material. Although frequently applied, the fusion method has serious limitations. Firstly, a major disadvantage is that the method is only applied when the drug and matrix are compatible and when they mix well at the heating temperature. When the drug and matrix are incompatible two liquid phases or suspension can be observed in the heated mixture which results in an inhomogeneous solid dispersion and this problem can be prevented by using surfactants. Secondly, another problem may arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions. Thirdly, many substances, either drugs or carriers, may decompose during the fusion process at high temperatures. Traditional fusion method usually produces soft, tacky materials with poor flow properties and

compressibility. Therefore, Gahoi et al., in 2011, prepared lumefantrine (LMF) solid dispersion by a novel solid dispersion technique 'Dispersed Fusion' to improve dissolution rate with particular attention to technological characteristics of granules. This novel 'Dispersed Fusion' technique involves spraying of molten drug and hydrophilic inert carrier on diluent in fluidized bed. They found that the drug particle size in agglomerates was significantly reduced in 'Dispersed Fusion' technique indicating strong impact of technique

Solvent Evaporation Method:

Tachibana and Nakamura were the two researchers who firstly applied solvent evaporation method for the preparation of solid dispersions. Drug (b-carotene) and carrier (PVP) were Solid Dispersions: An Approach to Enhance the Bioavailability of Poorly Water-Soluble Drugs International Journal of Pharmacology and Pharmaceutical Technology (IJPPT), ISSN: 2277 – 3436, Volume-I, Issue-1 40 dissolved in a common solvent (chloroform) and solvent was evaporated to form the solid mass . Basically, this solvent evaporation method involves two steps and these are: (i) preparation of a solution containing both matrix material or carrier and drug and (ii) the removal of the solvent resulting in the formation of the solid mass. Nature of the solvent used and the rate and temperature of evaporation of the solvent are the critical factors which can affect the formed mass . One of the major advantages of this method is that thermal decomposition of the drugs can be prevented as low temperature is required for the evaporation of the organic solvents. This method has several disadvantages these are: (i) high cost of preparation, (ii) difficulty in selecting a common solvent for both the drug and carrier and complete solvent removal from the product can be a lengthy process, and (iii) crystal forms are difficult to reproduce. Many researchers studied solid dispersion of valdecoxib, carbamazepine, fexofenadine hydrochloride, and glibenclamide using solvent evaporation method

Spray Drying:

Spray drying method consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed within seconds, which may be fast enough to phase separation. Spray drying usually yields drugs in the amorphous state, but sometimes the drug may be partially crystallized during processing. Polyglycolized glycerides (Gelucire) are available with a range of properties depending on their hydrophilic lipophilic balance (HLB) over the range of 1 to 18 and melting point between 33o and 70°C. Preparation of SDs by conventional spray drying with polyglycolized glycerides has been problematic because a sticky and tacky mass of polyglycolized glycerides is obtained. Therefore, spray drying technique for polyglycolized glycerides has been used with its combination highmelting lipids to solve this problem.

Lyophilization (freeze drying) :

An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the SDs. However, the most important advantage is that the risk of phase separation is minimized as soon as the solution is vitrified. Singh et al., in 2011, dissolved some selected solid dispersions in a minimum amount of cyclohexanol. Then this solution was rapidly solidified by transferring small portions with a Pasteur pipette onto the inner surface of a cold flask rotating in a -50°C methanol bath. After achieving a certain layer thickness, the flask was attached to the vacuum adaptor of the lyophilizer. The solvent was then sublimed under a pressure of 8-10mmHg and condensed onto a -75°C condenser. When the solvent was completely removed, they found that the nature of the powder residue was porous, light and fluffy mass. Lokamatha et al., in 2011, prepared SDs of nevirapine (NVP) with the objective of

dissolution enhancement by kneading and freeze drying technique using a novel carrier of low molecular weight dextran (DEX) at varied concentrations of drug:carrier (3:1 and 1:1w/w). They first dispersed NVP and DEX in water, and then the whole solution is stirred for 3 h. The solution is then frozen overnight and then lyophilized over a period of 24 h using a freeze drier. Then the dried powder was sieved through #120 and stored in dessicator. They found that SDs of NVP: DEX, prepared by freeze drying method exhibited a higher release rate than prepared by kneading method.

Supercritical Fluid Technology:

Supercritical fluid (SCF) technology offers tremendous potential and the low operating conditions (temperature and pressure) make the method more attractive for pharmaceutical research. In the pharmaceutical field, the supercritical fluid technology was industrially applied in the early 1980's. A supercritical fluid exists as a single phase above its critical temperature and pressure . The most commonly used supercritical fluids for a variety of applications include supercritical fluid carbon dioxide, nitrous oxide, water, methanol, ethanol, ethane, propane, n-hexane and ammonia . Carbon dioxide is one of the most commonly used SCFs because of its low critical temperature (Tc = 31.1°C) and pressure (Pc = 73.8 bar). Apart from being nontoxic, nonflammable, and inexpensive, the low critical temperature of CO2 makes it attractive for processing heat-labile molecules . This technique consists of dissolving the drug and the inert carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel s. This SCF technology provides a novel alternative method of preparation of small particles with higher surface area, free flowing property, and a very low content of residual organic solvent and this technology also avoids most of the drawbacks of the traditional methods

DEPRESSION

Monika Kaushik , Rajiv Kumar Arora, Minakshi Gupta

Faculty of Pharm. Sciences, Baba Mastnath University, Asthal Bohar, Rohtak

INTRODUCTION

Depression is a serious medical disorder with biological causes, just as high blood pressure or diabetes is. It can be treated effectively in most people. Despite this, many people mistakenly believe that depression is normal for older people, or that little can be done about it. We may think it is a character flaw, a sign of weakness, or something that we should be able to "snap out of." It's time to dispel these and other myths about depression. While it is true that depression is more common in older people than in the general population, it is not an inevitable part of aging. Nor is it something that we can control at will, or something of which to be ashamed. These persistent biases contribute to the underrecognition and undertreatment of depression, as well as other mental disorders.

SYMPTOMS OF DEPRESSION

Depression is more than feeling blue. Deep sadness is often compounded by other emotional, mental, and physical symptoms, including those noted below. Symptoms may range from mild to severe, and may wax and wane over time. When symptoms interfere with normal day-to-day activities, depression may be the cause.

- Prolonged sadness or unexplained crying spells
- Significant changes in appetite and sleep patterns
- Irritability, anger, worry, agitation, anxiety, pessimism, indifference
- Loss of energy and enthusiasm, persistent sluggishness
- Feelings of guilt, worthlessness, hopelessness, helplessness
- Inability to concentrate or make decisions
- Loss of enjoyment from once-pleasurable activities
- Withdrawal from social contacts, isolation
- Unexplained aches and pains
- Recurring thoughts of death or suicide
- Memory loss

CAUSES OF DEPRESSION

Depression is a brain disorder characterized by changes in certain brain chemicals called neurotransmitters. According to the National Institute of Mental Health, recent brain-imaging research has shown that, in depression, some of the brain circuits responsible for mood, sleep, appetite, thinking, and behavior malfunction, and the regulation of critical neurotransmitters is impaired. Scientists are still trying to determine what causes these chemical imbalances; many experts believe a combination of genetic, psychological, and environmental factors are involved. The precise contribution of inherited genes is unclear. Some types of depression run in families, suggesting that there is a genetic basis for the disorder. However, many people with depression have no family history, and not everyone with a family history of depression develops the condition. Environmental factors that might trigger depression include grief from the loss of a loved one, serious financial difficulties, or problems in relationships — all factors that may put

an individual under serious stress. (See "What's New in Brain Research.") Other factors that are linked to depression include low self-esteem, consistent pessimism, and a tendency to be overwhelmed by stress, attributes that may in reality be an early form of depression or may predispose a person to depression.

TYPES OF DEPRESSIVE DISORDERS

Recent brain research suggests that depression may be a chronic condition whose symptoms occur to varying degrees throughout life in susceptible persons. Studies have shown, for example, that people who have even one depressive "episode" in their life are at increased risk for developing major depression. Depression in later life may in fact be a recurrence of an earlier episode. A diagnosis of depression might specify one of two primary types: unipolar depression or bipolar disorder.

Unipolar depression

Can be further differentiated as either major depression or dysthymia

Major depression- It may be diagnosed if five or more depressive symptoms (are experienced nearly every day in a two-week period, especially if the symptoms interfere with daily life.

Dysthymia - This is a less severe but no less important form of depression, usually involving two or more symptoms that may not disable, but keep a person from feeling good and functioning well.

Bipolar disorder (manic-depressive illness) While not as common as unipolar depression, bipolar disorder is just as serious, and is associated with an even higher risk of suicide. Bipolar disorder is a brain-based mental illness separate from unipolar depression. It involves a cycle of mood changes from severe highs (mania) to severe lows (depression), interspersed with normal periods. Mood changes may happen quickly, sometimes over the course of a single day, but more commonly, bipolar disorder involves intensive periods of mania lasting for several days, followed by lengthy periods of depression.

TREATMENT FOR DEPRESSION

Even when depression is recognized, people may not get adequate treatment. However, once the right therapy is found, the vast majority of people with depression can be treated effectively, which improves quality of life and reduces the risk of suicide and premature death from other medical conditions. A combination of antidepressant medications and psychotherapy (talk therapy) is often the most effective approach to treatment, especially in older persons. Treatment for depression may need to continue for a long time, perhaps even indefinitely, just as treatment for chronic medical conditions such as diabetes or high blood pressure must continue throughout life. People over 75 may respond more slowly to treatment, or be more susceptible to recurring depression, even with treatment. Regular and ongoing consultations with a physician experienced in treating depression in the elderly is critical, so that treatment adjustments may be made as necessary. Current antidepressants influence the function of neurotransmitters. Three major types of antidepressants are available: tricyclic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors (SSRIs). Developed more recently, SSRIs tend to have fewer side effects than the older drugs. Different people respond differently to antidepressants, and finding the one that provides effective relief of symptoms is often a process of trial and error. Sometimes the dose may need to be adjusted, or a combination of medications may be needed. The full effect of an antidepressant may not occur for three to four weeks, sometimes longer. If improvement is not seen after several weeks on one medication, another

one may be tried, on the doctor's recommendation. Psychotherapy is an important part of depression treatment, particularly in older people. The most effective types of psychotherapy for depression include Cognitive-Behavioral Therapy (CBT) and Interpersonal Therapy (IPT). Administered by a psychiatric professional (usually a psychiatrist or licensed psychotherapist), these talk therapies work to help a person develop strategies for coping with day-to-day challenges, learn to counter negative thoughts and behaviors that accompany depression, and resolve any relationship conflicts that may be contributing to depression. People with short-term depression, such as that associated with medical illness, trauma, or loss of a loved one, may benefit from shorter courses of psychotherapy.

CONCLUSION

Depression is not an inevitable part of growing old. It is a serious medical condition resulting from an imbalance in brain chemicals, which may be triggered by a number of factors — genetic, psychological, and environmental. Know the warning signs for depression, and if you notice them in yourself or others, seek medical attention.

MECHANISM, CURRENT&PROSPECTIVE MODALITIES OF CANCER CHEMOTHERAPY

Savitri Kumari*, Minakshi Gupta[1], Anusha[1]

Assistant Professor, Faculty of Pharmaceutical Sciences, Baba Mastnath University, Asthal Bohar, Rohtak (124001)

INTRODUCTION

Cancer is one of the most widespread and feared diseases in the Western world today - feared largely because it is known to be difficult to cure. The main reason for this difficulty is that cancer results from the uncontrolled multiplication of subtly modified normal human cells. One of the main methods of modern cancer treatment is drug therapy (chemotherapy). The majority of drugs used for the treatment of cancer today are cytotoxic (cell-killing) drugs that work by interfering in some way with the operation of the cell's DNA. Cytotoxic drugs have the potential to be very harmful to the body unless they are very specific to cancer cells - something difficult to achieve because the modifications that change a healthy cell into a cancerous one are very subtle. A major challenge is to design new drugs that will be more selective for cancer cells, and thus have lesser side effects. Initially the specificity of drugs was worked out simply by testing on animals, but now it is possible to use our knowledge of cancer cell biology to actively design drugs to be more specific. However, animal tests still need to be carried out at some point. As with any pharmaceutical, new anticancer drugs are developed in a three-step process.

Step 1 - Initial discovery

A wide range of compounds, both natural and synthetic, are tested in high-capacity screens to discover molecules with useful properties.

Step 2 - Molecular modification of a known compound

A molecule that shows suitable properties is chemically altered to give it the best combination of properties to make the most effective anti-cancer drug.

Step 3 - Development into a useful pharmaceutical

Because the above process is very time-consuming and expensive, the new discovery is usually patented at this time so that the discoverers can eventually recover some of these costs. The most effective route for synthesising the molecule is then worked out. A long process of advanced testing is then begun, ending up with tests on patients in specialised hospitals. If the results are favourable, the drug is then able to be released for use.

The process of drug development is very long and involved, with maybe only one in ten thousand of the molecules originally tested finally being clinically used. This article describes different types of drug interactions and discusses the development of the cytotoxic drug *asulacrine* from the less cytotoxic *amsacrine*.

PRINCIPLES OF CHEMOTHERAPY

Many forms of chemotherapy are targeted at the process of cell division. The rationale being that cancer cells are more likely to be replicating than normal cells. Unfortunately as their action is not specific, they are associated with significant toxicity. An understanding of the principles of tumour biology and cellular kinetics is helpful to appreciate the mechanisms of action of cancer chemotherapy.

Mechanism of cell death

There are two main types of cell death: apoptosis and necrosis. Necrotic cell death is caused by gross cell injury and results in the death of groups of cells within a tissue. Apoptosis is a regulated form of cell death that may be induced or is preprogrammed into the cell (e.g. during

development) and is characterized by specific DNA changes and no accompanying inflammatory response. It can be triggered if mistakes in DNA replication are identified. Loss of this protective mechanism would allow mutant cells to continue to divide and grow, thereby conserving mutations in subsequent cell divisions. Many cytotoxic anticancer drugs and radiotherapy act by inducing mutations in cancer cells which are not sufficient to cause cell death, but which can be recognized by the cell, triggering apoptosis.

Some basic Facts about Cancer

- Cancer cells have lost the normal regulatory mechanisms that control cell growth and multiplication
- Cancer cell have lost their ability to differentiate (that means to specialize)
- Benign cancer cell stay at the same place
- Malignant cancer cells invade new tissues to set up secondary tumors, a process known as metastasis
- Chemicals causing cancer are called mutagens
- Cancer can be caused by chemicals, life style (smoking), and viruses genes that are related to cause cancer are called oncogenes. Genes that become onogenic upon mutation are called proto-oncogenes

Some current and prospective modalities of cancer chemotherapy

Category	**Function**	**Examples**
Antimetabolites	Interfere with intermediary metabolism of proliferating cells	Methotrexate, 5-fluorouracil
Monoclonal antibodies	Target cancer cells that express specific antigen	Herceptin (Genentech), Zevalin (IDEC Pharmaceuticals/Schering-Plough)
Mitosis inhibitors	Target microtubules and associated proteins required in cell division	Taxol
Steroid hormones	Block steroid- and hormone-dependent growth of certain tumours	Tamoxifen, flutamide
Alkylating/cross-linking agents	Damage DNA and result in death of growing cells	Endoxan, cisplatin, cyclophosphamide
Signal-transduction agents	Modulate communication between cells	Gleevec (Novartis), Tarceva (OSI), Iressa (AstraZeneca), LY900003 (ISIS 3521) (Eli Lilly)
Telomerase inhibitors	Affect telomere maintenance required for tumour growth	BIBR1532 (Boehringer Ingelheim)

TUMOUR GROWTH

The kinetics of any population of tumour cells is regulated by the following:

- **doubling time:** the cell cycle time, which varies considerably between tissue types;
- **growth fraction:** the percentage of cells passing through the cell cycle at a given point in time which is greatest in the early stages;

- **cell loss:** which can result from unsuccessful division, death, desquamation, metastasis and migration. Tumours characteristically follow a sigmoid-shaped growth curve, in which tumour doubling size varies with tumour size. Tumours grow most rapidly at small volumes. As they become larger, growth is influenced by the rate of cell death and the availability of blood supply.

The Use of Antibodies in Cancer Therapy

- Monoclonal antibodies recognize epitopes with high selectivity and high affinity, often in the picomolar range
- The recognized epitope should be tumor specific (tumor marker)
- Must be internalized by receptor-mediated endocytosis
- Antibodies that undergo internalization may be linked to radioisotopes or toxins to initiate cell killing
- Commonly used toxins include Pseudomonas exotoxin and Diphteria toxin, both of which can kill cells with a single internalized molecule
- Being large proteins delivery is a problem, especially across the blood-brain barrier
- Antibodies that have been produced in mice must be humanized in order to reduce immunogenicity

REFERENCES:

1. Skipper HE, Schabel FM, Wilcox WS. Experimental evaluation of potential anti-cancer agents. XIII On the criteria and kinetics associated with 'curability' of experimental leukaemia. Cancer Chemotherapy Reports. 1964; 35: 1–111.
2. Herscher LL, Cook J. Taxanes as radiosensitizers for head and neck cancer. Current Opinion in Oncology. 1999; 11: 183–6.
3. Guichard SM, Danks MK. Topoisomerase enzymes as drug targets. Current Opinion in oncology. 1999; 11: 482–9.
4. Henk JM. Concomitant chemotherapy for head and neck cancer: saving lives or grays? Clinical Oncology (Royal College of Radiologists (Great Britain)). 2001; 13: 333–5. Brief summary of important issues and trials with respect to the role of chemotherapy and radiotherapy in head and neck cancers.
5. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet. 2000; 355: 949–55. Main metaanalysis on the effect of chemotherapy on nonmetastatic head and neck squamous-cell carcinoma.
6. Forastiere A, Koch W, Trotti A, Sidransky D. Head and Neck Cancer. New England Journal of Medicine. 2001; 345: 1890–1900. Very good summary of the important advances in the treatment of patients with head and neck cancer and the future importance of molecular biology.
7. Haffty BG. Concurrent chemoradiation in the treatment of head and neck cancer. Hematology/Oncology Clinics of North America. 1999; 13: 719–42.
8. Hong WK, Endicott J, Itri LM, Doos W, Batsakis JG, Bell R et al. 13-Cis retinoic acid in the treatment of oral leukoplakia. New England Journal of Medicine. 1986; 315: 1501–5.
9. Hong WK, Lippman SM, Itri LM, Karp DD, Lee JS, Byers RM et al. Prevention of second primary tumours with isotretinoin in squamous-cell carcinoma of the head and neck. New England Journal of Medicine. 1990; 323: 795–801.

DENDRIMERS, SILICA MATERIALS, CARBON NANOMATERIALS AND MAGNETIC NANOPARTICLES AS DRUG CARRIERS

Sneh Lata*, Savitri

Faculty of Pharmaceutical Sciences, Baba Mastnath University, Asthal Bohar, Rohtak-124001

ABSTRACT

Nanoparticles are particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. Present review reveals dendrimers, silica materials, carbon nanomaterials and magnetic nanoparticles as drug carriers.

Keywords: Nano particle drug delivery system, dendrimers, silica materials, carbon nanomaterials and magnetic nanoparticles .

INTRODUCTION

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as polyethylene glycol (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability. On the other hand, polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties.

DENDRIMER NANOCARRIERS

Dendrimers are unique polymers with well-defined size and structure. Dendritic architecture is one of the most popular structures observed throughout all biological systems. Some of the examples of nanometric molecules possessing dendritic structure include: glycogen, amylopectin, and proteoglycans. In the structure of dendrimer, in contrast to the linear polymer, the following elements can be distinguished: a core, dendrons, and surface active groups. The core is a single atom or molecule (only if it has at least two identical functional groups) that dendrons are attached to. The dendrons (dendrimer arms) are molecules of monomer linked with the core, forming layers and building successive generations (their growth is spatially limited). Biocompatibility and physicochemical properties of dendrimers are determined by surface functional groups. Selection of a core, type of a monomer and surface functional groups

determine the usability of dendrimers in medical applications. Cytotoxicity of dendrimers and their so-called polyvalence is particularly relevant for biomedical purposes. Dendrimers cytotoxicity depends on the core material and is strongly influenced by the nature of the dendrimers surface. For example, changing the surface amine groups into hydroxyl ones may result in lower levels of cytotoxicity. The term *polyvalence* defines the number of active groups on a dendrimers surface. The presence of several surface functional groups enables a sumultanoeus interaction with a number of receptors, thus, it enhances biological activity. There are a few ways of connecting biologically active compounds to dendrimers. The drug may be encapsulated in the internal structure of dendrimers or it can be chemically attached or physically adsorbed on dendrimers surface. The choice of the immobilization method depends on the drug properties. Encapsulation is used when drugs are labile, toxic, or poorly soluble. In turn, chemical attachment provides the possibility to control quantity of drugs on dendrimers surface by controlling the number of covalent bonds . The selectivity of both methods may be enhanced by attaching on the dendrimers surface such targeting agents as folic acid [40] or epidermal growth factor.The surface of dendrimers provides an excellent
platform for an attachment of specific ligands, which may include folic acid, antibodies, cyclic targeting peptides – arginine-glycine-aspartic acid (RGD), selective A3 adenosine receptor, silver salts complexes antimicrobial agents [14], or poly(ethylene glycol) (PEG). The attached compounds can improve surface activity as well as the biological and physical properties of dendrimers. Poly(amido amide) (PAMAM) is a dendrimer which is frequently used in biomedical applications.

SILICA MATERIALS

Silica materials used in controlled drug delivery systems are classified as xerogels and mesoporous silica nanoparticles (MSNs), e.g., MCM-41 (Mobil Composition of Matter) and SBA-15 (Santa Barbara University mesoporous silica material). They exhibit several advantages as carrier systems, including biocompatibility, highly porous framework and an ease in terms of functionalization [11]. Among inorganic nanoparticles, silica materials are the carriers which most often are chosen for biological purposes. Silica xerogels possess an amorphous structure with high porosity and enormous surface area. A porous structure (shape and pore dimensions) depends on synthesis parameters. Sol-gel technique is frequently used to form silica xerogels loaded with drugs. A modification of the synthesis conditions, such as the ratio of reagents, temperature, concentration of the catalyst, and pressure of drying, allows to alter properties of xerogels used in controlled drug release. Phenytoin, doxorubicin, cisplatin, metronidazole, nifedipine, diclofenac, and heparin are examples of drugs which have been loaded into xerogels using this technique. The best known types of mesoporous silica nanomaterials are MCM-41 with a hexagonal arrangement of the mesopores and SBA-15 with a well-ordered hexagonal connected system of pores. The MSNs, in comparison with xerogels, possess more homogenous structure, lower polydispersity and higher surface area for adsorption of therapeutic or diagnostic agents. The mechanism of drug loading into mesoporous silica material is a chemical or physical adsorption. By these processes, diverse types of drugs, including anticancer drugs, antibiotics, and heart disease drugs, have been embedded into MNSs. The drug release is usually controlled by diffusion. The silicalites and mesoporous silica nanoparticles potential application in photodynamic therapy has been also studied . The MSNs properties make them an excellent material for various pharmaceutical and biomedical ap-plications. The structure of MSNs enables the incorporation of both small and large molecules, adsorption of DNA, and gene transfer. This gives a possibility of using these nanomaterials in a combined therapy.

CARBON NANOMATERIALS

Carbon nanocarriers used in DDS are differentiated into nanotubes (CNTs) and nanohorns (CNH). CNTs are characterized by unique architecture formed by rolling of single (SWNCTs – single walled carbon nanotubes) or multi (MWCNTs – multi walled carbon nanotubes) layers of graphite with an enormous surface area and an excellent electronic and thermal conductivity [15]. Biocompatibility of nanotubes may be improved by chemical modification of their surface. Such adjustment can be implemented by covalent anchoring of PAMAM dendrimers , amphiphilic diblock copolymers, or PEG layers [16] on CNTs surface or dispersion within a hyaluronic acid matrix. Due to their mechanical strength, SWCNTs have been used as a support to improve properties of other carriers, e.g., polymeric or non-polymeric composites .There are three ways of drug immobilization in carbon nanocarriers, which are: encapsulation of a drug in the carbon nanotube [11], chemical adsorption on the surface or in the spaces between the nanotubes(by electrostatic, hydrophobic, *p-p* interactions and hydrogen bonds) , and attachment of active agents to functionalized carbon nanotubes (f-CNTs). Encapsulation has the advantage over the two remaining methods as the drug is protected from degradation during its transport to the cells and is released only in specific conditions.

Drug release from carbon nanotubes can be electrically or chemically controlled. To prevent the unwanted release of the drug, the open ends of CNTs were sealed with polypyrrole (PPy) films. Homing devices, i.e., folic acid and epidermal growth factor, were attached to improve selectivity of such drug delivery systems. Nanohorns – a type of the only single-wall nanotubes exhibit similar properties to nanotubes. Their formation process does not require a metal catalyst, thus, they can be easily prepared with very low cost and are of high purity. The immobilization of drugs may rely on adsorption on nanohorns walls or nanoprecipitation of drugs with nanohorns. A comparison of these two paths of cisplatin incorporation into nanohorns showed that nanoprecipitation is much more effective (almost 3-fold increase in the number of molecules entrapped in nanohorns) than adsorption. The toxicity of carbon nanomaterials also depends on their unique well-defined geometric structure. The toxic potential of carbon nanotubes can result from the high length to diameter ratio and the toxicity of the sole material, which is graphite. In addition, some impurities, such as residual metal and amorphous carbon, contribute to the level increase of reactive oxygen species (ROS), thus, inducing the oxidative stress in cells. Recent studies have pointed out the similarity in carcinogenic potential between CNT and asbestos. Carbon nanotubes have been shown to cause necrosis or apoptosis of macrophage cell lines and changes in cell morphology.

MAGNETIC NANOPARTICLES

Magnetic nanoparticles exhibit a wide variety of attributes, which make them highly promising carriers for drug delivery. In particular, these are: easy handling with the aid of an external magnetic field, the possibility of using passive and active drug delivery strategies, the ability of visualization (MNPs are used in MRI), and enhanced uptake by the target tissue resulting in effective treatment at the therapeutically optimal doses [11]. However, in most of the cases where magnetic nanocarriers have been used, difficulties in achieving these objectives appeared. It is most likely associated with inappropriate features of magnetic nanoparticles or inadequate magnet system. Magnetic nanoparticles, for instance, tend to aggregate into larger clusters loosing the specific properties connected with their small dimensions and making physical handling difficult. In turn, magnetic force may not be strong enough to overcome the force of blood flow and to accumulate magnetic drugs only at target site. Therefore, designing magnetic drug delivery systems requires taking into consideration many factors, e.g., magnetic properties

and size of particles, strength of magnetic field, drug loading capacity, the place of accessibility of target tissue, or the rate of blood flow. Depending on magnetic properties, MNPs can be divided into pure metals (such as cobalt, nickel , manganese, and iron, their alloys and oxides. However, narrowing the area of MNPs applications only to biomedicine reduces significantly the choice of magnetic material. Such a restriction results from the lack of knowledge of the negative effects which the majority of these nanomaterials have on the human body. Iron oxide nanoparticles, due to the favorable features they exhibit, are the only type of MNPs approved for clinical use by Food and Drug Administration. These attributes are: facile single step synthesis by alkaline co-precipitation of Fe2+ and Fe3+, chemical stability in physiological conditions [13] and possibility of chemical modification by coating the iron oxide cores with various shells, i.e., golden, polymeric, silane , or dendrimeric. In addition, iron oxides – magnetite and maghemite – occur naturally in human heart, spleen and liver , which indicates their biocompatibility and non-toxicity at a physiological concentration. It is essential to estimate a safe upper limit of MNPs for biomedical use. Connecting a drug with MNP may be achieved by covalent binding, electrostatic interactions, adsorption, or encapsulation process. Targeting of drug-MNPs conjugates to diseased tissues (magnetic targeted drug delivery systems – MTDDS), depending on their size and surface chemistry, can be carried out by passive or active mechanism. Passive targeting is a result of enhanced vascular permeability and retention (EPR) of tumor tissues. Active strategy relies on the attraction of nanoparticle to the affected site by using recognition ligands (e.g., antibodies) attached to the surface of MNPs and by handling of an external magnetic field. Therapeutic activity of diverse drugs incorporated into iron oxide nanocarriers have been tested and reported. MNPs have been examined for multitasking treatment as biosensors (diagnosis) and drug carriers (therapy) simultaneously.

CONCLUSION

Nanocarriers as drug delivery systems are designed to improve the pharmacological and therapeutic properties of conventional drugs. Although there are several nanoparticle-based therapeutic agents which are currently being developed and are under preclinical evaluation, only a handful of nanoparticle drugs are available on the pharmaceutical market. Nanoparticles of diameter 10 nm can remain in cells and induct chronic inflammatory response and fibrosis of tissue. An additional problem is the lack of knowledge concerning the distribution of drug carriers and the unpredictability of the process. Thus, in our opinion, the magnetic targeted drug delivery system is one of the most attractive strategy target therapy. Magnetic nanoparticles have their unique magnetic properties and they can be attracted by magnetic fields, thus, acting as drug carriers in a target therapy. In addition, inorganic magnetic nanoparticles containing the iron and gadolinium serve as an excellent contrast enhancing agents in MRI (approved by FDA – Food and Drug Administration). A real therapeutic breakthrough can be achieved solely by carrying out painstaking studies in the field of nano-therapy. Using nanosystems in therapies of diseases may contribute to achieving an effective cancer treatment. There is still more research work yet to be done on nanoparticles.

REFERENCES:

1. Bagul R., Mahajan V., Dhake A., New approaches in nanoparticulate drug delivery system, International journal of current pharmaceutical research, 2012,vol-4(3),29-30.
2. Mohanraj V. J. and Chen Y., Research article,Nanoparticle-A Review, tjpr,june2006; 5(1); 561-573.
3. Mukharjee S., Ray S.and Thakur R.S., Review article, solid lipid nanoparticles: A Modern Formulation Approach in Drug Delivery System, ijps,2009,vol-71(4),349-358.
4. Shinde A. J.,solubilization of poorly soluble drug review, pharmainfo.net, nov-2007. On-Http://www.pharmainfo.net./reviews/solubilization-poorly-soluble-drug-review.
5. Garg Rajeev, review/nanoparicles-review, pharmainfo.net, dec 2007.

6. Shreeraj, review/ overview brain targeting drug delivery system, Pharmainfo.net, june 2009. On-Http://www.pharmainfo.net./reviews/overview-brain-targeting-drug-delivery-system.
7. Jain S, Jain NK. Resealed erythrocytes as drug carriers. In: Jain NK, editor. Controlled and Novel Drug Delivery. New Delhi: CBS Publishers and Distributors; 2002. p. 256-257.
8. Robinson J. R. & Alani Adam W.G, Extended release & targeted drug delivery, Gennarao A. R.-editor, Remington,; The science and practice of pharmacy, 21st edition, vol-1st, Philadelphia, Lippincott Williams & Williams; 2000-06;951-957.
9. Ajima K, Murakami T, Mizoguchi Y, Tsuchida K, Ichihashi T, Iijima S, Yudasaka M: Enhancement of in vivo anticancer effects of cisplatin by incorporation inside singlewall carbon nanohorns. ACS Nano, 2008, 2, 2057–2064.
10. Amato G: Silica-encapsulated efficient and stable si quantum dots with high biocompatibility. Nanoscale Res Lett, 2010, 5, 1156–1160.
11. Arruebo M, Fernández-Pacheco R, Ibarra, MR, Santamaría J: Magnetic nanoparticles for drug delivery. Nano Today, 2007, 2, 22–32.
12. Arsawang U, Saengsawang O, Rungrotmongkol T, Sornmee P, Wittayanarakul K, Remsungnen T, Hannongbua S: How do carbon nanotubes serve as carriers for gemcitabine transport in a drug delivery system? J Mol Graph Model, 2011, 29, 591–596.
13. Asmatulu R, Zalich MA, Claus RO, Riffle J: Synthesis, characterization and targeting of biodegradable magnetic nanocomposite particles by external magnetic fields. J Magn Magn Mater, 2005, 292, 108–119.
14. Balogh L, Swanson DR, Tomalia DA, Hagnauer GL, McManus AT: Dendrimer-silver complexes and nanocomposites as antimicrobial agents. Nano Lett, 2001, 1, 18–21.
15. Beg S, Rizwan M, Sheikh AM, Hasnain MS, Anwer K, Kohli K: Advancement in carbon nanotubes: basics, biomedical applications and toxicity. J Pharm Pharmacol, 2011, 63, 141–163.
16. Bhirde AA, Patel S, Sousa AA, Patel V, Molinolo AA, Ji Y, Leapman RD et al.: Distribution and clearance of PEG-single-walled carbon nanotube cancer drug delivery vehicles in mice. Nanomedicine, 2010, 5, 1535–1546.

POLYMERS IN THE PHARMACEUTICAL APPLICATIONS

Bijender Sagar[1*]

Assistant Professor,[1]Shri Baba Mastnath Institute of Pharmaceutical Sciences and Research, Asthal Bohar, Rohtak-124001 (Haryana) E-mail: bijendersagar@rediffmail.com

1. INTRODUCTION

Biopolymers, synthetic polymers and their derivatives are commonly used in medicine and pharmacy. Recently, particular interest of scientists has been focused on biomedical polymers, especially those used for drug delivery systems, therapeutic systems and macromolecular prodrugs. The aforementioned applications have opened new exciting prospects for medicine, because specially designed polymers are capable of delivering medicinal substances to the target diseased tissues and cells together with dosing those drugs according to controlled specified pharmacodynamics. Particular attention has recently been paid to chemistry of biocompatiable and biodegradable polymers, because they have an advantage of being readily hydrolyzed into removable and non-toxic products, which can be subsequently eliminated by metabolic pathways. Furthermore, the biomedical polymers have to be synthesized now using friendly for the environment and safe for human health, effective natural initiators, co-initiators and/or catalysts. Therefore, the main objective of this work is to discuss various polymers recommended for the pharmaceutical applications.

2. Polymers in the pharmaceutical applications

Macromolecules are applied in pharmacy as the pharmacological substances, blood substitutes, drug delivery and therapeutic systems, in the synthesis of macromolecular prodrugs and in the technology of prolonged release drug formulations.

2.1 Polymers with the pharmacological effects and polymeric blood substitutes

One of the most interesting polymers used in pharmacy, are those exerting a pharmacological effect. DIVEMA, copolymer of divinyl ether-maleic anhydride (Florjanczyk & Penczek, 1998; Papamatheakis *et al.*, 1978) is an example of such compound with antitumoral and antiviral properties.

Methylcellulose taken orally is not absorbed from the alimentary tract. However, it detains water on swelling and in consequence causes relaxation of the stercorous mass (Tonnesen & Karlsen, 2002; Zejc & Gorczyca, 2002).

A linear polymer of uronic acids - alginic acid (mannuronic acid conjugated β-1,4 and L-guluronoic acid glycosidically conjugated β-1,4) is mainly obtained from the *Laminaria algae*. This polymer neutralizes hydrochloric acid (Janicki *et al.*, 2002; Zejc & Gorczyca, 2002). Its action relies on detaining of water in stomach followed by reduction of irritations and pain.

A polyvinylpyrrolidone has found an application as anti-diarrhoeal drug (Tonnesen & Karlsen, 2002; Zejc & Gorczyca, 2002). Its amphoteric properties normalize pH in stomach and intestines through acids or bases adsorption, which are usually raised as result of fermentation or putrefaction.

A polyvinylpyrrolidone was the first synthetic polymer used as the blood substitutes. Its solutions were mainly used to treat the shock after the burns and, in the case when the blood transfusion was not indicated (Janicki *et al.*, 2002; Florjanczyk & Penczek, 1998; Zejc & Gorczyca, 2002).

Currently, the solutions of polysaccharides (e.g. dextran), modified starch derivatives and modified gelatin products (polygeline, oksopolygelin, liquid gelatin) are commonly used as the

blood substititues (Janicki *et al.*, 2002; Zejc & Gorczyca, 2002). The dextran with the average molecular weight ranged from 40 000 to 70 000 Da is used as 6 or 10% solution.

2.2 Macromolecular prodrugs

A prodrug is a modified therapeutic agent, which is metabolized into active precursor in human body (Janicki *et al.*, 2002). Over the recent years, the conception of macromolecular prodrug has appeared as macromolecule that has therapeutic agents in the structure; the released drug becomes pharmacologically active during hydrolytic biodegradation of the polymer (Ouchi & Ohya, 1995). In general, the therapeutic agent could be incorporate into polymer chain, might be end-capped or may form a pendant group of the macromolecular chain.

Macromolecular prodrugs are mainly used in the cancer therapy. For example, 5- fluorouracil can be applied locally or orally in the therapy of the alimentary tract, urinary bladder and prostate gland cancers.

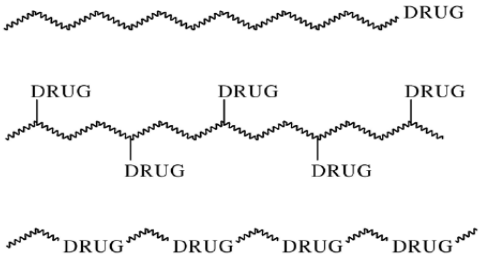


Fig: Structure of the macromolecular prodrugs

2.3 Polymers in the technology of prolonged release drug formulations

Macromolecules have also found the application in the technology of prolonged release drug formulations. They are mainly intended to ensure the constant concentration of the therapeutic agent in the certain time (e.g. 8-24 hours), in the patient body. In the technology of prolonged release drug formulation, natural polymers and their modified derivative (e.g.: starch, cellulose) as well as synthetic polymers are used e.g.: polyethylene, polypropylene, polyvinyl chloride, polyvinyl alcohol, polyvinyl acetate, polyacrylic acid, polycarbophile, polyacrylamides, polyacrylates, polyethylene glycol, poly(amino amide)s, polyurethanes, siloxanes, homoor copolymers of lactide and glycolide, poly(ε -caprolactone), polyorthoesters (Cardamone *et al.*, 1997; Ertan *et al.*, 1997; Huang *et al.*, 1994).

2.4 Polymers in the therapeutic systems technology

The polymers used in the therapeutic systems are the drug forms that are dosing or releasing drug in the exact time with the controlled rate (Janicki *et al.*, 2002; Muller & Hildebrand, 1998). They are designed to ensure constant concentration of the therapeutic agent in the body.

Therapeutic system	Polymer	Drug
Implantation therapeutic system	copolymers of lactide and glicolide, silicone	Estradiol, Goserelin
Oral therapeutic system	polyvinyl alkohol, polyacetale vinyl, polyamides, polyethylene glycol, poliacrylate, silicone, homo- or copolymers of lactide, glicolide and ε-caprolactone	Acetazolamide, Glipizide, Metoprolol, Nifedipine, Oksiprenolol KCl, Li_2SO_4, $FeSO_4$
Ocular therapeutic system	copolymers of acetate vinyl and ethyl	Pilocarpina
Transdermal therapeutic system	copolymers of acetate vinyl and ethyl, poliacrylate, silicone, polyurethanes, polyolefines, polyethylene glycol	Acetate Noretisterone, Buprenorphine, Clonidyne, Estradiol, Fentanyl, Flurbiprofen, Hyoscine, Isosorbide dinitrate, Nicotyne, Nitroglycerin, Testosterone
Uterus therapeutic system	silicone	Progesterone

3. CONCLUSIONS

From this review, it is clear that macromolecules have been extremely active research area over the last years. The discovering of new drug forms, e.g.: new therapeutic systems and macromolecular prodrugs is simply demanded by the market and industry presently. Promising avenues of research have also emerged for the enzymatic approach. Increasing interest has also been dedicated to the polymers containing natural compounds in macromolecules that have been incorporated into though the polymerization process. Clearly, the future development of biodegradable and bioresorbable polymers will be based on discovering macromolecules with not only appropriate chemical, physical and mechanical properties but also suitable biological properties.

4. REFERENCES

1. Cardamone M., Lofthouse S. A., Lucas J. C., Lee R. P., O'Donoghue, M. & Brandon M. R. (1997). *In vitro* testing of a pulsatile delivery system and its *in vivo* application for immunisation against tetanus toxoid. *J of Cont. Rel.*, Vol.47, No.3, (Sept. 1997), pp. 205-219, ISSN 0168-3659
2. Ertan G., Karasulu E., Demirtas D., Arici M. & Guneri T. (1997). Release characteristics of implantable cylindrical polyethylene matrices. *Journal of Pharmacy and Pharmacology*, Vol.49, No.3, (Nov. 1996), pp. 229-235, ISSN 0022-3573
3. Florjanczyk Z. & Penczek S. (1998). *Chemia polimerow*, Wydawnictwo Politechniki Warszawskiej, ISBN 83-86569-35-2, Warsaw, Poland
4. Huang S. J., Ho L-H., Hong E. & Kitchen O. (1994). Hydrophilic-hydrophobic εεεεbiodegradable polymers: Release characteristics of hydrogen-bonded, ring containing polymer matrices. *Biomaterials*, Vol.15, No.15, (Oct. 1994), pp. 1243-1247, ISSN 0142-9612
5. Janicki S., Fiebig, A. & Szmitowska M. (2002). *Farmacja stosowana*, PZWL, ISBN 83-20037-78-6, Warsaw, Poland
6. Muller R. H. & Hildebrand G. E. (1998). *Technologia nowoczesnych postaci lekow*, PZWL, ISBN 83-20022-06-1;Warsaw, Poland
7. Ouchi T. & Ohya Y. (1995). Macromolecular prodrugs. *Progress in Polymer Science (Oxford)*, Vol. 20, No.2, (January 1995), pp. 211-257, ISSN 0079-6700
8. Papamatheakis J. D.; Schultz R. M.; Chirigos M. A. & Massicot J. G. (1978). Cell and tissue distribution of ^{14}C-labeled pyran copolymer. *Cancer Treatment Reports*, Vol. 62, No.11, (Feb. 1978), pp. 1845-1851, ISSN 0361-5960
9. Tonnesen H. H. & Karlsen J. (2002). Alginate in drug delivery systems. *Drug Development and Industrial Pharmacy*, Vol.28, No.6, (Aug. 2001), pp. 621-630, ISSN 0363-9045
10. Zejc A. & Gorczyca M. (2002). *Chemia Lekow*, PZWL, ISBN 83-200-2709-8, Warsaw, Poland

ENTERIC COATING TECHNOLOGY

Anusha, Minakshi Gupta, Savitri

Assistant Professor, Shri Baba Mastnath University of Pharmaceutical Sciences And Research, Asthal Bohar, Rohtak (124001)

ABSTRACT

Of all the drug delivery systems, oral drug delivery remains the most preferred option for the administration of various drugs. As very few drugs are coming out of research and development and the existing drugs are suffering from the problem of resistance and side-effects as well, there is an ever-growing need to focus more on alternate methods of drug delivery. Recently, extended release and enteric-release technology has become a very useful tool in the medical practice as they overcome the problems of conventional oral therapy and offer numerous advantages as well. The delivery of drug to the intestinal region can be achieved by applying coating of enteric polymers on the solid dosage form. Colon-specific drug delivery is being evaluated as a promising option not only for colonic pathologies but for systemic absorption of drugs as well. Various semi-synthetic and synthetic polymers are being used for producing an enteric coated drug product to provide the desired site-specific effect. Enteric coating increases the stability of drugs in gastric fluids and dissolves in the intestinal pH to release the drug for absorption.

Keywords: Enteric coating, colon-specific delivery, systemic absorption, enteric coating polymers.

INTRODUCTION

Oral site-specific drug delivery systems have attracted a great deal of interest recently for the treatment of a variety of bowel diseases and also for improving systemic absorption of drugs, which are unstable in the stomach. However, the micro-environment in the gastrointestinal tract and varying absorption mechanisms generally cause hindrance for the formulation scientist in the development and optimization of oral drug delivery. Delivery of therapeutic agent into the intestinal region could be accomplished by the application of an enteric coating on a solid dosage form. Several approaches have been attempted and reported during the last decade to develop new methodologies for site-specific drug release, including pH sensitive drug release and time controlled drug release. Among these, the time controlled release systems such as sustained or delayed-release dosage forms are very promising. Nevertheless, due to the potentially large variation of gastric emptying time of dosage forms in human, these dosage forms may show high inter patient variability in the site of drug delivery. On the other hand, pH sensitive delivery systems such as enteric coating dosage forms offer a simple and practical means for intestinal drug delivery. Colon is being evaluated as a promising site for the drug delivery, not only for local colonic pathologies but also for the systemic drug delivery of protein and peptide drugs. This site may also be useful in the treatment of diseases susceptible to diurnal rhythm such as asthma, arthritis, etc. As a site for drug delivery, colon offers a near neutral pH, reduced digestive enzymatic activity, a long transit time and an increased responsiveness to absorption enhancers. This has led to the development of various systems for targeting drugs to the colon. These include pH-controlled release systems, enzyme-controlled delivery systems (including prodrugs and polysaccharides based delivery systems), time controlled release systems and pressure/ osmotically controlled release systems.

COATING OF SOLID DOSAGE FORMS

Film coating of solid dosage forms is a highly sophisticated process, first described in 19309. Its obvious advantages resulted soon in replacement of the traditional sugar coating by the emerging technology. Thus the first film-coated tablet became commercially available in 1954. The technology advanced with the introduction of the semi-synthetic cellulose derivatives and the synthetic acrylic polymers in the early 1950s.

FILM COATINGS ARE APPLIED FOR SEVERAL REASONS:

1. Taste masking and moisture/light protective coatings
2. Improved product appearance
3. Improved mechanical resistance (reduced friability)
4. Modified drug release (e.g. Gastric resistant or extended release coatings)

The properties and performance of the final coat is strongly affected by the polymer properties and the formulation parameters. The coating formulation may contain other major components besides the polymer such as solvent, plasticizer or pigments which can affect the performance of the coat by changing e.g. the mechanical properties.

BASED ON THEIR ORIGIN OR PREPARATION:

- Natural polymers
- Semi-synthetic polymers
- Synthetic polymers

NATURAL POLYMERS

Natural polymers are mostly subjected to several purification steps, but without chemical modification. Usually, related to their origin, they are mixture of different compounds, subjected to a certain variability of their composition and thus the variability in the resulting performance.

SEMI-SYNTHETIC POLYMERS

These are derivd from a natural substance, receiving its specific property after certain chemical modifications. E.g. the cellulose derivatives Synthetic polymers are fully chemically synthesized, e.g. methacrylic acid copolymers.

PROTECTIVE COATINGS

Sometimes, thin films of water soluble polymers are often applied for masking the unpalatable taste or odor, to improve the stability of moisture sensitive products or for better mechanical resistance of the coated product during handling16. Such protective coatings need to remain intact for the short time of swallowing the dosage form. Thereafter, they should dissolve instantaneously to assure immediate drug release without retardation. Polymers employed for this purpose are mostly water soluble, such as cellulose ethers (e.g. HPMC, PVA, PVP).

FUNCTIONAL COATINGS

Film coatings applied to achieve a certain desired release profile of the incorporated drug are generally called functional or modified-release coatings. Those, intended to protect the drug from the acidic environment of the gastric medium or to prevent the drug release in this part of GIT, are commonly called enteric coatings. Extended-release coatings, in contrast, are required to control the release of the drug over a prolonged period of time.

EXTENDED RELEASE COATINGS

The patient compliance is strongly decreasing in cases where multiple daily administrations are necessary to maintain constant blood levels of the drug. Thus, extended release polymers were developed to provide a sustained action by releasing the drug in a controlled manner over a period of time. Waxes and some natural polymers were already discovered earlier to be useful for this purpose. Their mechanism of drug release is based on slow degradation or erosion.

ENTERIC COATINGS

An enteric coating is a barrier applied to oral medication that controls the location in the digestive tract where it is absorbed. Enteric refers to the small intestine; therefore enteric coating on the dosage form prevents the release of drug before it reaches the small intestine. Most enteric coatings work by presenting a surface that is stable to highly acidic pH of stomach, but breaks

down rapidly at a less acidic (relatively more basic) pH. Enteric coating is suitable for drugs that have irritant effect in stomach (like aspirin), drugs which are unstable in acidic pH of stomach. Thus, enteric coating is aimed to prevent the formulations from gastric fluid in the stomach and release the drug component in the intestinal region or once it has passed into the duodenum.

Some of the most important reasons for the application of enteric coating to the dosage form are as follows:

1. To protect the acid-labile drugs from the acidic pH of gastric fluid. Example: enzymes and certain antibiotics.
2. To prevent gastric distress or nausea due to irritation caused by certain drugs.
3. Example: Sodium salicylate.
4. To deliver drugs intended for the local action in intestines. Example: intestinal antiseptics could be delivered to their site of action in a concentrated form and bypass systemic absorption in the stomach.
5. To deliver drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.
6. To provide a delayed release component to repeat action tablets.

ENTERIC COATING POLYMERS

An ideal enteric coating material should possess the following properties:

1. Resistance to gastric fluids.
2. Ready susceptibility to or permeability to intestinal fluids.
3. Compatibility with most of the coating solution components and the drug substances.
4. Stability alone and in the coating solutions i.e. the film should not change upon aging.
5. Formation of a continuous film on the dosage form.
6. Non-toxic and non-irritant.
7. Low cost.
8. Ease of application without specialized equipment.
9. Ability to be readily printed or to allow film to be applied to debossed tablets.

Enteric coating polymers can be classified into 3 groups based on chemical compositions as listed below:

1. Polymethacrylates
    - Methacrylic acid / Ethyl acrylate
    -
2. Cellulose esters
    - Cellulose acetate phthalate (CAP)
    - Cellulose acetate trimellitate (CAT)
    - Cellulose acetate succinate
    - Hydroxyl propyl methyl cellulose acetate succinate (HPMCAS)
    - Hydroxyl propyl methyl cellulosephthalate
3. Polyvinyl derivatives
    - Polyvinyl acetate phthalate (PVAP)

Commercial enteric polymers are available as powder, aqueous dispersions and organic solution.

CONCLUSION

By the above discussion, it can be easily concluded that enteric coated drug products are helpful in increasing the efficiency of the dosage form and overcoming the problems of patient compliance and conventional therapy. The market for enteric coated products has come a long way and will continue to grow in future with further advancements in the technology. At present

there remains a scarcity of new polymeric materials but one unique approach is to use the combinatorial methods to design arrays of new polymeric materials. Thus, colon specific drug delivery offers a wide scope for drug targeting techniques and improved bioavailability of active drug molecule as well.

REFERENCES

1. Fukui E, Miyamura N, Uemera K, et al. Preparation of enteric coated timed-release press-coated tablets and evaluation of their function by in vitro and in vivo tests for colon targeting. Int. J. Pharm. 2000; 204: 7- 15.
2. Rubinstein A, Approaches and opportunities in colon specific drug delivery, Crit. Rev. Ther. Drug Carrier Syst. 1995; 12: 101-149.
3. Tozer T N, Friend D R, McLeod A D. Kinetic perspectives in colonic delivery. S.T.P. Pharma Sci. 1995; 5: 5-28.
4. Kinget R, Kalale W, Vervoort L, Mooter G V. Colonic drug targeting. J. Drug Target. 1998; 6: 129-149.
5. Sinha V R, Kumria R. Polysacchharides in colon specific drug delivery: A review. Int. J. Pharm. 2001; 224: 19-38.
6. Sinha V R, Kumria R. Colonic drug delivery: prodrug approach. Pharm Res. 2001; 18: 557-564.
7. Leopold C S. Coated dosage form for colon specific drug delivery. Pharm. Sci. Tech Today. 1999; 5: 197-204.
8. Kibbe A H. Kibbe A H: Handbook of Pharmaceutical Excipients. 3rd ed. London: Pharmaceutical press; 2000, 99-101, 462-464.

NANOTECHNOLOGY: A CONCISE REVIEW

Minakshi Gupta*, Anusha Rohilla

Deptt of Pharm Sciences, Baba Mast Nath University, Asthal Bohar (Rohtak) Haryana e-mail: minakshi.sbmnipsr@gmail.com

ABSTRACT:

Nanoparticulate technology is of particular use in developing a new generation of more effective cancer therapies capable of overcoming many biological, biophysical and biomedical barriers that the body stages against a standard intervention. Targeted delivery of drug molecules to tumor tissue is one of the most interesting and challenging endeavors faced in pharmaceutical field, due to the critical and pharmacokinetically specific environment that exists in tumor. Over these years, cancer targeting treatment has been greatly improved by new tools and approaches based on nanotechnology. Nanoparticles show much promise in cancer therapy by selectively gaining access to tumor due to their small size and modifiability.

KEYWORDS: Nanotechnology; Cancer, Liposomes, Nanomedicine, Carbon nanotubes.

INTRODUCTION

Nanocarriers emerged as powerful tools for drug delivery, imaging and diagnosis due to their size, ease to architect and surface modification characteristics. Various nanocarriers including liposomes, dendrimers, nanocrystals, magnetic nanoparticles, nanogels and biodegradable nanoparticles possesses increase drug bio-availability and reduce side effects. Nanotechnology offers great opportunities to improve and aid these conventional therapies by virtue of its nanotools [1]. Targeting and localized delivery are the main challenges in cancer therapy. Development of functional and multifunctional system for active and passive delivery can be help to overcome these challenges. The approaches for nanoparticles are basically targeted to the pathophysiology of diseased sites like leaky vasculature of the cancer tissues. The nanocarriers can alter the pharmacokinetic parameters and the biodistribution of the anticancer drug in significant amount as compared to free drug due to nano size of the carrier. Nanocarriers are 1–1000 nm sized drug delivery systems which emerged as powerful tools for drug delivery, imaging and diagnosis due to their size, simple preparation methods and surface modification characteristics. Various drug delivery and drug targeting systems including liposomes, dendrimers, nanocrystals, liposomes, magnetic nanoparticles, nanogels and biodegradable nanoparticles increase drug bio-availability and reduce side effects [2]. In this review, we first discuss the the various nanotechnology based drug delivery and drug targeting srategies including liposomes, dendrimers, carbon nanotubes, nanocrystals and biodegradable nanoparticles. Secondly, we discuss various methods of preparation of nanoparticles. We also discuss various selective targeting strategies using nanoparticles with special emphases on Poly(ethylene glycol)-modified nanoparticles both by passive and active targeting for achieving effective cancer treatment

Liposomes were described by a british hematologist Prof Alec D. Bangham as spherical phospholipid vesicles composed of a bilayer membrane which surrounds an aqueous interior. But these conventional liposomes have major limitations as they are rapidly cleared by RES due to adsorption of opsonin proteins on the phospholipid membrane of liposomes. This limitation is overcome by PEGylated liposomes. PEGylated liposomes also known as sterically stabilized or 'Stealth' liposome which prevents opsonization, hence engulfment by mononuclear phagocytes is

avoided and prolonged circulation is achieved . Liposomal drug delivery to tumor is affected by long circulation time, stability (drug retention) and small vesicle size of liposome [3].

Dendrimers are highly branched molecule of size 1–15 nm with a well-defined core, an interior region, and a large number of end groups. Dendrimers contain three different regions: core, branches and surface. The water solubility, monodispersity, encapsulation ability, and large number of functionalizable peripheral groups of dendrimers make these an ideal carrier for drug delivery [4,5].

Carbon nanotubes are large molecules of carbon atoms that was discovered in the late 1980s. In the field of cancer, carbon nanotubes have generally been used for the transportation of DNA cargoes into the cell and for thermal ablation therapy, in the same way as that of nanoshells. Past efforts to deliver siRNA to target cells have often been effected by the instability of siRNA and low efficiency of uptake [6].

Polymeric nanoparticles are better alternative than other nanosystems due to their inherent properties such as biocompability, nonimmunogenicity, nontoxicity, and biodegradability. Polymeric nanoparticles are versatile drug delivery system, which has ability to overcome physiological barriers, and guide the drugs to specific cells or intracellular compartments; either by passive or ligand mediated targeting approaches [7]. The release pattern of drug can be controlled by selecting the appropriate polymeric carriers [8] . Nanoparticles with size less than100 nm and with hydrophilic surfaces are relatively less prone to opsonization and clearance by RES uptake which helps in targeted drug delivery to tissues other than the RES and thus circulation time of nanoparticles get prolonged in the blood. Such long circulating nanoparticles are known as 'sterically stabilized nanoparticles' or 'biomimetic nanoparticles' [9]. Functionalized nanoparticles are gaining widespread attention now a days. Polymeric nanoparticles systems are attractive modules for site- specific delivery. Nanoparticles can be made to reach a target site with the help of their size and surface modification with site specific recognition ligands [10]. Functionalized polymeric nanoparticles can provide controlled spatial and temporal delivery of biologically active substances to desired sites. The application of various nanosystems in cancer treatment is enlisted in table 1.

Table 1: Applications of various nanosystems in cancer therapy[11]

Nanosystem	**Size**	**Applications in cancer therapeutics**
Nanoparticles	10-1000nm	Targeted drug delivery, MRI and ultrasound image contrast agents, angiogenesis, permeation enhancers, reporters of apoptosis etc.
Nanocrystals	100nm	Improved formulation for poorly-soluble drugs
Nanowires	Variable length/diameter	DNA mutation detection, Disease protein biomarker detection, gene expression detection
Nanoshells	60-400nm	Tumor-specific imaging, deep tissue thermal ablation
Liposome	100-200nm	Controlled release drug delivery
Quantum dots	2-10nm	Optical detection of genes and proteins in animal models and cell assays, tumor and lymph node visualization.
Carbon nanotubes Single-walled	1-2nm diameter, variable length	DNA mutation detection, disease protein biomarker detection

Multi-walled	20-25nm diameter,variable length	

These nanotools treat the abnormal cells, detect mutation or identify biomarker in cancer cell by (i) thermotherapy by photo-thermal ablation therapy using silica nanoshells, carbon nanotubes; magnetic field-induced thermotherapy using magnetic nanoparticles[12]; photodynamic therapy by quantum dots as photosensitizes and carriers [13], (ii) chemotherapy by nano-structured polymer nanoparticles, dendrimers and nanoshells, and (iii) radiotherapy by carbon nanotubes, dendrimers for boron neutron capture therapy[14]. Representative examples of nanocarrier-based drugs have been illustrated in Table 2.

Table2: Representative examples of nanocarrier-based drugs

Nanocarrier	Compound	Indication	Reference
Nanocrystals	Fenofibrate	Treatment of high cholesterol level	[15]
Polymeric micelles	Doxorubicin, Paclitaxel	Cancer targeting	[16,17]
Albumin bound nanoparticles	Paclitaxel	Metastatic Breast cancer	[18]
Liposomes	Doxorubicin	Combination therapy of recurrent breast cancer, ovarian cancer, Kaposi's sarcoma	[19]
Liposomes	Daunorubicin	Kaposi's sarcoma	[20]
Nanoparticle	Vincristine	Relapsed aggressive non-Hodgkin's lymphoma (NHL)	[21]
Nanolipidic particle	Polyphenol	Alzheimer's disease	[22]
Single walled carbon nanotubes	Acetylcholine	Neurotransmitter	[23]
nanocapsule	Indomethacin	Inflammation	[24]
Liposomes	Amphotericin-B	Severe fungal infection	[25]

REFERENCES:

1. Jagdale G, Warad S: Nanocochelates: a novel approach. World Journal of Pharmacy and Pharmaceutical Sciences 2013, 2(5): 2539-2559.
2. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R: Nanocarriers as an emerging platform for cancer therapy. Nature Nanotechnology 2007, 2: 751-760.
3. Samad A, Sultana Y, Aqil M: Liposomal drug delivery systems: an update review. Curr Drug Deliv 2007, 4(4): 297-305.
4. Morgan MT, Nakanishi Y, Kroll DJ, Griset AP, Carnahan MA, Wathier M, Oberlies NH, Manikumar G, Wani MC, Grinstaff MW: Dendrimers-encapsulated camptothecins: increase solubility, cellular uptake and cellular retention affords enhanced anticancer activity in vitro. Cancer Research 2006, 66(24): 11913-11921.
5. Malik A, Chaudhary S, Garg G, Tomar A: Dendrimers: A tool for drug delivery. Advances in Biological Research 2012, 6(4): 165-169.
6. Kelly Y, Kim MA: Oncology nanotechnology platforms and physiological challenges for cancer therapeutics. Nanomedicine: nanotechnology, biology and medicine 2007, 3: 103-110.

7. Jawahar N, Meyyanathan SN: Polymeric nanoparticles for drug delivery and targeting: A comprehensive review. Int J Health Allied Sci 2012, 1(4): 217-223
8. Vlerken LE, Amiji MM: Multi-functional polymeric nanoparticles for tumour targeted drug delivery. Expert Opin. Drug Deliv 2006, 3(2): 205-216.
9. Pandey S, Kumar S: An overview on multifunctional nanomedicines for targeted drug delivery. IJPI's journal of pharmaceutics and cosmetology 2011, 1(3): 119-28.
10. Sha J, Kaiming Y: Nanoparticle-mediated drug delivery and gene therapy. Biotechnology 2007, 23(1): 32-41.
11. Nahar M, Dutta T, Murugesan S, Asthana A, Mishra D, Rajkumar V, Tare M, Saraf S, Jain NK: Functional polymeric nanoparticles: an efficient and promising tool for active delivery of bioactives. Crit Rev Ther Dr ug Carrier Syst 2006, 23(4): 259-318.
12. Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, Felix R, Schlag PM: Hyperthermia in combined treatment of cancer. The Lancet Oncology 2002, 3: 487–497.
13. Juarranz A, Jaen P, Rodríguez FS, Cuevas J, Gonzalez S: Photodynamic therapy of cancer. Basic principles and applications. Clinical and Translational Oncology 2008, 10: 148-154.
14. Murphy JO, Sacchini VS: New innovative techniques in radiotherapy for breast cancer. Minerva Chir 2013, 68(2): 139-154.
15. Zuo B, Sun Y, Li H, Liu X, Zhai Y, Sun J, He Z: Preparation and in vitro/in vivo evaluation of fenofibrate nanocrystals. Int J Pharm 2013, 455(1-2): 267-75.
16. Kim D, Lee ES, Oh KT, Gao ZG, Bae YH: Doxorubicin-loaded polymeric micelle overcomes multidrug resistance of cancer by double-targeting folate receptor and early endosomal pH. Small 2008, 4(11):2043-50.
17. Saif MW, Podoltsev NA, Rubin MS, Figueroa JA, Lee MY, Kwon J, Rowen E, Yu J, Kerr RO: Phase II clinical trial of paclitaxel loaded polymeric micelle in patients with advanced pancreatic cancer. Cancer Invest 2010, 28(2):186-94.
18. Cortes J, Saura C: Nanoparticle albumin-bound (*nab*™)-paclitaxel: improving efficacy and tolerability by targeted drug delivery in metastatic breast cancer. **EJC Supplements 2010, 8(1): 1-10.**
19. Yang Z, Zhang Y, Yang Y, Sun L, Han D, Li H, Wang C: Pharmacological and toxicological target organelles and safe use of single-walled carbon nanotubes as drug carriers in treating Alzheimer disease. Nanomedicine 2010,
20. Harris L, Batist G, Belt R, Rovira D, Navari R, Azarnia N, Welles L, Winer E; TLC D-99 Study Group: Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicenter trial as first-line therapy of metastatic breast carcinoma.Cancer 2002, 94(1): 25-36 .
21. Song X, Zhao Y, Wu W, Bi Y, Cai Z, Chen Q, Li Y, Hou S: PLGA nanoparticles simultaneously loaded with vincristine sulfate and verapamil hydrochloride: systematic study of particle size and drug entrapment efficiency. Int J Pharm 2008, 350(1-2):320-9.
22. Smith A, Giunta B, Bickford PC, Fountain M, Tan J, Shytle RD: Nanolipidic particles improve the bioavailability and alpha-secretase inducing ability of epigallocatechin-3-gallate (EGCG) for the treatment of Alzheimer's disease. Int J Pharm 2010, 389(1-2): 207-12.
23. Yang Z, Zhang Y, Yang Y, Sun L, Han D, Li H, Wang C: Pharmacological and toxicological target organelles and safe use of single-walled carbon nanotubes as drug carriers in treating Alzheimer disease. Nanomedicine 2010.
24. Miyazaki S, Takahashi A, Kubo W: Poly n-butylcyanoacrylate (PNBCA) nanocapsules as a carrier for NSAIDS: In vitro release and in vivo skin penetration. **J Pharm Pharmaceut Sci 2003, 6(2): 238-245.**
25. Moen MD, Lyseng-Williamson KA, Scott LJ: Liposomal amphotericin B: a review of its use as empirical therapy in febrile neutropenia and in the treatment of invasive fungal infections. Drugs 2009, 69(3): 361-92.

HIV-AIDS - FACTS AND FIGURES

Balvinder Singh, Anuradha Pannu, Pawan Jalwal, Rajiv Kumar Arora

Deptt. of Pharma. Sciences, Baba Mastnath University, Asthalbohar (Rohtak) Haryana. E-mail-balvindersinghpharmaco@gmail.com

ABSTRACT

AIDS is one of the most dreaded infectious threats to human health. Millions of people have been infected with HIV and the syndrome remains among the top five fatal diseases. The causative agent for the disease, the HIV, which is a retrovirus has two subtypes of HIV; the most common is HIV-1 which occurs world over, and HIV-2 found mainly in Africa. The HIV infection causes depletion of CD4+ lymphocytes and that result in cellular immunodeficiency. WHO is putting their best efforts in curbing this menace.

KEYWORDS : AIDs, HIV, CD4+, T- lymphocytes, DNA, RNA.

INTRODUCTION

AIDS is one of the most dreaded infectious threats to human health. Millions of people have been infected with HIV and the syndrome remains among the top five fatal diseases (1).The causative agent for the disease, the HIV, which is a retrovirus has two subtypes of HIV; the most common is HIV-1 which occurs world over, and HIV-2 found mainly in Africa(2). AIDS has resulted in millions of deaths; and the WHO estimates that approximately 40.3 million peoples were living with HIV as of December 2005. The HIV infection causes depletion of CD4+ lymphocytes and that result in cellular immunodeficiency. The virus targets primarily the CD4+ T lymphocytes and cells of the monocyte macrophage lineage but also invades the CNS targeting brain macrophages and microglia (3).

THE HIV- 1 LIFE CYCLE

AIDS is caused by human immunodeficiency virus type 1 (HIV-1), a member of family of retroviruses that possess complex genomes and exhibit cone-shaped capsid core particles (4-6). The general features of mature HIV virion and ribbon representation of structurally characterized viral proteins are shown in figure 1.1 and figure 1.2 present the general scheme of HIV replication cycle (7). It contains six steps. The replication cycle starts by the binding of the virus envelope protein to CD4+ on the cell surface, a protein that normally functions in immune recognition. The viral protein then fuses into the cell membrane (8-11) after un-coating of the virus, an intracellular reverse transcriptase catalyzes the reverse transcription of the viral RNA in the cytosol. The mechanism of this RT-dependent DNA synthesis has been well studied in-vitro and in-vivo (12-14). Once synthesized, the viral cDNA is translocated to the nucleus with matrix protein, IN and other viral proteins as a preintegration complex (15).

The viral cDNA is then integrated into the host genome by the catalytic action of IN. Multiple unspliced and spliced mRNA are synthesized and transported out of the nucleus for translocation. The translocation is a very complicated process initialized by the synthesis of regulatory protein Tat, Rev and Nef, and then the polypeptides: Gag and Gag-pol and protease are formed. Viral RNA and the proteins assemble at the host cell surface and buds from the cell surface to form an immature particle.

Finally, as protease cleaves polyproteins into structural proteins, such as the matrix protein p17 (MA), capsid protein p24 (CA) and nucleocapsid protein p7 (NC) and functional enzymes (including itself), the structural proteins rearrange and forms the mature infectious virus particle. The whole life cycle is usually divided into two phases: early phase ends with the integration of

the viral genetic information into the chromosome of the host cell, while the late phase includes viral protein expression and virus maturation(7).

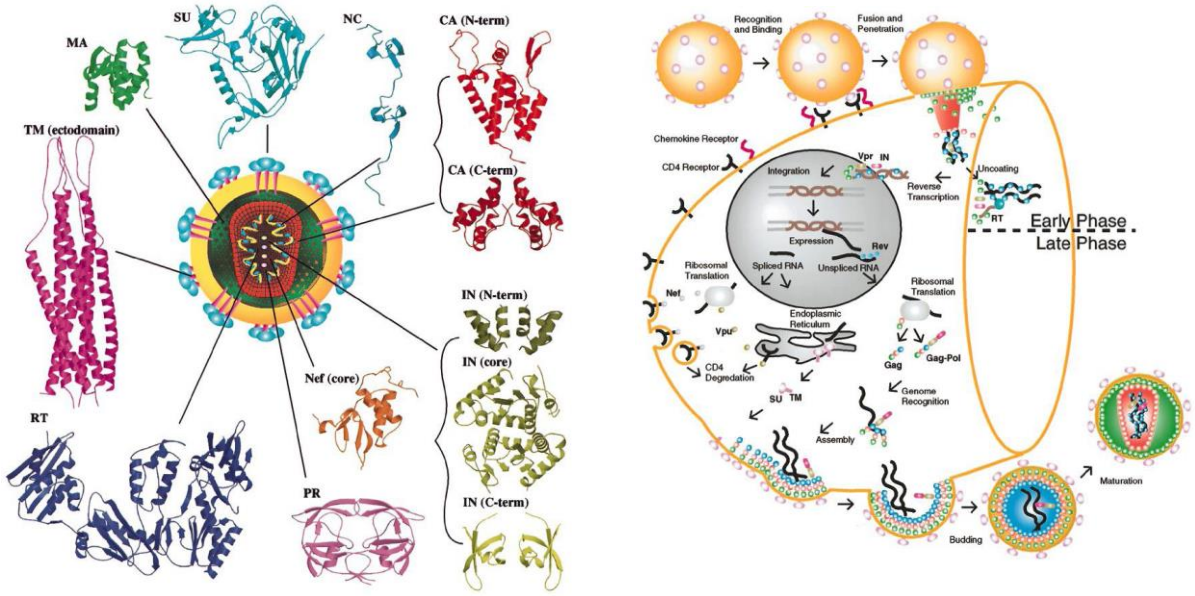


Figure 1: Representation of HIV-1 virion surrounding by the known structure of viral proteins and protein fragments(7). *SU: surface glycoprotein gp 120, MA: matrix protein p17, TM: transmembrane protein gp41, RT: reverse transcriptase, PR: protease,IN: integrase, CA: capsid protein p24, NC: nucleocapsid protein p7.*

Figure 2: General features of HIV-1 life cycle(7).

HIV/AIDS - Key facts(16) as on 2013

- HIV continues to be a major global public health issue, having claimed more than 39 million lives so far. In 2013, 1.5 [1.4–1.7] million people died from HIV-related causes globally.
- There were approximately 35.0 [33.2–37.2] million people living with HIV at the end of 2013 with 2.1 [1.9–2.4] million people becoming newly infected with HIV in 2013 globally.
- Sub-Saharan Africa is the most affected region, with 24.7 [23.5–26.1] million people living with HIV in 2013. Also sub-Saharan Africa accounts for almost 70% of the global total of new HIV infections.
- HIV infection is usually diagnosed through blood tests detecting the presence or absence of HIV antibodies.
- There is no cure for HIV infection. However, effective treatment with antiretroviral (ARV) drugs can control the virus so that people with HIV can enjoy healthy and productive lives.
- In 2013, 12.9 million people living with HIV were receiving antiretroviral therapy (ART) globally, of which 11.7 million were receiving ART in low- and middle-income countries. The 11.7 million people on ART represent 36% [34–38%] of the 32.6 [30.8–34.7] million people living with HIV in low- and middle-income countries.

- Paediatric coverage is still lagging in low- and middle-income countries. In 2013 less than 1 in 4 children living with HIV had access to ART, compared to over 1 in 3 adults.

The most advanced stage of HIV infection is **Acquired Immunodeficiency Syndrome (AIDS)**, which can take from 2 to 15 years to develop depending on the individual. AIDS is defined by the development of certain cancers, infections, or other severe clinical manifestations.

SIGNS AND SYMPTOMS

The signs and symptoms of HIV vary as per the stage of infection. There bmay be no symptoms or an influenza-like illness including fever, headache, rash or sore throat. As the infection progresses, the individual can develop other signs such as swollen lymph nodes, weight loss, fever, diarrhoea and cough which later may develop into severe illnesses such as tuberculosis, cryptococcal meningitis, and cancers such as lymphomas and Kaposi's sarcoma etc.

TRANSMISSION

HIV can be transmitted via the exchange of a variety of body fluids from infected individuals, such as

- blood,
- breast milk,
- semen and
- vaginal secretions.

Please note that any individual cannot become infected through ordinary day-to-day contact such as kissing, hugging, shaking hands, or sharing personal objects, food or water.

RISK FACTORS FOR CONTRACTING HIV

- sharing contaminated needles, syringes;
- having unprotected sex;
- receiving unsafe injections, blood transfusions and
- medical procedures that involve unsterile cutting or piercing.

PREVENTION

1. Male and female condom use
2. Testing and counselling for HIV and STIs
3. Voluntary medical male circumcision
4. Antiretroviral (ART) use for prevention
5. Harm reduction for injecting drug users
6. Elimination of mother-to-child transmission of HIV (eMTCT)

REFERENCES:

1. Montagnier L. Origin and evaluation of HIVs and their role in AIDS pathogenesis. Journal of Acquired Immunodeficiency Syndrome 1988; 1:517-20.
2. Singh H, Kapoor VK. Antiviral Drugs In: Medicinal and Pharmaceutical Chemistry. Second ed. Delhi: Vallabh Prakashan; 2009.
3. Bagasra O, Lavi E, L.Bobroski, Khalili K, Pestaner JP, Tawadros R, et al. Cellular reservoirs of HIV-1 in the central nervous system of infected individuals: Identification by the combination of in situ polymerase chain reaction and immunohistochemistry. AIDS 1996; 10:573-85.
4. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immunodeficiency syndrome (AIDS). Science 1983; 220(4599):868-71.

5. Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and risk for AIDS. Science 1984; 224(4684):500-3.
6. Levy JA, Hoffmann AD, Kramer SM, Landis JA, Shimabukuro JM, Oshiro LS. Recovery of AIDS-associated retroviruses from patients with AIDS or AIDS related conditions and clinically healthy individuals. J infect Dis 1984; 152:734-8.
7. Turner BG, Summers MF. Structural biology of HIV. J Mol Biol 1999; 285(1):1-32.
8. Doranz BJ, Rucker J, Yi Y, Smyth RJ, Samson M, Peiper SC, et al. A dual-tropic primary HIV-1 isolate that uses fusin and the beta-chemokine receptors CKR-5, CKR-3 and CKR-2b as fusion cofactors. Cell 1996; 85(7):1149-58.
9. Feng Y, Broder CC, Kennedy PE, Berger EA. HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. Science 1996; 272:872-7.
10. Clapham PR, Weiss RA. Immunodeficieny viruses. Spoilt for choice of coreceptors. Nature 1997; 388:230-1.
11. Moore JP. Coreceptors: implications for HIV pathogenesis and therapy. Science 1997; 276(5309):51-2.
12. Goff SP. Retroviral reverse transcriptase: synthesis, structure, and function. J Am Chem Soc 1990; 116:1581-2.
13. Whitcomb JM, Hughes SH. Retrovirus reverse transcription and integration: progress and problems. Annu Rev Cell Biol 1992;8:275-306.
14. Katz RA, Skalka AM. The retroviral enzymes. Annu Rev Biochem 1994; 63:133- 73.
15. Miller MD, Farnet CM, Bushman FD. Human immunodeficiency virus type 1 preintegration complexes: studies of organization and composition. J Virol 1997; 71(7):5382-90.
16. Fact sheet N°360, Updated November 2014, WHO

LEAD OPTIMIZATION IN DRUG DISCOVERY & DEVELOPMENT

Arun Kumar*, Dr. Rajiv Tonk, Pawan Jalwal

Faculty of pharmaceutical sciences, baba mastnath university, asthal bohar, rohtak-124021

ABSTRACT

The synthetic modification of a biologically active compound, to fulfil all stereoelectronic, physicochemical, pharmacokinetic and toxicological properties required for clinical usefulness. The new lead optimization paradigm demands that companies move to parallel processes that evaluate binding affinity, ADME, drug properties, etc. earlier in the process in order to cut the time and costs lost in failed leads. Lead optimization methods has become one of the primary focuses of research organizations involved in drug discovery in the last decade. Chemical lead optimization from high-throughput screening (HTS) to clinical candidate identification is now one seamless process that draws on new technologies for accelerated synthesis, purification, and screening of directed, iterative compound libraries. Advances In high-throughput screening technologies allow detection of new allosteric modes of target modulation, which provides new chemotypes and target opportunities. With the incorporation of drug metabolism and pharmacokinetics (DMPK) inputs early in the lead optimization work flow, molecules are not optimized solely for target potency and selectivity. Moreover, "closed-loop" work flows are in place such that synthesis and primary screening operate on a 1-week turnaround for up to 48 compounds/week with DMPK data cycling every other week to guide compound design, which provides expedited timelines for the development of proof-of-concept compounds and clinical candidates with limited human resources.

INTRODUCTION

Lead optimization in drug discovery has changed significantly over the past five years and no longer is fragmented into separate hit-to-lead and lead optimization phases. Hit to lead (H2L) also known as lead generation is a stage in early drug discovery where small molecule hits from a high throughput screen (HTS) are evaluated and undergo limited optimization to identify promising lead compounds. These lead compounds undergo more extensive optimization in a subsequent step of drug discovery called lead optimization (LO). The drug discovery process generally follows the following path that includes a hit to lead stage:

- target validation (TV) → assay development → high-throughput screening → hit to lead (H2L) → lead optimization (LO) → preclinical drug development → clinical drug development

The hit to lead stage starts with confirmation and evaluation of the initial screening hits and is followed by synthesis of analogs (hit expansion). Typically the initial screening hits display binding affinities for their biological target in the micromolar (10^{-6} molar concentration) range. Through limited H2L optimization, the affinities of the hits are often improved by several orders of magnitude to the nanomolar (10^{-9} M) range. The hits also undergo limited optimization to improve metabolic half life so that the compounds can be tested in animal models of disease and also to improve selectivity against other biological targets binding that may result in undesirable side effects.

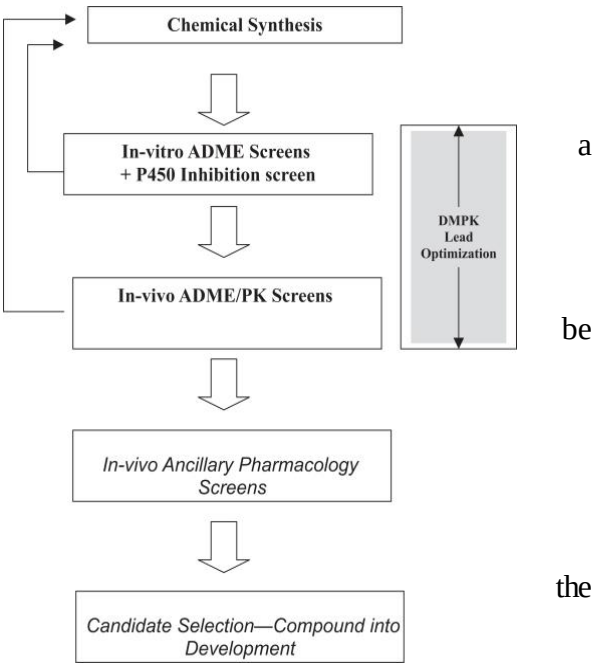
LEAD GENERATION AS PART OF NEW DRUG DISCOVERY

Contemporary parallel and combinatorial chemical synthesis produces large arrays of compounds that are available for evaluation in new drug discovery. Furthermore, other improvements by structural chemists using a variety of tools, such as X-ray crystallography, structural modeling and ligand/substrate docking algorithms, and by molecular biologists developing high-throughput binding targets and cell-based activity assays provide drug discovery scientists with an unprecedented level of structural-based rational designs to guide the synthesis

of new chemotypes as potential drug leads. Along with the advancement of chemistry and biology, new automated *in vitro* activity screening tools have become commercially available which can carry out complex, programmable and adaptable robotic operations to test hundred of thousands of compounds in a speedy and precise manner. As a result, these new forces have worked together to increase our ability to create new chemical entities (NCEs) that exhibit the targeted pharmacological activity.

Lead Optimization:

In order to understand the needs of lead optimization, it is important to define the basic characteristics of drug-like leads. As shown in Table1, there are at least five essential properties that need to be considered in order for a compound to be drug-like: potency, bioavailability, duration, safety and reasonable pharmaceutical properties. In addition, there are some other important properties, such as selectivity, efficacy and dose-proportionality, to be considered. A successful clinical drug candidate must at least meet the minimal acceptance criteria for each of these five properties for the type of drug program that is being developed. A major deficit in any one of the properties may prevent the compound from progressing from the drug development stage to the clinical phase or to the market. During the discovery phase of lead optimization, the goal of the process is to find NCEs that fall into the acceptable range for each of these five properties. Among the five essential properties, three belong to the domain of DMPK: oral bioavailability, duration and safety issues. Hence, the lead optimization in discovery DMPK could be divided into three categories.



Nature of lead optimization leading to candidate.

Table 1

Property	**Definition/ Requirement**
Potency	The intrinsic ability of a compound to produce a desirable pharmacological response (usually measured via high throughput in vitro screens)
Oral Bioavailability	The ability of a compound to pass through multiples barriers, such as the GI tract and the liver in order to reach the target
Duration (Half-life)	The ability of the compound to remain in circulation (or at the target site) for sufficient time to provide a meaningful pharmacological response
Safety	The compound has sufficient selectivity for the targeted response relative to non-targeted responses so that an adequate therapeutic index exists
Pharmaceutical Acceptability	The compound has suitable pharmaceutical properties, such as a reasonable synthetic pathway, adequate aqueous solubility, reasonable rate of dissolution, good chemical stability, etc.

GENERAL PROPERTIES OF DRUG-LIKE LEAD COMPOUNDS.

Lead compounds that survive the initial screening are then "optimized," or altered to make them more effective and safer. By changing the structure of a compound, scientists can give it different properties. For example, they can make it less likely to interact with other chemical pathways in the body, thus reducing the potential for side effects. Hundreds of different variations or "analogues" of the initial leads are made and tested. Teams of biologists and chemists work together closely: The biologists test the effects of analogues on biological systems while the chemists take this information to make additional alterations that are then retested by the biologists. The resulting compound is the candidate drug. Even at this early stage, researchers begin to think about how the drug will be made, considering formulation (the recipe for making a drug, including inactive ingredients used to hold it together and allow it to dissolve at the right time), delivery mechanism (the way the drug is taken – by mouth, injection, inhaler) and large-scale manufacturing (how you make the drug in large quantities)

Hit Conformation

After hits are identified from a high throughput screen, the hits are confirmed and evaluated using the following methods:

- Re-testing: compounds that were found active against the selected target are re-tested using the same assay conditions used during the HTS.
- Dose response curve generation: several compound concentrations are tested using the same assay, an IC_{50} or EC_{50} value is then generated.
- Orthogonal testing: Confirmed hits are assayed using a different assay which is usually closer to the target physiological condition or using a different technology.
- Secondary screening: Confirmed hits are tested in a functional assay or in a cellular environment. Membrane permeability is usually a critical parameter.
- Chemical amenability: Medicinal chemists evaluate compounds according to their synthesis feasibility and other parameters such as up-scaling or costs
- Biophysical testing: Nuclear magnetic resonance (NMR), Isothermal Titration Calorimetry, dynamic light scattering, surface plasmon resonance, dual polarisation interferometry, microscale thermophoresis (MST) are commonly used to assess whether the compound binds effectively to the target, the stoïchiometry of binding, any associated conformational change and to identify promiscuous inhibitors.
- Hit ranking and clustering: Confirmed hit compounds are then ranked according to the various hit confirmation experiments.
- Freedom to operate evaluation: Hit compound structures are quickly checked in specialized databases to determine if they are patentable

Hit Expension

Following hit confirmation, several compound clusters will be chosen according to their characteristics in the previously defined tests. An Ideal compound cluster will:

- have compound members that exhibit a high affinity towards the target (less than 1 µM)
- Moderate molecular weight and lipophilicity (usually measured as cLogP). Affinity, molecular weight and lipophilicity can be linked in single parameter such as ligand efficiencyand lipophilic efficiency to assess druglikeness
- show chemical tractability
- be free of Intellectual property
- not interfere with the P450 enzymes nor with the P-glycoproteins
- not bind to human serum albumin
- be soluble in water (above 100 µM)

- be stable
- have a good druglikeness
- exhibit cell membrane permeability
- show significant biological activity in a cellular assay
- not exhibit cytotoxicity
- not be metabolized rapidly
- show selectivity versus other related targets

The project team will usually select between three and six compound series to be further explored. The next step will allow the testing of analogous compounds to define Quantitative structure-activity relationship (QSAR). Analogs can be quickly selected from an internal library or purchased from commercially available sources. Medicinal chemists will also start synthesizing related compounds using different methods such as combinatorial chemistry, high-throughput chemistry or more classical organic chemistry synthesis.

LEAD OPTIMIZATION PHASE

The objective of this drug discovery phase is to synthesize lead compounds, new analogs with improved potency, reduced off-target activities, and physiochemical/metabolic properties suggestive of reasonable *in vivo* pharmacokinetics. This optimization is accomplished through chemical modification of the hit structure, with modifications chosen by employing knowledge of the structure-activity relationship (SAR) as well as structure-based design if structural information about the target is available.

Lead optimization is concerned with experimental testing and confirmation of the compound based on animal efficacy models and ADMET (*in vitro* and *in situ*) tools.

Application of ADME-Tox tools has increased the success rate of drug development as well as helped in reducing the cost and time factors. The use of *in silico* and *in vitro* ADME-Tox has found universal acceptance. *In silico* tools provide a much higher throughput, but they suffer from adequate predictability, which limits their use. However, the reliance on*in silico* models is due to their ability to predict which compounds should be synthesized based on confirmed hits and structural modifications since it helps in selecting a drug-like compound. The best way to implement the ADME-Tox property prediction is the integration of both *in silico* and *in vitro* approaches to supplement each other for the production of candidate drugs.

COMPOUND LIBRARY

A ‘compound library’ is a collection of compounds, just as we use ‘library’ for a collection of books. Like a book library the variety of compounds (diversity) in the collection can be very narrow (e.g. specialist Ferens library), very big but relatively narrow (Brynmor Jones, academic), big and diverse (city library). Compound libraries can therefore be the screened of lead compounds as often they have been made for totally different projects (e.g. antifungal agent naftifine was a by-product from chemical research into new agents for treating disorders of the central nervous systems). A disadvantage of such libraries is that they are often quite small and therefore of limited or restricted structural diversity

REFERENCES

1. Chaturvedi PR, Decker CJ, Odinecs A. Curr. Opin. Chem. Biol. 2001;5:452–63. [PubMed]
2. Korfmacher WA. Curr. Opin. Drug. Discov. Devel. 2003;6:481–5. [PubMed]
3. Korfmacher W. In: In Integrated Strategies for *Drug Discovery using Mass Spectrometry*. Lee MS, editor. John Wiley and Sons, Inc; Hoboken, NJ: 2005. pp. 359–378
4. Roberts SA. Xenobiotica. 2001;31:557–89. [PubMed]
5. Eddershaw PJ, Beresford AP, Bayliss MK. Drug. Discov. Today. 2000;5:409–414. [PubMed]
6. Eddershaw PJ, Dickins M. Pharm. Sci. Technol. Today. 1999;2:13–19. [PubMed]
7. Egan WJ, Walters WP, Murcko MA. Curr. Opin. Drug. Discov. Devel. 2002;5:540–9. [PubMed]

8. Riley RJ, Martin IJ, Cooper AE. Curr. Drug. Metab. 2002;3:527–50. [PubMed]
9. Kumar GN, Surapaneni S. Med. Res. Rev. 2001;21:397–411. [PubMed]
10. Bertrand M, Jackson P, Walther B. Eur. J. Pharm. Sci. 2000;11(Suppl 2):S61–72. [PubMed]
11. Kariv I, Rourick RA, Kassel DB, Chung TD. Comb. Chem. High, Throughput, Screen. 2002;5:459–72. [PubMed]
12. Meador V, Jordan W, Zimmermann J. Curr. Opin. Drug. Discov. Devel. 2002;5:72–8. [PubMed]
13. Mandagere AK, Thompson TN, Hwang KK. J. Med. Chem. 2002;45:304–11. [PubMed]
14. Hidalgo IJ. Curr. Top. Med. Chem. 2001;1:385–401. [PubMed]
15.] van De Waterbeemd H, Smith DA, Beaumont K, Walker DK. J. Med. Chem. 2001;44:1313–33.[PubMed]
16. Wang Z, Hop CE, Leung KH, Pang J. J. Mass Spectrom. 2000;35:71–6. [PubMed]
17. Cogburn JN, Donovan MG, Schasteen CS. Pharmaceut Res. 1991;8:210–216. [PubMed]
18. Chiou WL, Barve A. Pharmaceut Res. 1998;15:1792–1794.
19. Deprez-Poulain R, Deprez B (2004). "Facts, figures and trends in lead generation". *Curr Top Med Chem* **4** (6): 569–80. doi:10.2174/1568026043451168. PMID 14965294.
20. Keserű GM, Makara GM (August 2006). "Hit discovery and hit-to-lead approaches". *Drug Discov. Today* **11** (15-16): 741–8. doi:10.1016/j.drudis.2006.06.016. PMID 16846802.
21. Bleicher KH, Böhm HJ, Müller K, Alanine AI (May 2003). "Hit and lead generation: beyond high-throughput screening". *Nat Rev Drug Discov* **2** (5): 369–78. doi:10.1038/nrd1086.PMID 12750740.
22. Cockbain J (2007). "Intellectual property rights and patents". In Triggle JB, Taylor DJ. *Comprehensive Medicinal Chemistry* **1** (2nd ed.). Amsterdam: Elsevier. pp. 779–815. doi:10.1016/B0-08-045044-X/00031-6. ISBN 978-0-08-045044-5.

MEDICINAL VALUES AND POTENTIAL APPLICATIONS OF: FENUGREEK

Upma[1], Shilpi Arora[1]

Department of Pharmaceutical Sciences and research, Baba Mastnath University, Asthal bohar, Rohtak

Science has shown multiple times that a healthy diet and lifestyle are the prime factors in overall health and wellbeing. Consuming the correct proportions of vitamins and minerals from original food sources can combat many symptoms of poor health such as extra weight, fatigue, and even many illnesses. In fact, there is a growing consensus of individuals promoting and living a lifestyle where food is used as a form of medicine. Healthy foods, such as fresh fruits and vegetables or meats, dairy and high fiber carbohydrates, contain the full amount of vitamins and minerals required on a daily basis. In addition of helping the body perform at the optimum level, these antioxidants, vitamins, and minerals also contribute to preventing overall aging as well as chronic diseases such as cancer and heart disease

FENUGREEK: - Trigonella foenum-graecum L. Family: Fabaceae (Leguminosae)

Habitat and Cultivation:

Native to North Africa and countries bordering the eastern Mediterranean, fenugreek grows in open areas and is widely cultivated, notably in India. Fenugreek requires well-drained, good soil of medium texture. Tolerated pH range is 5.3 to 8.2. Seeds are sown directly in the garden in spring, as soon as the danger of frost is past. The plant reaches a height of 0.3 to 0.8 meters and has trifoliate leaves. White flowers appear in early summer and develop into long, slender, yellow-brown pods containing the brown seeds of fenugreek commerce. The reported life zone of fenugreek is 8 to 27 degrees centigrade with an annual precipitation of 0.4 to 1.5 meters and a soil pH of 5.3 to 8.2). The plant thrives in full sun on rich, well-drained soils. Growth is slow and weak in cold temperatures and wet soils.

CHEMICAL CONSTITUENTS:

Diosgenin, a steroid sapogenin found in fenugreek is the starting compound for over 60% of the total steroid production by the pharmaceutical industry Other sapogenins found in fenugreek seed include yamogenin, gitogenin, tigogenin, and neotigogens Fenugreek seeds contain alkaloids,including trigonelline, gentianine and carpaine compounds. Extract of fenugreek is obtained by alcoholic extraction. Fenugreek seeds contain alkaloids, including trigonelline,gentianine and carpaine compounds. The seeds also contain fiber fenugreekine, a component that may have hypoglycemic activity. Crude fiber is composed of cellulose, which is a complex molecule composed of glucose molecules.

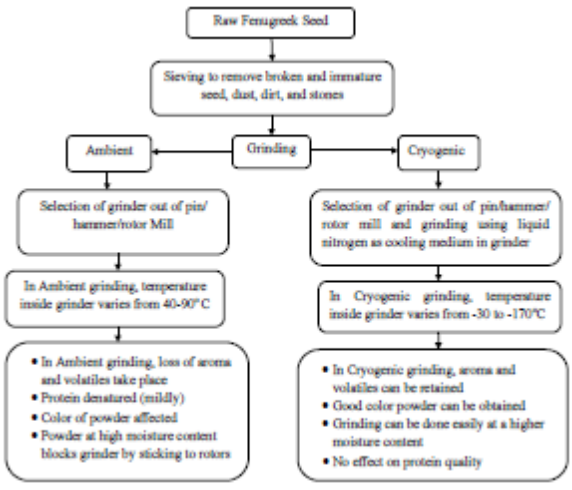


Figure 1: The different grinding methods of fenugreek and their features.

USES: Fenugreek Seeds are aromatic, bitter, carminative, galactogouge, antibacterial and may be eaten raw or cooked. Fenugreek is a digestive aid. As an emollient it is used in poultices for boils, cysts and other complaints. Reducing the sugar level of the blood, it is used in diabetes in conjunction with insulin. It also

lowers blood pressure. Fenugreek relieves congestion, reduces inflammation and fights infection. Fenugreek contains natural expectorant properties ideal for treating sinus and lung congestion, and loosens & removes excess mucus and phlegm. Fenugreek is also an excellent source of selenium, an anti-radiant which helps the body utilize oxygen. Fenugreek is a natural source of iron, silicon, sodium and thiamine. Fenugreek is also thought to be anti-diabetic and to lower blood cholesterol levels. Externally, the seeds may be applied as a paste to treat abscesses, boils, ulcers, and burns, or used as a douche for excessive vaginal discharge. The seeds also freshens bad breath and help restore a dulled sense of taste. In China, fenugreek is used as a pessary to treat cervical cancer uterine contractions.

MEDICINAL USES OF FENUGREEK:

Anticarcinogenic activities and complementary cancer therapy

Fenugreek is a promising protective medicinal herb for complementary therapy in cancer patients under chemotherapeutic interventions because fenugreek extract shows a protective effect by modifying the cyclophosphamide induced apoptosis and free radical-mediated lipid peroxidation in the urinary bladder of mice. Diosgenin ($C_{27}H_{42}O_3$) is a crystalline steroid sapogenin found in fenugreek and used as a starting material for the synthesis of steroid hormones such as cortisone and progesterone. It has been found to be potentially important in treatment cancer. It has the ability to prevent invasion, suppress proliferation and osteoclastogenesis experiment on animals. It improves peripheral glucose utilization, contributing to improvement in glucose tolerance and exerts its hypoglycemic effect by acting at the insulin receptor level as well as at the gastrointestinal level. It reported increased erythrocyte insulin reception due to fenugreek consumption and they concluded with the help of intravenous glucose tolerance test that fenugreek in the diet reduced the area under the plasma glucose curve significantly and shortened the half-life of plasma glucose by the increased metabolic clearance.

Sharma (1986) reported that injection of fenugreek seed extracts improved plasma glucose and insulin responses and reduced urinary concentrations. Daily administration of 25 g fenugreek seed powder in diabetic insulin suffering patient reduced fasting plasma glucose profile, glycosuria and daily insulin requirement (56 to 20 units) and resulted in significant reductions in serum cholesterol concentrations. The post-prandial blood glucose levels in targeted subjects were reduced significantly by giving raw and germinated fenugreek compared to those without fenugreek or boiled fenugreek

Antioxidant

Fenugreek contains phenolic and flavonoid compounds which help to enhance its antioxidant capacity . It shows the major medicinal and general uses and application of the fenugreek.

Balch suggested that fenugreek has powerful antioxidant property that has beneficial effect on liver and pancreas; since antioxidant properties have been linked to health benefits of natural products; such properties are studied with germinated fenugreek seeds which are observed to be more beneficial than dried seeds because of the fact that germinated seed increases the bioavailability of different constituents of fenugreek. An aqueous fraction of fenugreek exhibits the highest antioxidant activity compared to other fractions and the quantity of phenolic and flavonoid compounds are related to antioxidant activity. These studies reveal significant antioxidant activity in germinated fenugreek seeds which may be due to the presence of flavonoids and polyphenols . Furthermore, Grover et al. reported that mustard and fenugreek seeds showed hypoglycemic and antihyperglycemic activity in diabetic mice and they have attributed that the health benefits may be due to the presence of antioxidant carotenoids in those spices.

S. No.	Application of fenugreek	Responsible component of fenugreek	References
General uses of fenugreek			
1.	Culinary (colour, flavour, aroma)	Seed, leaves	23
2	Vegetable	Leaves and seeds	7
3	Ingredients in bread making with maize and wheat flour	Seeds	8
4	Forage	Leaves, straws, immature seeds (proteins, vitamins, carbohydrates)	3
5	Spice and seasoning	Leaves and seeds	6, 3
6	Cosmetics	Seeds, leaves	2
7	Paints	Seeds, leaves	2
8	Paper industries	Leaves, seeds	2
9	Organoleptic character improver	Seeds, leaves	6
10	Maple syrup and artificial flavouring	Trigonelline	2
11	Holy fumigants & embalming rites	Smoke of fenugreek leaves	26
12	Food	Mixed with flour for bread, yellow dye	6
13	Functional food	Dietary fibre, galactomannan	2
14	Flavouring	Curries, condiments, pickles, chutneys	6
15	Colouring dye	Seeds	2
16	Food Gum	Seed	18
17	Fenugreek as a food stabilizer, adhesive and emulsifying agent	Seed	14, 3
18	Perfume	Fenugreek oil	6
19	Insect repellent	Fenugreek oil	26
20	Alcoholic beverages and perfumery	Seeds	14
21	Bread-making along with wheat and maize flour	Seeds	27, 28
Medicinal uses of fenugreek			
1	Reduces the sugar level of the blood	Seeds	10
2	Reduces perspiration, fever, allergies, bronchitis and congestion	Seeds, leaves	82
4	Helps in loosening excess mucus and phlegm	Seeds, leaves	62
5	Treats sinus and lung congestion	Seed	56
6	Acts as anti-infection agent	Seeds, leaves	18
7	Reduces congestion	Seed	10
8	Lowers blood pressure	Seeds and leaves	3
9	Carminative flatulence (prevents gas formation in digestive tract)	Seed and leaves	29
3	Aphrodisiac	Seed leaves	28
4	Pharmaceutical (raw material for hormones and therapeutic drugs)	Steroids, flavonoids, alkaloids	2
5	Wounds and sore muscles treatment	Seeds and leaves	29
6	Anti-bacterial agent	Seeds and leaves	3
7	Anti-cancer agent	Seeds, leaves	3, 29
8	Anti-ulcer agent	Seeds leaves	3
9	Anti-nociceptive (Pain reducing)	Seeds leaves	30
10	Anthelmintic agent	Seeds and leaves	31
11	Induces labor during child birth and delivery	Seed	30
12	Induces growth and reproduction hormones	Diogenin hormones	2
13	For immunomodulatory function	Hormones	29, 3
14	Hypocholesterolemic	Whole fenugreek seed	9, 3
15	Hypoglycemic	Methanolic and aqueous extracts of seeds	32
16	Gastro- and hepatoprotective	Leaves and seeds	2
17	Antioxidant	Seed, leaves	33
18	Diabetes management	Seed	
19	Cardiovascular health	Bioactive compound	2
20	Hair strengthening agent	Fresh leaves, fenugreek seed	33
21	Prevents constipation	Seed	3
22	Improves digestion	Seed, leaves	
23	Stimulates liver and spleen	Seed, leaves	
24	Purifies blood	Seed, leaves	
25	Serves as appetizer	Seed, leaves	
26	Poultice for ulcers, boils and abscess	The twigs and leaves	
27	Lowering of blood cholesterol	Seed, leaves	24

REFERENCES:

1. Thomas JE, Bandara M, Lee EL, Driedger D, Acharya S (2011) Biochemical monitoring in fenugreek to develop functional food and medicinal plant variants. N Biotechnol 28: 110-117.
2. Blank I (1996) The flavor principle of fenugreek. Nestlé research center. 211th ACS Symposium. New Orleans 24-28.
3. Sowmya P, Rajyalakshmi P (1999) Hypocholesterolemic effect of germinated fenugreek seeds in human subjects. Plant Foods Hum Nutr 53: 359-365.

4. Brar JK, Rai DR, Singh A, Kaur N (2011) Biochemical and physiological changes in fenugreek (*Trigonella foenum-graceum L.*) leaves during storage under modified atmosphere packaging. Journal food science and technology.
5. Senthil A, Mamatha BS, Vishwanath P, Bhat KK, Ravishankar GA (2010) Studies on development and storage stability of instant spice adjunct mix from seaweed. Journal of food science and technology 48: 6.
6.Thirunavukkarasu V, Anuradha CV, Viswanathan P. Protective effect of fenugreek (Trigonella foenum graecum) seeds in experimental ethanol toxicity. Phytother Res. 2003;17(7):737-43.
7 .Sharma RD, Raghuram TC, Rao NS. Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes. Eur J Clin Nutr 1990; 44:301-306.
8Raghuram TC, Sharma RD, Pasricha S, Menon KK, Radhaiah G (1992) Glycaemic index of fenugreek recipes and its relation to dietary fiber. International journal of diabetes in developing countries 12: 1-4.
9. Sowmya P, Rajyalakshmi P (1999) Hypocholesterolemic effect of germinated fenugreek seeds in human subjects. Plant Foods Hum Nutr 53: 359-365.
10. Blank I, Lin J, Devaud S, Fumeaux R, Fay LB (1997) The principal flavour components of fenugreek *(Trigonella foenum graecum)*. In: Risch, SJ and Chi, TH (eds) Spices: Flavour Chemistry and Antioxidant Properties. ACS, Washington, DC.
11. Youssef MK, Wang Q, Cui SW, Barbut S (2009) Purification and partial physicochemical characteristics of protein free fenugreek gums. Food Hydrocoll 23: 2049-2053.
12. Brummer Y, Cui W, Wang Q (2003) Extraction, purification and physicochemical characterization of fenugreek gum. Food hydrocoll 17: 229-236.

A COMPREHENSIVE REVIEW ON NEBULISER TECHNOLOGY

Pawan Jalwal*, Balvinder Singh, Arun Kumar

Faculty of Pharmaceutical Sciences, Baba Mastnath University, Email: pawan_jalwal@rediffmail.com

ABSTRACT

A 'nebuliser' is actually the small plastic container that is filled with a medicine solution. A compressor (usually electric) is used to blow air or oxygen through this solution to make a fine mist of medicine. This mist is breathed into the lungs through a mouthpiece or mask. A nebuliser is a device that converts a liquid into aerosol droplets and must be loaded with the medication before each treatment. There are three types of nebulisers: **jet nebulisers**, which can nebulise all drugs and can be disposable; **ultrasonic nebulisers**, which are silent but can only nebulise aqueous solutions and may heat the drug; and **mesh nebulisers**, which can be used to nebulise aqueous solutions, but can be less efficient in nebulising suspensions. The latter are silent, portable and small. They can reduce the nebulisation time without reducing drug efficiency, but disinfecting and cleaning can be difficult.

KEYWORDS: nebulizer, jet nebulisers, ultrasonic nebulisers, meshes nebulisers etc.

INTRODUCTION

The lungs/ airways represent a unique organ system in the human body, their structure allowing air to come into contact with blood, this being one of the principle adaptations permitting existence of terrestrial life. This adaptation also makers airways a useful route of drugs administration in inhaled or aerosol form. Numerous techniques have been developed to aerosolize liquids, re-suspend particles, or to generate aerosol particles. Inhalation drug delivery has been used for many years for the delivery of pharmacologically active agents to treat respiratory tract diseases. Inhalation route is used because of its inherent advantages of low dose requirement, instant effectiveness and its non-invasiveness. Inhalation is gaining increasing acceptance as a convenient, reproducible and non-invasive method of drug delivery to the lung tissue and the systemic circulation. In fact inhalation of aerosolized drugs has become a well-established means of treating localized disease states within the lung including asthma. Pulmonary delivery of drug also avoids first pass effect and is generally more acceptable by patients than an injection. There are three methods of targeted drug delivery systems are used to lungs, i.e., dry powder inhalers, metered dose inhalers and the most recent drug delivery system that is nabulisers.

A 'nebuliser' is actually the small plastic container that is filled with a medicine solution. A compressor (usually electric) is used to blow air or oxygen through this solution to make a fine mist of medicine. This mist is breathed into the lungs through a mouthpiece or mask. A nebuliser is a device that converts a liquid into aerosol droplets and must be loaded with the medication before each treatment. There are three types of nebulisers: **jet nebulisers**, which can nebulise all drugs and can be disposable; **ultrasonic nebulisers**, which are silent but can only nebulise aqueous solutions and may heat the drug; and **mesh nebulisers**, which can be used to nebulise aqueous solutions, but can be less efficient in nebulising suspensions. The latter are silent, portable and small. They can reduce the nebulisation time without reducing drug efficiency, but disinfecting and cleaning can be difficult.

THREE PARTS OF NEBULISERS

1. Face mask or mouthpiece.
2. Nebuliser chamber – This a part which actually changes the liquid solution of the drug into a mist.

3. Power source – A compressor that supplies the nebuliser with the gas to change the solution into a mist.

ADVANTAGES OF NEBULISERS

- Some drugs for inhalation are available only in solution form.
- Some patients cannot master the correct use of metered-dose inhalers or dry powder inhalers.
- Some patients prefer the nebuliser over the other aerosol generating devices.
- There are two types of medical nebulisers: the **Jet nebuliser**, which is powered by compressed air and the **Ultrasonic nebuliser** which derives the energy required to aerosolize drugs from high-frequency sound waves.
- Co-ordination is unimportant so they can be used by patients of all ages, including young babies;
- Nebulised therapy is effective in severe asthma, so is often used to treat acute exacerbations.
- No cooperation required from the child.
- Even very young and very sick children can be nebulised with a face- mask.
- Almost immediate effect of reliever medication by direct delivery to the lungs.

DISADVANTAGES OF NEBULISERS

- That they are cumbersome, expensive (both the machine and the drugs),
- Treatment takes a long time - often around ten minutes.
- Noisy and scary for a small child.
- Expensive, compared to a spacer and metered dose inhaler.
- Bulky, difficult to carry about.
- Needs electricity, though manually operated ones are available sometimes.
- Needs several minutes for a single dose.
- May harbour infection, especially if one machine is used for many patients.

TYPES OF NEBULISERS

- Jet nebulisers
- Ultrasonic nebulisers
- Mesh nebulisers

JET NEBULISERS

Principle: Jet nebulisers are driven either by a portable compressor or from a central air supply. Essentially, a high-speed airflow through a narrow nozzle orifice entrains and disperses the liquid into droplets (primary generation) via a viscosity-induced instability. Droplet dispersion is improved by impaction on a baffle structure adjacent to the nozzle orifice transferring kinetic energy further into increased droplet surface area (secondary generation).

The resulting droplet size distribution still contains only a small fraction of respirable aerosol (droplets below 5µm to 6µm in size) and the large droplets are recirculated with in the nebuliser by means of secondary impaction structures. This process is associated with evaporation effects that cause the gas phase to be nearly saturated with vapour, as well as a temperature decrease within the nebuliser. A considerable part of the vapour arises from the larger recirculating droplets, thus increasing drug concentration in the remaining liquid. Therefore, assessment of nebuliser systems cannot be conducted with a simple gravimetric measurement alone, but also requires chemical assays. It requires a pressurized gas supply as the driving force for liquid atomization. Compressed gas is delivered through a jet, causing a region of negative pressure. The solution to be aerosolized is entrained into the gas stream and is sheared into a liquid film.

For nebulisation of suspensions, preferential containment of suspension particles in larger droplets can occur if the suspended particles are of similar size as the nebulised droplets, so that chemical assay may be necessary for proper particle sizing of some nebulised suspensions. For liposomal formulations, disruption of liposomes can occur due to mechanical stresses during nebulisation, possibly during primary generation [(4)] and/or secondary generation, although such disruption is device-specific and is most pronounced for large liposomes.

With jet nebulisers, all commercially available inhalation solutions and suspensions can be administered. Mechanical damage, which may cause denaturation of sensitive drug compounds (i.e. proteins and peptides), is minimized. Further advantages of nebulisers are their ability to deliver high doses of drug to the lungs and the minimal co-ordination and effort required for inhalation in comparison to pMDIs or DPIs. Nebulisers fill a niche in the treatment of young children and the elderly, especially in exacerbations and emergency situations.

Ultrasonic nebulisers

Ultrasonic nebulisers use the vibration (1.2–2.4 MHz) of a piezo-electric crystal to generate the aerosol. Vibrations are transmitted to a liquid drug, generating a liquid-drug fountain comprising large and small droplets. Large droplets drop into the liquid-drug reservoir or are thrown onto the side of the nebuliser and recycled. Small droplets are stored in the nebulisation chamber to be inhaled by the patient or leave the nebuliser with the airflow produced by a ventilator. Like the jet nebuliser, some residual mass is trapped in the nebuliser, but there is little leakage since there is no gas source to transport the aerosol out of the nebuliser during exhalation. There are two types of ultrasonic nebulisers.

- Standard nebulisers are those where the drug is directly in contact with the piezo-electric transducer. This contact causes the drug temperature to increase due to heating of the transducer. In addition the piezo-electric transducer is difficult to disinfect.
- Ultrasonic nebulisers with a water interface use a volume of water between the piezo-electric transducer and a separate reservoir for the drug. Water reduces drug heating and the drug is not in contact with the transducer. Ultrasonic nebulisers do not nebulise suspensions or liquids with high viscosity or a high surface tension, the residual mass is often >50% of the drug mass loaded in the nebuliser and the aerosol is heated. Ultrasonic nebulisers are silent, but often bulky.

MESH NEBULISERS

New nebulisers based on mesh technology have recently been introduced into the market. They can operate with batteries and are small enough to be carried. They are efficient, silent and comply with active drug compounds. Mesh nebulisers can be classified into two types: **static mesh and vibrating mesh nebulisers**.

1. Static mesh nebulisers

Static mesh nebulisers apply a force on the liquid drug to push it through a static mesh. The first mesh nebuliser had a limited introduction in the 1980s by Omron Healthcare (Bannockburn, IL, USA). The Micro air® NE-U22V nebuliser uses an ultrasonic transducer to generate vibration (180 kHz) of the liquid drug and push the droplets through the static mesh, which can then be inhaled directly by the patient. Unlike jet and ultrasonic nebulisers, the aerosol is not recycled in the mesh nebuliser.

Droplets generated through the mesh have a ~3 μm, which are produced by electroplating. The Micro air® NE-U22V can nebulise aqueous solutions and suspensions. The residual volume in the nebuliser reservoir is ~0.3 mL. The mesh cannot be disinfected by an autoclave process, and, instead, should be submerged in a 0.1% solution of benzalkonium for 10–15 min. Other cleaning

agents such as bleach must not be used due to a risk of corrosion. The Omron mesh must be cleaned by generating a distilled water aerosol. It can be loaded with a maximum volume of 7 mL.

2. Vibrating mesh nebulisers

Vibrating mesh nebulisers use mesh deformation or vibration to push the liquid drug through the mesh. An annular piezo element, which is in contact with the mesh, is used to produce vibration around the mesh, and the liquid drug is in direct contact with the mesh. Holes in the mesh have a conical structure, with the largest cross-section of the cone in contact with the liquid drug. The mesh deforms into the liquid side, thus pumping and loading the holes with liquid. This deformation on the other side of the liquid-drug reservoir ejects droplets through the holes, which can be inhaled by the patient. The Aeroneb® Go is a vibrating mesh nebuliser (Nektar Therapeutics, San Carlos, CA, USA), which utilizes a horizontal mesh containing 1,000 holes obtained by electrolysis, and vibrates at 100 kHz. It consists of a nebuliser and a separate battery pack or AC power adapter. There is a reservoir above the mesh, and the aerosol is produced towards the bottom of the nebuliser. Droplets ejected from holes at a moderate velocity are selected by impaction on the nebuliser base. Residual drug mass is negligible in the reservoir, but can be appreciable in the nebuliser. The aerosol leaves the nebuliser in standing cloud at low velocity.

BASICALLY TWO TYPES OF DRUGS CAN BE NEBULIZED:

- **Reliever drugs**
- **Controller drugs**

Reliever drugs

Reliever drugs are those drugs that relieve the symptoms of asthma. They are the drugs used when a child has an acute attack of asthma, with wheezing, severe cough, inability to participate in physical activity, and difficulty in breathing. Over the past few years, better and better drugs have become available, along with devices to deliver the drugs directly to the lungs. This has made reliever therapy very effective and safe. For example, Salbutamol and terbutaline are airway dilators that are commonly used and give quick relief. Ipratropium is another drug that can be mixed with one of the dilator drugs to give additional effect in relieving airway obstruction of asthma.

Short acting beta agonists

These are the mainstay of the acute asthma therapy today. Two drugs are available in India - **salbutamol and terbutaline**. The two drugs are fairly similar; they have quick onset of action, and the action lasts 4-6 hours. They are available as oral forms (syrups, tablets, capsules, and slow release forms), injections, and inhaled forms (metered dose inhalers, dry powder inhalers, and solutions for nebulisation). The best therapeutic effect is seen with the inhaled forms. The drug is used in very low doses, it goes straight to the lungs, and the rest of the body has minimal exposure to the drug and give quick, potent action and low incidence of side effects. Oral forms are also much used, though these drugs have unreliable absorption and action. The incidences of side effects like a fats heart rate, tremor, and vomiting is also much greater. The slow release forms offer the advantage of prolonged duration of action, but must be swallowed whole, a task possible only for older children.

Anticholinergics

These drugs act by inhibition of the cholinergic nerves, and so reverse some airway narrowing. Not effective enough to be used alone, but useful when added to inhaled short acting beta agonists for the management of acute, severe asthma. The only drug of this class in use today is

Ipratropium bromide, which is available as metered dose inhalers and as a solution for use with nebulisers.

Controller drugs:

These are the drugs that control a child's asthma. Children with mild, intermittent asthma do not need any controller therapy; all children with more severe forms of asthma should be on controller therapy. This therapy is aimed at keeping the asthma under control, thus protecting the lungs from irreversible damage and allowing the child a normal life. For example, budesonide has recently become available in India for nebulisation. It has no role in the treatment of an acute attack, and nebulisers are too tedious for the long- term daily therapy of asthma.

Sodium cromoglycate

This drug is believed to reduce the inflammation in the airways and so reduce the acute attacks of asthma. It is the safest of all anti asthma drugs. It is often taken by children for years, and side effects are rare. The onset of action takes some weeks, and many patients do not benefit at all. Cromoglycate is the drug of choice for initiating treatment in mild asthma. It is also useful as pretreatment in children who suffer from exercise-induced asthma. A puff of this drug, taken before participating in games, will protect the child. Problems with the drug include dosing four times a day, and cost significantly higher than corticosteroids.

Inhaled steroids

The steroids used for inhalation have some properties in common - they act on the surface of the airways, and the liver rapidly inactivates them. This latter property prevents side effects. The three drugs available in India are **beclomethasone, budesonide, and fluticasone**. The most recent used inhaled steroid is ciclesonide in the form of metered-dose inhalers and dry powder inhalers. These drugs are reliably effective in asthma. They reduce airway inflammation and bronchial hyper responsiveness, and prevent the deterioration in lung function that is an accompaniment of asthma. Used regularly, they can allow the child to have a normal life. At low doses, and used with precautions to reduce side effects, they have been found to be very safe at low doses. At high doses, too, they are far safer than the doses of oral steroids that would be required to maintain equivalent control of asthma.

Advantages of this class drugs is that they need to be taken only twice a day. They are less expensive than cromoglycate, and more effective Side effects include fungal infection of the mouth, hoarseness, and cough. At high doses, they may also cause growth reduction, and suppression of the pituitary and adrenal glands, though these effects are controversial. They may sometimes cause cataracts, and thinning of the bones.

In-vitro characterization of nebulizers

Factors	Tests
The important tests being conducted for the pharmaceutical development studies of nebulisers	Minimum fill justification. Extractables / Leachables. Individual stage particle size distribution. Droplet size distribution and drug output (excluding metered dose nebulisers). Shaking requirements. Compatibility (excluding metered dose nebulisers). Preservative efficacy (excluding single dose nebulisers). Physical characterization. Device development.

Including these tests, some tests are conducted for metered dose nebulisers only.	Dose uniformity and fine particle mass through container life. Single dose fine particle mass. Actuator deposition. Initial and re-priming requirements. Cleaning requirements. Performance after temperature cycling. Robustness
Various tests included in the drug product specification for nebulisers products.	Description. Assay. Delivered dose uniformity (excluding single dose nebulisation). Fine particle mass. Weight. Microbial limits (excluding single dose nebulisation). Leachables. Preservative content. Number of actuations per container (for metered dose nebulisation).
On the basis of physicochemical properties of the drug product, the tests for nebulisers solution are	Description. Osmolality (or osmolarity). Surface tension. Viscosity. pH Buffering capacity Specific gravity.

Minimum fill justification

A study should be conducted to demonstrate that the individual container minimum fill, as defined by the drug product manufacturing process, is sufficient to provide the labeled number of actuations. The final doses should meet the drug product specification limits for delivered dose uniformity and fine particle mass.

Extractable / Leachables

Detail and justification of the study design (solvent used, temperature, and storage time) and the result should be provided. Identification of the compounds should be attempted and safety assessment should be conducted. A study should be conducted to determine the extractables profile from the container closure components that are in contact with the formulation during storage and / or use.

Individual stage particle size distribution

Using a multistage impactor or impinger, the drug mass on each stage and the cumulative mass undersize a given stage should be determined rather than the percentage of emitted dose as these can hide variations in delivered dose. A plot of cumulative percentage less than a stated cut-off diameter versus cut-off diameter should usually be provided. From this, the Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) may be determined, if appropriate (in the case of log-normal distribution).

Shaking requirements

For products requiring shaking before use, a study should be conducted to demonstrate that the shaking instructions provided to the consumer are adequate. The possibility of excessive shaking leading to foaming and inaccurate dosing should be examined by testing the delivered dose uniformity.

Compatibility

Compatibility should be demonstrated with all diluents over the range of dilution proposed in the labeling and with respect to the principal drug as well as the co-administrated drug. Parameter

such as precipitation, pH, and droplet size distribution, output rate and total drug output should be tested, and differences from the original product should be assessed for their significance.

Preservative efficacy

For products containing a preservative, a study should be conducted to demonstrate the effectiveness of the preservative at the lower specification limit for the preservative concentration.

Physical characterization

Physical characterization such as solubility, size, shape, density, rugosity, charge, and crystallinity of the drug substances and / or excipients may influence the homogeneity and reproducibility of the finished product. Development studies should include physical characterization of drug substance and excipients, relevant to their effect on the functionality of the product.

Device development

The development of the device should be described. Any changes implemented in the design (e.g. change of component materials) and /or manufacturing process of the device (e.g. scale up from single cavity to multiple cavity tooling) during the development of the product should be discussed in terms of the impact on the product performance characteristics (e.g. delivered dose, fine particle mass, etc.).

Delivered dose uniformity and fine particle mass through container life

A study should be conducted to demonstrate the consistency of the minimum delivered dose and the fine particle mass through the life of the container from the first (post-priming) dose until the last labeled dose. At least ten doses from the combination of the beginning, middle, and end of the container should be tested. A sufficient number of containers of containers should be tested in order to evaluate intra-batch variability. The dose obtained should meet the drug product specification limits for delivered dose uniformity and fine particle mass.

The doses between the last labeled dose and the last container exhaustion dose should also be tested for delivered dose uniformity and fine particle mass, and information on the tail-off profile should be provided. At least three containers from two different batches should be investigated.

Delivered dose uniformity and fine particle mass over patient flow rate range

A study should be conducted to demonstrate the consistency of the minimum delivered dose and the fine particle mass over the range of flow rates achievable by the intended patient population at constant volume. For each flow rate (minimally the minimum, median, and maximum achievable rate), the results obtained should be compared against the drug product specification limits for delivered dose uniformity and fine particle mass.

Actuator deposition

The amount of drug deposited on the actuator should be determined and, where applicable, demonstrated to be consistent with any correction factor used to support ex-valve label claims.

Initial priming of the container

A study should be conducted to determine the number of actuations that should be fired to waste (priming actuations) prior to the consumer using the product for the first time. The number of priming actuations required until the subsequent doses meet the drug product specification limits for delivered dose uniformity should be determined.

Re-priming of the container

A study should be conducted to determine the length of time that the product may be stored without use (after initial priming) before re-priming, as well as the number of re-priming actuations required.

Cleaning requirements

The study should be conducted under conditions of normal patient usage, in accordance with recommendations for priming, dosing intervals, and typical dosing regimen. Since most products demonstrate acceptable performance with a weekly cleaning regimen, any requirement for more frequent cleaning may adversely affect patient compliance and should therefore be fully warranted and justified.

Performance after temperature cycling

Containers should be stored in various orientations and cycled between recommended storage conditions and a temperature below freezing (0ºC). For suspension products cycling between the recommended storage conditions and a high temperature should be considered. Storage time should be at least 24 hours under each condition, and containers should be stored under each condition at least five times.

Robustness

The product performance should be investigated under conditions to simulate use by patients. This includes activating the device at the frequency indicated in the instructions for use. Carrying the inhaler between use and simulation of dropping the device, etc. should be considered.

Description

A description of both the formulation and the full device should be given where applicable.

Assay

The amount of drug substance in one actuation should also be determined by calculating the mean of the content uniformity or delivered dose uniformity test results, with corrections as necessary to convert from "per dose" amounts to "per actuation" amounts. Limit of ± 15% of the label claim apply.

Delivered dose uniformity and fine particle mass over patient flow rate range

A study should be conducted to demonstrate the consistency of the minimum delivered dose and the fine particle mass over the range of flow rates achievable by the intended patient population at constant volume. For each flow rate (minimally the minimum, median, and maximum achievable rate), the results obtained should be compared against the drug product specification limits for delivered dose uniformity and fine particle mass.

REFERENCES:

1. W H Finlay, The Mechanics of Inhaled Pharmaceutical Aerosols, Academic Press, 2001.
2. J H Dennis, S C Stenton, J R Beach, A J Avery, E H Walters and D J Hendrick, " Jet and Ultrasonic Nebuliser Output: Use of a New Method for Direct Measurement of Aerosol Output", Thorax, 45 (1990), pp. 728-732.
3. W H Finlay, K W Stapleton and Zuberbuler, "Predicting Lung Dosages of a Nebulised suspension: Pulmicort (Budesonide)", Particulate Sci. Tech., 15 (1997), pp. 243-251.
4. K M G Tayler and S J Farr, "Preparation of Liposomes for Pulmonary Drug Delivery", Liposome Preparations and Related Techniques, G Gregoriadis (ed.), 2nd ed., Vol. 1, Boca Raton, Florida: CRC Press, 1999, pp. 177-195.
5. R W Niven, M Speer and H Schreier, "Nebulisation of Liposomes II. The Effects of Size and Modelling of Solute Release Profiles", Pharm. Res., 8 (1991), pp. 217-221.
6. Nikander K, Turpeinen M, Wollmer P. The conventional ultrasonic nebulizer proved inefficient in nebulizing a suspension. J Aerosol Med 1999; 12: 47–53.
7. Nebulizer Technologies. Modified-Release Drug Delivery Technology. Knoch M, Finlay W, eds. 1st Edn. New York, Marcel Dekker Inc, 2002; pp. 849–856.
8. Dhand R. Nebulizers that use a vibrating mesh or plate with multiple apertures to generate aerosol. Respir Care 2002; 47: 1406–1418.
9. Knoch M, Keller M. The customised electronic nebuliser: a new category of liquid aerosol drug delivery systems. Expert Opin Drug Deliver 2005; 2: 377–390.

PRODUCTION OF PHARMACEUTICAL COMPOUNDS THROUGH MICROBIAL FERMENTATION

Rajiv Kumar Arora, Monika Kaushik, Balvinder Singh

Faculty of Pharm. Sciences, Baba Mastnath University, Asthal Bohar, Rohtak

INTRODUCTION

The original definition of fermentation is 'the anaerobic conversion of sugar to carbon dioxide and alcohol by yeast', and most of us will have had first-hand experience of the fermentation process through its most famous and popular use – the brewing of beer.

This original definition has been expanded over time to 'the conversion of organic materials into relatively simple substances by microorganisms – essentially efficient, flexible bio factories.' During their growth and lifespan microorganisms build a wide range of different molecules types required for viability and multiplication; adaptation to changing environment; stressful conditions and defence against hostile, competitive microbial threats.

Microorganisms that are typically used within the pharmaceutical industry include: prokaryotes such as Bacteria (e.g. Escherichia coli, Staphylococcus aureus) and Streptomycetes (e.g. *Streptomyces* spp, *Actinomyces* spp), eukaryotes such as Filamentous Fungi (e.g., *Nigrospora* spp, *Aspergillus* spp,) and Yeast (e.g. *Saccharomyces cereviciae*, *Pichia pastoris*).

The molecules that are of primary interest to the pharmaceutical industry are small molecules such as short peptides and low molecular weight organic molecules, larger molecules including proteins and nucleic acids (DNA, RNA) and macromolecules such as lipids and carbohydrate polymers, plus various combinations of product types, for example lipopolysaccharides, lipopeptides, peptidoglycan.

Any of these product types could potentially serve as a drug's Active Pharmaceutical Ingredient (API).

MICROBIAL FERMENTATION

Microbial fermentation is the basis for the production of a wide range of pharmaceutical products, targeting practically any medical indication. Examples range from anti cancer cytotoxic drugs and vaccines, anti infectious disease antibiotics and vaccines, to hormonal disorder therapy and many other indications. Natural biosynthesis of endogenous molecules involves specific multi-step complex routes, some of which can be manipulated for the biosynthesis of foreign molecules. Microorganisms may be genetically modified (recombinant technology) or metabolically engineered by substantial alteration of their endogenous routes.The key elements of fermentation development are strain selection and optimization, media and process development, and finally, scale-up to maximize productivity. Downstream processing utilizes various technologies for extracting, concentrating and purifying the product from a dilute fermentation broth.

Fermentation derived product diversity – the recovery and selective purification of the specific desired product out of the whole molecular repertoire – makes fermentation technology a multi-disciplinary methodology encompassing microbiology, organic chemistry, biochemistry and molecular biology. When fermenting volumes larger than 10 L, necessary biosafety measures are taken, especially when Risk Group 2 (RG2) pathogens are used. These include Biosafety Level 2 Large Scale (BSL2-LS) containment facility design and special operational procedures. As these

products can be toxic and hazardous, their recovery and purification require adequate chemical/biochemical facilities and equipment including isolators for handling High-Potent APIs (HPAPIs). Under cGMP fermentation procedures, quality is built into the entire process ensuring that regulatory agencies requirements are met in terms of safety, product identity, quality and purity. Deposited in temperature controlled bio-storage, strains handled under strict aseptic procedures will be identified and characterized for homogeneity (absence of foreign growth).

WHY CHOOSE MICROBIAL FERMENTATION?

Fermentation is the only route to chemical APIs that relies solely on microorganisms with no equivalent in other biologic systems (e.g. mammalian cells). Examples: antibiotics/secondary metabolites made in fungi serving as anti cancer or anti infectious agents, or lipid A made in gram negative bacteria serving as adjuvants.

These organic molecules can be obtained through multi-step synthesis from their building blocks. However, organic molecules are very complex in nature, potentially encompassing structures such as chiral centers, large stereospecific rings or unique conjugated double bond systems. Going down the synthetic route not only requires significant development but is time consuming and entails higher costs than the fermentation option.

The semi-synthetic approach draws upon the advantages of fermentation in the generation of new drugs. Natural molecules are produced through fermentation then modified synthetically, reducing toxicity, increasing potency and selectivity, and overcoming bacterial resistance to traditional antibiotics.

Fermentation might also be the sole source for natural therapeutic proteins exclusively expressed in microbial systems. Proteins are complex molecules of mid to high molecular weight. Their functionality and stability largely depend upon their secondary and tertiary structure, as well as various post-translational modifications, mainly glycosilation. The synthetic option is limited to very short peptides.

Recombinant technology enables the expression of foreign gene encoding for therapeutic proteins in microbial systems, including those from human source. Using microbial fermentation is advantageous for expression of proteins that do not require post-translational modifications as microbial systems, such as *E. coli*, lack post-translational mechanics.

A further approach is to reduce the protein expressed to the minimal effective domain (Nanobodies/Peptibodies in the case of antibodies). The principal advantages of fermentation over the mammalian system, as illustrated in the table below, are time and yield which ultimately translate to cost.

ADVANTAGES OF MICROBIAL FERMENTATION

Therapeutic proteins requiring modification, for example glycosilation of antibodies were, until recently, expressed in mammalian cell cultures. Driven by cost considerations, scientists looked to express glycosilated therapeutic proteins in microbial systems, resulting in a novel approach – Glycoengineering – whereby the endogenous glycosilation pathway in high yield expression recombinant yeast was modified. The modified pathway reproduced the human pathway therefore allowing the expression of humanized antibody fragments.

CONCLUSION

Although not a new technology, microbial fermentation continues to evolve and is now frequently the preferred production method for chemical compounds and therapeutic proteins, offering an optimal economic route, which allows pharmaceutical companies to shorten production processes and time to market.

A REVIEW ON NATURAL SOURCE AS DRUG AND DIETARY SUPPLEMENTS

Rishi pal[1] , Mangal Sain[2]

[1]. SBMNIPS&R, Baba mast Nath University, Asthal Bohar, Rohtak, Haryana(India)
[2] Dept of Pharmacology, JCP, Butana, Sonipat, Haryana (India)

ABSTRACT:

Natural food is the major source for serving the nutritional needs, but with growing modernization some traditional ways are being given up. Affluence of working population with changing lifestyles and reducing affordability of sick care, in terms of time and money involved, are some of the forces that are presently driving people towards thinking about their wellness. In Ayurveda, the traditional Indian medicine, remains the most ancient yet living traditions.There has been increased global interest in traditional medicine. Efforts to monitor and regulate traditional herbal medicine are underway. Increased side effects, lack of curative treatment for several chronic diseases, high cost of new drugs, microbial resistance and emerging, diseases are some reasons for renewed public interest in complementary and alternative medicines. Numerous nutraceutical combinations have entered the international market through exploration of ethnopharmacological claims made by different traditional practices. Although India has been successful in promoting its therapies with more research and science-based approach, it still needs more extensive research and evidence base. This provide an overview of the Indian Ayurvedic system of medicine and its role in translational medicine in order to overcome malnutrition and related disorder

INTRODUCTION:

India is known for its traditional medicinal systems ie. Ayurveda, Siddha, and Unani. Medical systems are found mentioned even in the ancient Vedas and other scriptures. The Ayurvedic concept appeared and developed between 2500 and 500 BC in India. The literal meaning of Ayurveda is "science of life," because ancient Indian system of health care focused on views of man and his illness. It has been pointed out that the positive health means metabolically well-balanced human beings. Ayurveda is also called the "science of longevity" because it offers a complete system to live a long healthy life. It offers programs to rejuvenate the body through diet and nutrition. It offers treatment methods to cure many common diseases such as food allergies, which have few modern treatments. However, one should be aware that Ayurvedic nutrition is not a "magic bullet" system but requires the full participation of the patient to succeed. It is an interactive system that is user-friendly and educational. It teaches the patient to become responsible and self-empowered.

Ayurveda is not a nutritional system for those seeking an escape or excuse to further abuse their body or mind. It is a system for empowerment, a system of freedom, and long life. Food is the major source for serving the nutritional needs, but with growing modernization some traditional methods are being given up. Hence, the modern food habits are affecting the balanced nutrition. There is an ever widening gap in nutrient intake due to which normal life is no longer normal

MEDICINAL PLANTS USED IN TRADITIONAL

As the Indian subcontinent is a vast repository of medicinal plants that are used in traditional medical treatments. The alternative medicines in the traditional systems are derived from herbs, minerals, and organic matter, while for the preparation of herbal drugs only medicinal plants are used. Use of plants as a source of medicine has been an ancient practice and is an important component of the health care system in India. In India, about 70 percent of rural population depends on the traditional Ayurvedic system of medicine. Most healers/practitioners of the traditional systems of medicine prepare formulations by their own recipes and dispense to the patients. In the Western countries, approximately 40 per cent of people are using the herbal medicine for the treatment of various diseases.

India is the largest producer of medicinal plants. There are currently about 250,000 registered medical practitioners of the Ayurvedic system, as compared to about 700,000 of the modern medicine. In India, around 20,000 medicinal plants have been recorded; however, traditional practitioners use only 7,000–7,500 plants for curing different diseases. The proportion of use of plants in the different Indian

systems of medicine is Ayurveda 2000, Siddha 1300, Unani 1000, Homeopathy 800, Tibetan 500, Modern 200, and folk 4500. In India, around 25,000 effective plant-based formulations are used in traditional and folk medicine. More than 1.5 million practitioners are using the traditional medicinal system for health care in India. It is estimated that more than 7800 manufacturing units are involved in the production of natural health products and traditional plant-based formulations in India, which requires more than 2000 tons of medicinal plant raw material annually. More than 1500 herbals are sold as dietary supplements or ethnic traditional medicines.

Nutraceuticals an important, essential and alternative approach for consumption in human:

Various risk factors related to health result from an imbalance in nutrition. These imbalances in India are widely prevalent leading to adverse outcomes. A certain section of the population consumes diet which does not provide sufficient calories, let alone sufficient nutrients. In India, nearly 20% of the total population and 44% of young children are undernourished and underweight. On the other hand, there is a huge population that is nourished in calorie intake but not in terms of nutrient intake. This segment would typically include lower middle to upper class population with sufficient purchasing capacity but probably less awareness about their nutrient requirements, leading to imbalanced nutritional uptake.

In fact, in our population about 30% in urban and 34% in rural areas consume more than the recommended number of calories with higher than recommended levels of dietary fats and could be the largest contributor in making India the future cardiovascular and diabetes capital of the world. The third population segment, which is about 80 million, consumes nutrients and calories more than those recommended for the lifestyle they have opted for. The main risk factors in developing countries like India are related to nutrition and contribute to nearly 40% of total death and 39% of total disease burden.

Natural herbs in medicines and in dietary supplement:

Dietary supplements and herbal remedies are popular complementary or alternative products for people. These are the supplements that are intended to supplement the diet and contain one or more dietary ingredients (including vitamins, minerals, herbs or other botanicals, amino acids, and other substances) or their constituents. These are intended to be taken by mouth as a pill, capsule, tablet, or liquid and are labeled on the front panel as being a dietary supplement. Such products may range from isolated nutrients, dietary supplements, and diets to genetically engineered "designer" foods, herbal products, and processed foods such as cereals, soups, and beverages.

These botanicals are sold in many forms as fresh or dried products, liquid or solid extracts, tablets, capsules, powders, tea bags, and so forth. For example, fresh ginger root is often used in various food stores; dried ginger root is sold packaged in tea bags, capsules, or tablets, and liquid preparations made from ginger root are also sold in the market. A particular group of chemicals or a single chemical may be isolated from a botanical and sold as a dietary supplement, usually in tablet or capsule form. An example is phytoestrogens from soy products and others.

CONCEPT OF NEUTRACEUTICAL WITH ALTERNATIVE DEFINATIONS

Traditional and herbal medicines are included in the definition of dietary or nutritional supplements in Canada. Japan does not mention traditional herbal medicines under functional foods for special health use. USA includes herbal and botanical in its definition. The Indian definition lists down the ingredients that a product should have, and it also specifies general properties of nutraceutical. Traditional medicines though have been excluded from the definition. There are three categories which have been considered under the nutraceuticals.

.**Dietary Supplements.** Supplements provide nutrients that are missing or are not consumed in sufficient quantity in a person's diet, that is, vitamin supplements, mineral supplements, macronutrients, antioxidants, tonics, herbal formulations like Chyawanprash, Musli pak, Ashwagandhadi leh, and nonherbal products like cod liver oil.

Functional Foods. Foods that have specific physiological benefits and/or reduce the risk of chronic disease, that is, nutrition fortified foods like fortified flour, fortified oil, fortified malt-based powder and probiotic foods like yogurt.

Functional Beverages. Liquids that quench thirst along with replenishing minerals provide energy, prevent ailments, and promote healthy life style, that is, sports and energy drinks, fortified juices, and glucose drinks and powder.

A product category can be classified into a specific need-segment based on its predominant use. The product segments catering to foundation and condition specific need are the largest and growing the fastest.

Nutraceutical products aim to fulfill specific needs of the persons based on which they may be classified as follows.

a) Enhancement segments: high protein supplements, energy drinks, sports drinks, glucose drinks, and so forth.

b) Specific condition segments: antioxidants, vitamin supplements, and mineral supplements.

c) Foundation segments: macronutrient supplements, nutrition fortified foods (fortified flour, soups, biscuits, etc.), probiotic foods (yogurt), and herbal formulation (chyawanprash, Ashwagandhadi-leh)

CONCLUSION:

The numerous nutraceutical combinations have entered the international market through exploration of ethnopharmacological claims made by different traditional practices. To truly consume a healthy diet, the vast majority of the diet must be composed of health-promoting foods and nutraceuticals but disease-promoting foods or junk food must be avoided. Ninety percent of the daily diet should be made up of nutrient rich plant foods, whose calories are accompanied by health-promoting phytochemicals, vegetables, fresh fruits, beans and legumes, raw nuts, seeds, and avocados, starchy vegetables, and whole grains. These foods or nutraceuticals construct a health-promoting, disease-preventing diet with protective substances. The rich nutrient food intake will provide maximum protection against not only infections, asthma, and allergies but also against heart disease and cancer in adulthood

REFERENCES:

1. http://www.ficci-nutraceuticals.com.
2. M. M. Pandey, S. Rastogi, and A. K. S. Rawat, "Indian herbal drug for general healthcare: an overview," The Internet Journal of Alternative Medicine, vol. 6, no. 1, p. 3, 2008.
3. R. P. Samy and S. Ignacimuthu, "Antibacterial activity of some folklore medicinal plants used by tribals in Western Ghats of India," Journal of Ethnopharmacology, vol. 69, no. 1, pp. 63–71, 2000.
4. D. John, "One hundred useful raw drugs of the Kani tribes of Trivandrum forest division, Kerala, India," International Journal of Crude Drug Research, vol. 22, no. 1, pp. 17–39, 1984.
5. C. Anesini and C. Perez, "Screening of plants used in Argentine folk medicine for antimicrobial activity," Journal of Ethnopharmacology, vol. 39, no. 2, pp. 119–128, 1993.
6. P. A. Cox and M. J. Balick, "The ethnobotanical approach to drug discovery," Scientific American, vol. 270, no. 6, pp. 82–87, 1994

A REVIEW ON DOSAGE FORMS AND ITS TYPES

Gaurav Khurana*

Department of Pharmaceutics SBMNIPSR, Rohtak **Email:** gaurav.khurana786@gmail.com

Dosage forms (also called **unit doses**) are essentially *pharmaceutical products* in the form in which they are marketed for use, typically involving a mixture of active drug components and nondrug components (excipients), along with other non-reusable material that may not be considered either ingredient or packaging (such as a capsule shell, for example).

THE NEED FOR DOSAGE FORMS

The potent nature and low dosage of most of the drugs in use today precludes any expectation that the general public could safely obtain the appropriate dose of a drug from the bulk material. Most drug substances are administered in milligram quantities, much too small to be weighed on anything but a sensitive prescription or electronic analytical balance.

Types

Oral

- Pill, i.e. tablet or capsule
- Specialty tablet like buccal, sub-lingual, or orally-disintegrating
- Thin film (e.g., Listerine Pocketpaks)
- Liquid solution or suspension (e.g., drink or syrup)
- Powder or liquid or solid crystals
- Natural or herbal plant, seed, or food of sorts (e.g., marijuana such as that found in "special brownies")
- Pastes (e.g., Toothpaste)

Inhalational

- Aerosol
- Inhaler
- Nebulizer
- Smoking
- Vaporizer

Parenteral

- Intradermal (ID)
- Intramuscular (IM)
- Intraosseous (IO)
- Intraperitoneal (IP)
- Intravenous(IV)

Topical

- Cream, gel, liniment or balm, lotion, or ointment, etc.
- Ear drops (otic)
- Eye drops (ophthalmic)
- Skin patch (transdermal)
- Vaginal rings
- Dermal patch

Suppository

- Vaginal (e.g., douche, pessary, etc.)
- rectal

- Urethral suppositories
- Nasal suppositories
- Ear cones

GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN

Before formulating a drug substance into a dosage form, the desired product type must be determined insofar as possible to establish the framework for product development.

TABLET

Tablets are solid preparations each containing a single dose of one or more active ingredients and usually obtained by compressing uniform volume of particles, some are prepared by molding.

Advantages

Compared to liquid dosage forms, tablets possess more chemical and physical stability 2- Packaging in blister packs can also enhance the stability of tablets. 3- They provide an accurately measured dose and low content variability of the unit dose. 4- Low manufacturing cost. 5- Easy to package and ship. 6- Simple to identify. (Coatings can be colored or stamped to aid tablet recognition)

Disadvantages of tablets as a dosage form:

1- Poor bioavailability of poorly soluble drugs or poorly absorbable drugs. 2- Some drugs may cause local irritation effect harm GI mucosa. 3- Some drugs resist compression into tablet. 4- Difficulty in swallowing in some patients; pediatrics and geriatrics.

- **Insufflations**

  These are medicated powders designed to be blown into the ear, nose, throat or body cavities by means of a device known as an *insufflator*. Bulk insufflation has largely disappeared and has been replaced by individual doses of powdered drugs supplied in hard capsules and inhaled from a device which breaks the capsule and allows the patient to inhale the powder. This type of insufflation is used mainly for drug delivery into the respiratory tract by inhalation.

- **Irrigation Solutions**

  These are sterile, pyrogen-free solutions usually intended for irrigation of body cavities, operation cavities, wounds or the urogenital system.

- **Linctuses**

  Linctuses are viscous, liquid oral preparations that are usually prescribed for the relief of cough. They usually contain a high proportion of syrup and glycerol which have a demulcent effect on the membranes of the throat. The dose volume is small (5ml) and, to prolong the demulcent action, they should be taken undiluted.

- **Liniments**

  Liniments are fluid, semi-fluid or, occasionally, semi-solid preparations intended for application to the skin. They may be alcoholic or oily solutions or emulsions. Most are massaged into the skin (counter-irritant or stimulating types) but some are applied on a warm dressing or with a brush (analgesic and soothing types). Liniments should not be applied to broken skin.

- **Lotions**

  These are fluid preparations for external application without friction. They are either dabbed on the skin or applied on a suitable dressing and covered with a waterproof dressing to reduce evaporation.

- **Lozenges**
  Lozenges are solid preparations consisting of sugar and gum, the latter giving strength and cohesiveness to the lozenge and facilitating slow release of the medicament. They are used to medicate the mouth and throat and for the slow administration of indigestion or cough remedies.
- **Mixtures**
  Mixtures are liquid oral preparations consisting of one or more medicaments dissolved or suspended in an aqueous vehicle. Official mixtures are not usually formulated for a long shelf-life.

OPHTHALMIC DOSAGE FORMS

Eye drops: Eye drops are saline-containing drops used as a vehicle to administer medication in the eye. Depending on the condition being treated, they may contain steroids, antihistamines or topical anesthetics. Eye drops sometimes do not have medications in them and are only lubricating and tear-replacing solutions.

OTIC DOSAGE FORMS:

Ear drops: - Ear drops are solutions, suspensions or emulsions of drugs that are instilled into the ear with a dropper. - It is used to treat or prevent ear infections, especially infections of the outer ear and ear canal.

DEPARTMENT OF ENGINEERING

TREND OF BRINGING THE DOCTOR HOME VIA TELEMEDICINE GAINING POPULARITY

Ajay Madaan

Assistant Professor, SBMN Engg College, Asthal Bohar, Rohtak (HR)

A recent report titled 'Foreseeing the Future of Healthcare' by Wipro and Dun & Bradstreet India revealed that while 70 per cent of India's population resides in rural areas, only one-fourth of the country's specialist physicians live in semi-urban areas, and even less than 5 per cent of them reside in rural areas. In the present scenario, remote delivery of medical advice along with diagnostic and healthcare services seems to be the best way to treat people living in villages. Here we are not talking about robot-doctors and tricorders but practical, low-bandwidth telemedicine and health monitoring technologies that will help the masses in India. "On an average, India has one doctor for every 1700 people, while the optimal average should be one doctor for every 600 citizens. In some cases, the ratio is up to one doctor for every 25,000 citizens. The United States has one doctor for every 350 citizens, and if India aspires to become a superpower, it needs to increase the number of doctors by six times. This is impossible as no country can organically grow their medical population six times quickly and meet the quality.

"Telemedicine can virtually deliver a doctor, specialist or super-specialist to a patient in a remote area through networking technology. In the case of Cisco's technology, the interaction between them is through video using a vernacular language. The doctor can read and see all the vital tests that are done on a patient. The patient can interact with the doctor as if the doctor is present in the same room. Finally, the doctor can dispense a prescription or recommend a course of treatment that can be taken by the patient just as he would do in a real-life situation. This fundamentally balances out the doctor-citizen imbalance we see in India as well as the urban-rural divide in terms of resource availability," he adds. Telemedicine and health monitoring technologies have been around in India for over a decade, and have been growing slowly and steadily. However, in recent times, several factors have boosted the growth of this sector. First of all, developments in the field of electronics, especially micro-electromechanical systems (MEMS) and system-on-chip (SoC) technologies, have vastly improved the size, quality and precision of medical equipment. Wireless technologies have enabled remote delivery of services. Information technology, especially the cloud, has improved the ways in which medical information is shared, stored and processed. The mobile phone, its services and apps have brought telemedicine and health monitoring to the masses—literally. In fact, the use of the mobile for keeping track of vital signs, analysing information collected by medical equipment, communicating health status to doctors and receiving advice from them has expanded the scope of telemedicine and health monitoring.

From being used only for delivering medical services remotely to rural areas initially, these technologies are now also being used to provide better services to patients in hospitals, take care of specially-challenged or aged people, monitor foetal health and even improve the fitness level of people. Let us take a look at the key components of telemedicine, as well as recent innovations and some promising technologies and products in this space.

What's inside?

There is a wide array of telemedicine and health monitoring equipment available today. Broadly, we can divide them into diagnostic and therapeutic equipment like electrocardiographs and pacemakers, imaging technologies like X-ray and magnetic resonance imaging (MRI), medical instruments like blood analysis systems and dialysis systems, patient monitoring and consumer products like remote monitoring

tools, insulin pumps and heart-rate monitors, as well as wellness equipment like pedometers and cardio trainers.

Such equipment can be thought of as having a layer of information and communication technology (ICT) atop a medical device. These usually comprise a combination of sensors, MEMS, low-power high-performance microcontrollers, wireless modules, signal conditioners, analogue-to-digital converters, etc, which work alongside user-friendly but powerful software.

The infrastructure required includes uninterruptible power supply and Internet—both of which are a challenge in the Indian landscape.

"With increasing penetration of mobile infrastructure into the remote areas, mobility is expected to play a larger role in healthcare as well. Solutions will have to be designed to be mobile, as we go along. 3.5G and 4G are going to have a huge impact on the ability to deliver healthcare at the patients' doorsteps. However, until the connectivity reaches rural areas, the impact will be seen only on the urban population and the changes will miss the vast majority of the population that lives in the rural areas," remarks Rajeev Kumar, founder director, Neurosynaptic Communications—a company that has made a mark in the Indian telemedicine arena with its ReMeDi solution.

"Availability of electricity is also a huge challenge in rural as well as semi-urban areas. Alternatives like solar are still too expensive, although the prices are coming down. Plus, operation, maintenance and support of the telemedicine infrastructure are always a problem in the absence of adequately trained personnel," he adds.

These challenges reflect in the design and engineering goals of telemedicine and health monitoring equipment.Design considerations and constraints According to Kumar, when developing telemedicine solutions, engineers should keep in mind data accuracy, patient safety, low power consumption, ease of use and ruggedness. At the same time, these solutions have to be very powerful and accurate.Software engineers also have to consider the rural environment when developing applications for remote healthcare. The software has to be light, capable of running on minimal resources. Considering the fact that it might be used by untrained professionals, the interface must be very simple. It must also support local languages.

Gupta adds, "While implementing ICT-based solutions, especially in rural areas of India, the designers will have to keep in mind that the infrastructure available is at the bare minimum. The solution should be capable of adapting to this infrastructural deficit and work its way around enabling the healthcare services on the lowest possible bandwidth with minimal resources. Thus, while solutions in the West might work on 5 MB, in India they need to work at 500 kB or lesser. Cisco's Health Presence 2.5, for instance, can work even at 300 kbps."

He further says, "The second design consideration is the language support. Cisco's solutions work around this using a special queuing technology that enables patients to find doctors who speak their language and have the right specialisation."

"The third design consideration in emerging countries is that patients sometimes want an unscheduled visit; we could call it ad hoc consultations. Cisco caters to these using scheduling systems, and also by bringing in 'presence' within the application to enable paramedics to find any doctor who may be available," Gupta stated.

In the race to overcome these constraints and come up with the best and most cost-efficient solution, the industry has absorbed several interesting technologies from the world of electronics and telecommunications. While some solutions are characterised by advanced technologies, others focus on understanding and catering to rural India.

Let us look at some of the telemedicine and health monitoring solutions being used in India, and what makes them successful.High-tech in small packages the extensive use of MEMS is one of the greatest developments in the field of telemedicine and health monitoring in the last few years.

"MEMS is the technology behind various types of silicon sensors and nano-pumps. STMicroelectronics provides consumer sensor technologies that include multiple-axis motion and orientation sensors, compass, pressure, temperature, sound (microphone) as well as biological and molecular compounds. These sensors can now be applied to monitor various aspects of the human anatomy and organ functions where accuracy and sensitivity are critical," says Vivek Sharma, regional vice president, Greater China and South Asia Region-India Operations, and director-India Design Centres, STMicroelectronics. ST adds these capabilities to its low-power microcontroller and communication chip technologies, and offers several innovative healthcare products.

ST's Body Gateway (BG), an integrated remote monitoring solution for advanced telemedicine platforms, is an interesting example. It is a lightweight and low-power electronic system for measurement and management of physiological parameters like electro-cardiogram (ECG), heart rate, breathing rate, weight, etc. A tiny module that can be taped to the patient's chest, the BG collects data from a suite of sensors, performs initial processing, stores the data and prepares it for transmission over a network to the remote application server. Another interesting solution is the eye pressure monitor to monitor Glaucoma. Developed by ST in collaboration with Sensimed, the solution is based on a smart contact lens that uses a tiny embedded strain gauge to monitor the curvature of the eye over an extended period of time, providing valuable disease management data that is not currently obtainable using conventional ophthalmic tests.

Switzerland-based Debiotech and ST have developed silicon-based microfluidic devices that deliver insulin using a miniature disposable insulin pump. Insulin pump therapy is emerging as an attractive alternative to individual insulin injections. The patient is connected to a programmable pump including a storage reservoir, from which insulin is infused into the tissue under the skin, day and night, according to the specific needs of the patient. The system uses miniature MEMS-based technology, and also supports remote administration.

Keeping safety in mind

When developing health monitoring solutions, one should remember that it is more often than not used by people with special health constraints or conditions. Hence the solution itself must be non-intrusive and harmless without adding to their strain or causing new complications.

The non-intrusive, cloud-based pregnancy monitoring solution offered by Wipro Healthcare is an interesting example. The solution, piloted in hospitals in Bengaluru and Delhi, has been deployed in collaboration with a UK-based start-up, which provides the device for measuring foetal heart rate, maternal heart rate and other vital signs. Wipro provides the embedded systems solutions along with storage and analytics technologies on mobile and cloud platforms.

The technology, based on the principle of ECG, is so sophisticated that it can detect and interpret even the faintest heartbeat of the foetus. The wearable device is small in size as against an ultrasound device, which is large and uncomfortable, especially for women in the last trimester. The technology is also non-intrusive for the foetus and there are no transmissions to the womb as like in the case of ultrasound devices. It accurately records maternal and foetal heart rate, and uterine activity, thereby providing information on foetal and maternal well-being. The device is suited for both antenatal care, and during active labour and delivery. The comprehensive solution helps gynaecologists to monitor patients 24/7 using information delivered to their mobile.This as well as Wipro's cardiac care solution are based on the Wipro AssureHealth platform, which leverages Microsoft's cloud, mobility and analytics offerings to allow care providers to monitor patients regularly and precisely. This is done through hosted services and

mobile apps that integrate medical devices, IT Infrastructure and 24×7 customer support, to deliver highly-scalable solutions.

Managing diversity and individual choices

When we speak of healthcare in a country, there is a lot of diversity. There is diversity in needs, culture, infrastructure and usage. So a telemedicine platform has to be able to encompass all of these smoothly."Cisco HealthPresence 2.5 gives a lot of choices to our customers. Our vision is to allow healthcare collaboration across any standard video endpoint, and Cisco provides almost ten choices from low-end desktop based to mid-end Tandberg-based to high-end truly-immersive-based video endpoints. In addition to high-quality audio and video, we believe in integrating with all the relevant medical devices and giving lots of choices to our customers based on standards-based medical device integration. We also want to make it very efficient for the doctors to do the consultation.

VERTICAL HANDOFF PERFORMANCE IN WLAN WIRELESS NETWORKS

Anil Dudy

Assist Prof. Electronics and communication, Shri Baba Mastnath Engg. college anildudy10@gmail.com

ABSTRACT

The WiFi handoff setup compares the data traffic received by different APs in the network. Since the initial stations of AP_0 are mobile ones, AP_0 receives data traffic only at the beginning and then at end of simulation when its stations start their tour and come back. Additionally, it receives data traffic when the stations started from south visit its section and get connected to it. In contrast to AP_0, AP_2 has stable stations, so the data traffic received by it does not drop to 0 like AP_0's traffic. As expected, its received data traffic doubles when the moving stations from west and south cross its section. AP_3 is visited by all moving stations at the same time. Hence, its received data traffic is tripled when this happens during simulation. Hence the throughput and delay for the wlan MS is obtained. The vertical handover setup consists of a gateway, application server providing voice service to the wimax BS and to the wlan router

Index Terms- AP, DCF, PCF, LAN, WLAN

1. INTRODUCTION

Communication is always necessary in building relations to mankind, when two persons meet they need some medium to interchange their views but due to distance barriers some tools are required to communicate each other. At the end of 19th century, renowned scientist Graham Bell laid the first stone in the field of communication using different tools regardless of distance. He invented first wired base telephony equipment. It was the solution for the voice communication for the people how far apart they are. After this radio based communication systems Era started. It was an extension of wired based networks.

In the beginning it was developed for some special purposes like military and police usage. With the passage of time these systems emerged to allow common peoples to communicate with each other, rather than using wired based network. After this the age of faster communic-ation and capabilities of voice get started and evolved into new telecommunication system. The capability to achieve wireless access anywhere, anytime, and any-place has become common expectation as it provides significant flexibility and freedom in mobility. But to achieve global mobility in heterogeneous networks for any mobile device requires seamless connectivity using vertical handoff. Since none of the existing wire-less frameworks provide practical solutions for vertic-al handoff. End-to-End Vertical Handoff (**E2EVH**) proposed in this paper offers a new concept to perform vertical handoff between heterogeneous wireless net-works. To deliver network services without interruption, E2EVH present a novel design to monitor the network availability, it then picks the best accessible network for application layer [1].

2. WIRELESS LAN SYSTEM

The Wireless Local Area Network (WLAN) is an unlicensed band of 802.11 ISM frequency band. 802.11 is one of the recent communication technologies of IEEE standard. It specifies medium access control (MAC) and physical layer that is why it is called Wireless LAN. It has three widely used types which operates on different frequency bands. These three types are 802.11a, 802.11b and 802.11g. 802.11a operates on 5 GHz frequency band and it gives the maximum data rate speed of 54 Mbps, which is higher than 802.11b because 802.11b operates on 2.4 GHz frequency band and give the maximum data rate speed of 11Mbps. 802.11b operates. 802.11g is recently developed standards of Wireless LAN. It also operates on 2.4 GHz

frequency band and give the maximum data rate speed of 54 Mbps. In 802.11 Wireless LAN standards, the two types of MAC protocols Distributed Coordination Function (DCF) and Point Coordination Function (PCF) are used. Nowadays the most applications available in the markets are uses DCF because it is simple, robust and easy to implement.

DCF is the basic MAC layer function in Wireless LANs, Which used Carrier Sense Multiple Access technique (CSMA) also with an addition of Collision Avoidance of (CA). It resolves the CA problems of the packets transmitted at the same time.

Architecture of Wireless LAN

Wireless Local Area Network instigate as an overlay to the Wired Local Area Network. Lightweight and Autonomous are two discrete architectures used in WLAN environment.

Each of the architectures has wide impact on wired LAN architecture. The selection of WLAN architecture is based on the consideration of building, future proof, integrated wired and Wireless LAN to accomplish high return on investment. Both architectures are popular but Lightweight architecture has plus advantages over the WLAN market.

2.1 Lightweight Model

Lightweight is the part of WLAN architecture. With most of wireless intelligence which residing at central controlling device, lightweight Wireless Access Point architecture have narrow functionality.

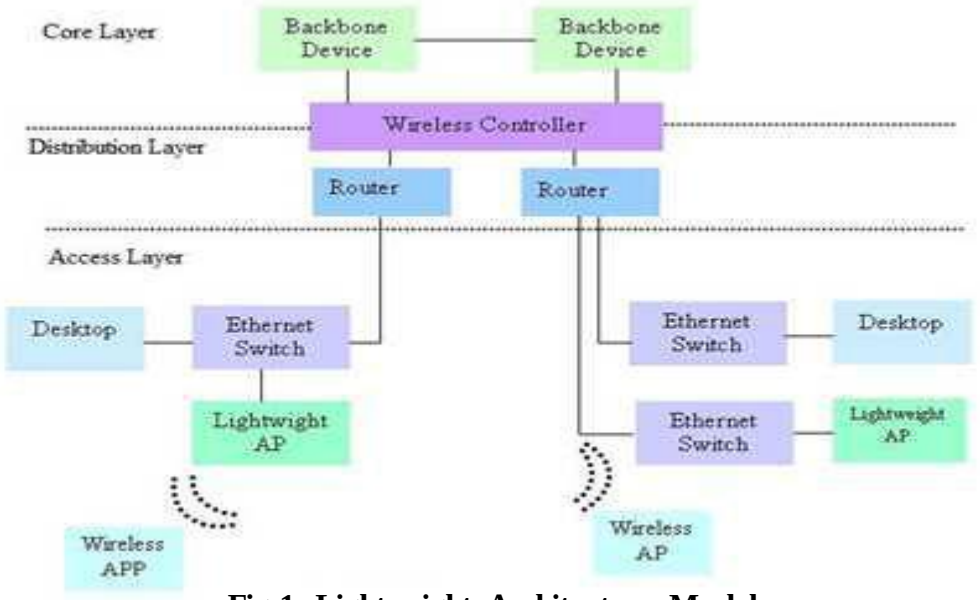


Fig 1: Lightweight Architecture Model

Lightweight model is simple. The devices that provide the communication to the end user as Access Layer are identified by lightweight. Distribution layer provide the inter communication and the top layer (Core Layer) of Lightweight model is responsible fast and consistent data between networks.

Wireless Access Point (WAP) resides at the interface of access layer and provides the communication interface to end user. In lightweight architecture model, the management of operation is easy because it give the permission to WAP from single device, because the lightweight WAP have the knowledge of visibility and attentiveness of the neighbours WAPs. They can observe and if any one of their neighbours becomes the victim of fault it notifies the wireless controller.

Lightweight WAP may be Self-healing because to pay compensation for unsuccessful counterpart, controller commands the neighbouring WAP to regulate their power level, where as in autonomous there is no concept of the visibility of its WAP neighbouring and in this case to perform self healing it cannot adjust the power level.

If single WAP is busy or overloaded then in this situation wireless controller can relieve the wireless client to neighbouring WAP. In critical applications such as VoIP, self-healing and load balancing are important issues.

2.2 Autonomous Model

In Autonomous Model WAP is not mandatory as shown in **Fig. 2**.

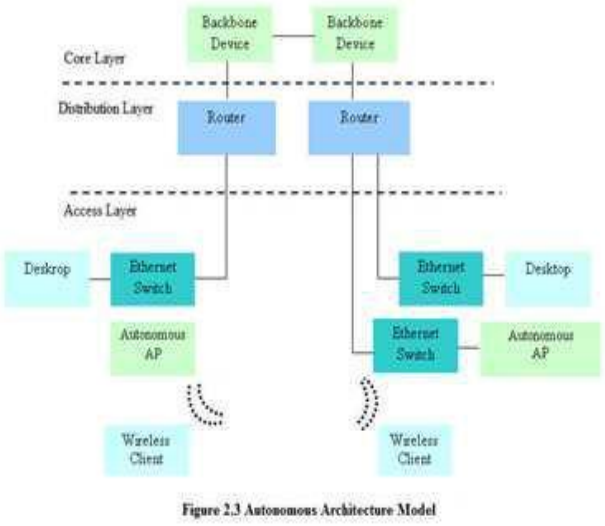


Fig 2: Autonomous Architecture Model

Autonomous Wireless Access Point sustains the switching and strong security as well as networking function that are indispensable to route the wireless traffic. As in autonomous system there is no concept of the visibility of WAP so it cannot make the load balancing. Autonomous model cannot differentiate whether nearest WAP is part of WLAN infrastructure or illegal rouge WAP. The difference between the autonomous and lightweight is negligible. The difference is only this that lightweight have one extra component (WLAN controller).

VERTICAL HANDOVER

Between the heterogeneous wireless networks the handover process can be set apart in to handover execution and handover decision process. In handover decision process both the mobile node and network decides that when the handover process will be occur. After taken handover decision, the handover execution process continues. The handover decision process involves supplementary network information such as replica address detection time in Mobile IPv6, when handover decision and detection process overlaps. The handover delay can be alienated in to three main mechanisms.

Discovery Time (t_d)

In this process via link layer beacon, the mobile terminal perceive that it is in the under the range of new wireless network from where it get the Router Advertisement (RA) of new access router. Through the RA and triggered-based router solicitation from access router in the visited network, the MT detects the coverage on new network.

Address Configuration Period (t_c)

In this period the MT receive the Router Advertisement (RA) and updates its routing table and assign the new Care of Address (CoA) to all its interfaces. This new CoA based on new access router accessible form RA.

Network Registration Period (t_r)

In this period the binding updates are transmit to Home Agent (HA) as well as correspondent node and collect the acknowledgement from correspondent node. As binding acknowledgement from correspondent node is elective, so we consider the situation when mobile node accept packet from correspondent.

Thus an IP level handover consist of td, tc and tr. This recommended that by optimizing IP-level vertical handover delay would really involve minimizing the discovery time and network registration period, where as address configuration period based on mobile device computing potential.

3. Simulation results

Horizontal handoff in WiFi network

This scenario shows the mobile station performance during horizontal handoff (roaming) between eight APs while the MS is moving in clock wise direction. This scenario shows WiFi wireless technology. This scenario also comprise one video conferencing server, one client connected to the server via L3 switch and wlan stations surrounding the access points. STA_0, STA_1, STA_2, STA_18, STA_19, STA_20 are roaming at a speed of 30 m/s around the access points and rest all stations are stationary. All the links used here are 100 BASE T links. The MS is roaming from AP0 to AP7 at the speed of 1 m/sec. The throughput of the MS that is stable between 10k – 20k bit/sec. But the throughput drops down during the handoff. The maxim delay points are 0.040 sec., which is considered to be tolerable for most applications.

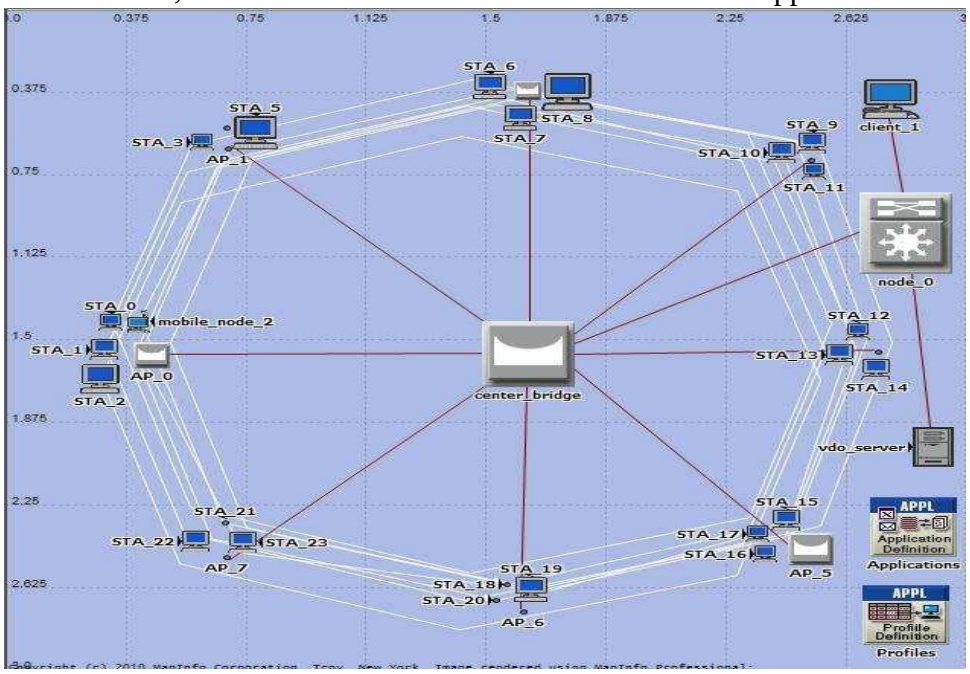


Fig. 3 : Set–up of WiFi Handoff

Table 1 : Wireless LAN Parameters (for mobile node)

BSS Identifier	0

Access Point Functionality	Disabled
Physical Characteristics	Direct Sequence
Data Rate (bps)	11 Mbps
Transmit Power (W)	0.002
Packet Reception-Power Threshold (dbm)	-95
CTS-to-self Option	Enabled
Short Retry Limit	7
Long Retry Limit	4
AP Beacon Interval (secs)	0.02
Max Receive Lifetime (secs)	0.5
Buffer Size (bits)	256000
Roaming Capability	Enabled
Large Packet Processing	Drop

Initially due to set up time, the delay is more. Then the mobile node and the stations start roaming around the access points and hence the delay is almost constant. Then after 9 minutes there is small increase in the delay which is again due to the non availability of stations. (bits/sec). The simulation time is 10 min. The throughput drops during handoff.

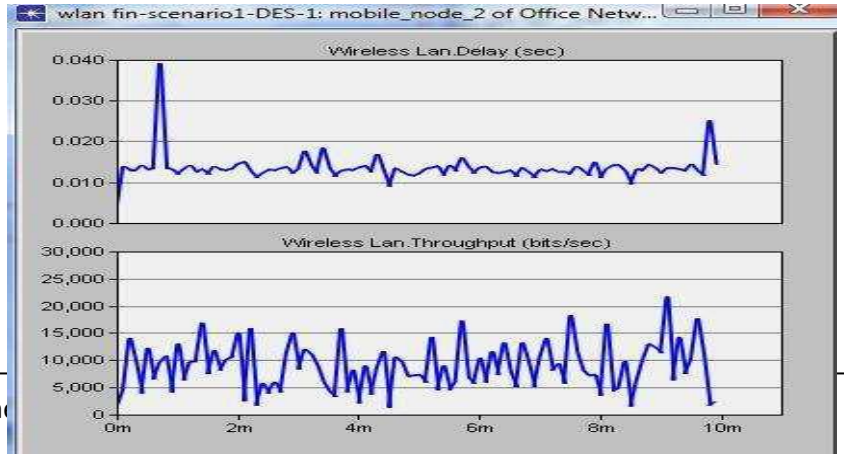


Fig 4 : Throughput and delay for MS in the WiFi set-up

Wlan Backbone

OPNET WLAN models support wireless-LAN backbones that consist of routers with WLAN interfaces belonging to the same BSS. These backbones can serve to WLAN EBSSs as well, where they are connected to the wireless backbone via their access points like they would be connected to a wired backbone. This scenario is built to provide an example on configuring such networks.

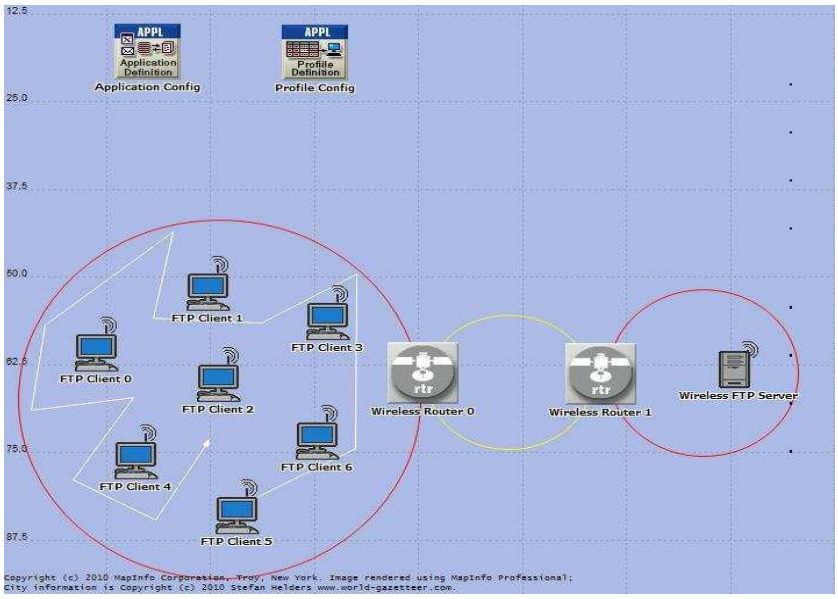


Fig 5 : Wlan network with wireless sever, router, wireless clients

The network contains wireless FTP clients and a wireless FTP servers. The clients and server belong to different wireless- LANs, BSS 0 and BSS 1, respectively. These two LANs connected to each other with two routers. These routers, which have two WLAN interfaces, serve as the access points for BSS 0 and BSS 1 and also compose the WLAN-backbone, which is the BSS 2. To achieve this, among the two WLAN interfaces of Wireless Router 0, the first interface, IF0, was configured as an access point and its BSS ID was set to 0. The access point fuctionality of the other interface, IF1, was disabled and its BSS ID was set to 2. The second router was also configured similarly. Hence, IF0s on the routers became the access points, and IF1s were connected to the backbone. The backbone-LAN, BSS 2, does not have an access point and doesn't need to have one, though it is possible to configure one of the backbone interfaces as an access point. Additionally the physical layer technology used by IF1s on the routers are set to "OFDM (802.11a)" to enable 802.11a data rates and their data rates are set to 54 Mbps. In other words, BSS 2 deploys the 802.11a PHY, while BSS 0 and BSS 1 use 802.11/11b PHYs. FTP client 5 is moving at a speed of 1 m/s in the defined trajectory path.

While all other clients are stationary.

Two routers form a wireless backbone network. FTP server, wireless router 1 is in one BSS, wireless router 0 and wireless router 1 are in other BSS, the FTP clients and wireless router 0 are in another BSS.

Table 2 : Wireless LAN Parameters (for Wireless FTP clients)

BSS Identifier	0
Access Point Functionality	Disabled
Physical Characteristics	Direct Sequence
Data Rate (bps)	2 Mbps
Transmit Power (W)	0.005
Packet Reception-Power Threshold (dbm)	-95
CTS-to-self Option	Enabled
Short Retry Limit	7
Long Retry Limit	4
AP Beacon Interval (secs)	0.02
Max Receive Lifetime (secs)	0.5
Buffer Size (bits)	256000
Roaming Capability	Enabled
Large Packet Processing	Drop

The performance of all the wireless FTP clients is observed and graphs obtained for delay, throughput and traffic received, traffic sent for the FTP clients. Since the FTP data is sent and received in the form of packets, hence the graphs show various sharp peaks.

Simulation time is taken as 4 Minutes.

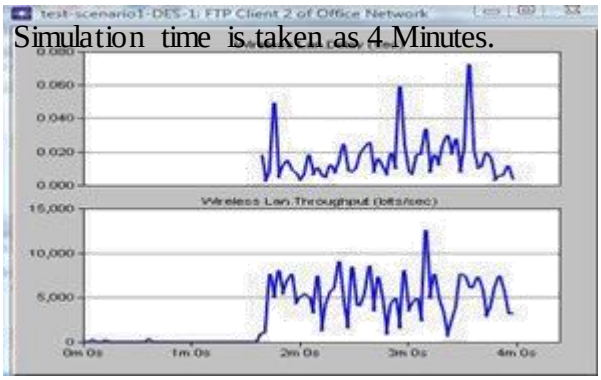


Fig 6: Traffic received and traffic sent (packets/sec) for FTP client 5

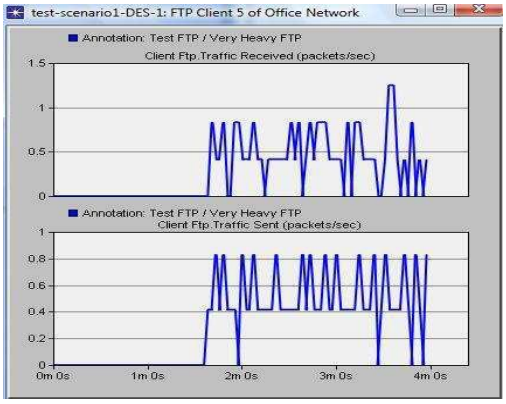
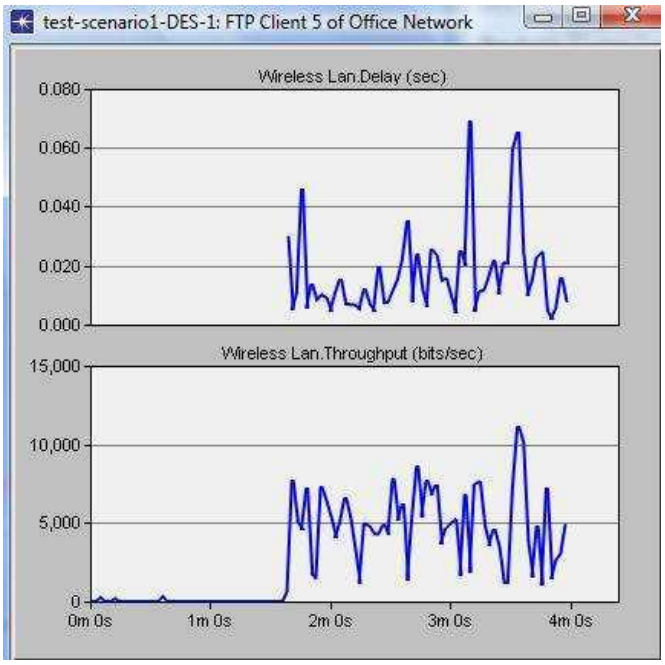
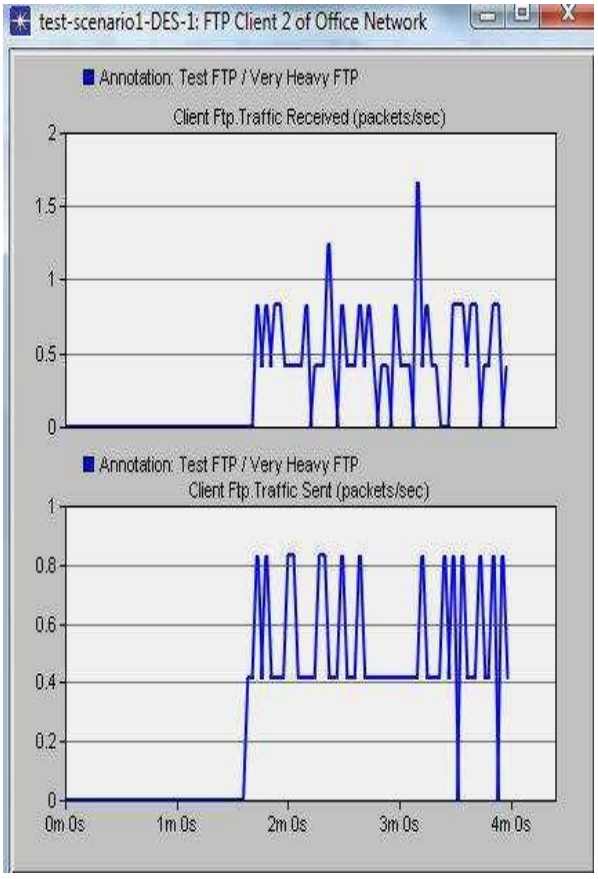


Fig. 8 : Delay and throughput for FTP client 2





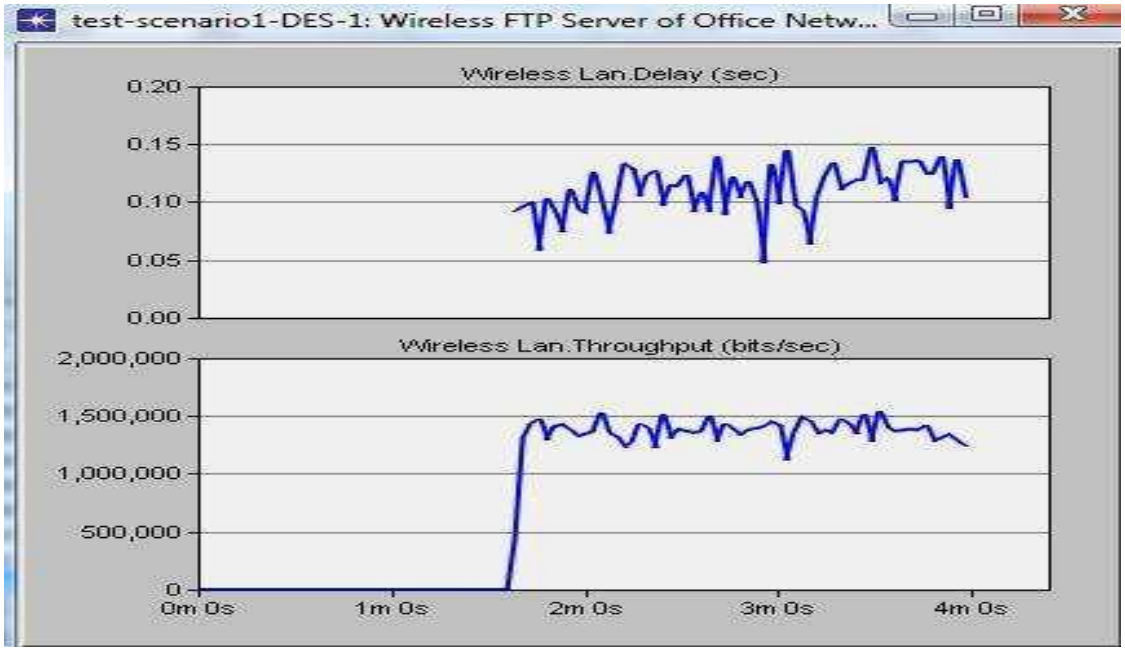


Figure 10: Delay and throughput for the Wireless

FTP Server

From the above graph it is clear that the set up time is more than 1 minute, after which the FTP data packets transmission starts.

Results saved with the scenario indicate the FTP traffic successfully flowing over the WLAN backbone between the wireless clients and server.

4. CONCLUSION

The vertical handover setup consists of a gateway, application server providing voice service to the wimax BS and to the wlan router. Initially both the mobile nodes are placed near the wimax BS from where they start roaming towards the wlan router. As they reach near the router, the wimax throughput is reduced and the WLAN throughput starts increasing which depicts vertical handoff triggering properties. The graphs for throughput and delay are obtained as expected.

REFERENCES:

(1)El-Hoiydi: On the Lifetime of Wireless Sensor Networks, IEEE Com- munications Letters, Vol. 9, No. 11, November 2005.

HOW TO IMPROVE SAFETY IN AUTOMOTIVE INDUSTRY: AIRBAG

Aditya Kaushik

Asst. Prof., S.B.M.N.E.C., Asthal Bohar, Rohtak Email: Adityakaushik15@gmail.com

INTRODUCTION

An airbag is a vehicle safety device. It is an occupant restraint system consisting of a flexible fabric envelope or cushion designed to inflate rapidly during an automobile collision. Its purpose is to cushion occupants during a crash and provide protection to their bodies when they strike interior objects such as the steering wheel or a window. Modern vehicles may contain multiple airbag modules in various side and frontal locations of the passenger seating positions, and sensors may deploy one or more airbags in an impact zone at variable rates based on the type, angle and severity of impact; the airbag is designed to only inflate in moderate to severe frontal crashes. Airbags are normally designed with the intention of supplementing the protection of an occupant who is correctly restrained with a seat belt. Most designs are inflated through pyrotechnic means and can only be operated once. Newer side-impact airbag modules consist of compressed air cylinders that are triggered in the event of a side impact vehicle impact.

TERMINOLOGY

Over time, various manufacturers have used different terms for airbags. In the 1970s, General Motors marketed its first airbag modules under the unwieldy name "Air Cushion Restraint System (ACRS)". Common terms in North America refer to a nominal role as a supplement to "active" restraints, i.e. seat belts. Because no action by a vehicle occupant is required to activate or use the airbag, it is considered a "passive" device. This is in contrast to seat belts, which are considered "active" devices because the vehicle occupant must act to enable them.

ORIGINS

The airbag specified for automobile use traces its origins to air-filled bladders as early as 1941.The invention is also credited independently to the German engineer Walter Linderer, and to the North American John W. Hetrick who in 1951 registered for the first of his airbag patents.[8] Linderer filed German patent #896,312 on October 6, 1951, which was issued on November 12, 1953, approximately three months after American John Hetrick was issued United States patent #2,649,311 on August 18, 1953.[9] Linderer's airbag was based on a compressed air system, either released by bumper contact or by the driver. Later research during the 1960s showed that compressed air could not inflate Linderer's airbag fast enough for maximum safety, thus making it an impractical system.

AS A SUPPLEMENT TO SEAT BELTS

Airbags for passenger cars were introduced in the United States in the mid-1970s, when seat belt usage rates in the country were quite low. Ford built an experimental fleet of cars with airbags in 1971, followed by General Motors in 1973 on Chevrolet vehicles. The early fleet of experimental GM vehicles equipped with airbags experienced seven fatalities, one of which was later suspected to have been caused by the airbag.

In 1974, GM made its "Air Cushion Restraint System" (ACRS) available as a regular production option (RPO code AR3) in full-size Cadillacs, Buick and Oldsmobile models. The GM cars from the 1970s equipped with ACRS had a driver-side airbag, a driver-side knee restraint (which consists of a padded lower dashboard), and a passenger-side airbag. The passenger-side airbag, protects both front passengers and unlike most newer ones, it integrated a knee cushion and a torso cushion, and it also had dual stage deployment which varied depending on the force of the impact. The cars equipped with ACRS

had lap belts for all seating positions but they did not have shoulder belts. Shoulder belts were already mandatory equipment in the United States on closed cars without airbags for the driver and outer front passenger seating positions, but GM chose to market its airbags as a substitute for shoulder belts.

As a supplemental restraint (SRS)

FRONTAL AIRBAGS

The auto industry and research and regulatory communities have moved away from their initial view of the airbag as a seat belt replacement, and the bags are now nominally designated as **Supplemental Restraint System (SRS)** or Supplemental Inflatable Restraints.

In 1981, Mercedes-Benz introduced the airbag in Germany as an option on its high-end S-Class (W126). In the Mercedes system, the sensors would automatically pre-tension the seat belts to reduce occupant's motion on impact (now a common feature), and then deploy the airbag on impact. This integrated the seat belts and airbag into a restraint system, rather than the airbag being considered an alternative to the seat belt.

Shaped airbags

The Citroën C4 provided the first "shaped" driver airbag, made possible by this car's unusual fixed hub steering wheel.

Side airbag

Side airbag inflated permanently for display purposes

Deployed curtain airbag and side torso airbag in a Citroën C4.

Deployed curtain airbag in an Opel Vectra

There are essentially two types of side airbags commonly used today, the side torso airbag and the side curtain airbag.

Most vehicles equipped with side curtain airbags also include side torso airbags. However some exceptions such as the Chevrolet Cobalt, 2007-09 model Chevrolet Silverado/GMC Sierra, and 2009-12 Dodge Ram do not feature the side torso airbag.

Side torso airbag

Side-impact airbags or side torso airbags (side thorax/abdomen airbags) are a category of airbag usually located in the seat, and inflate between the seat occupant and the door. These airbags are designed to reduce the risk of injury to the pelvic and lower abdomen regions. Some vehicles are now being equipped with different types of designs, to help reduce injury and ejection from the vehicle in rollover crashes. More recent side airbag designs include a two chamber system; a firmer lower chamber for the pelvic region and softer upper chamber for the ribcage.

Rear curtain airbag

In 2008, the Toyota iQ launched featuring the first production rear curtain shield airbag to protect the rear occupants' heads in the event of a rear end impact.

Seat cushion

In 2008 the Toyota iQ added a seat cushion airbag in the passenger seat. This is to prevent the pelvis from diving below the lap belt during a frontal impact or submarining. Later Toyota models such as the Yaris added the feature to the driver's seat as well.

CENTER AIRBAG

Front-center airbag of a Chevrolet Traverse deployed in an static out-of-position test. The purpose of the test was to find out how this airbag affects a 3 year old kid who is out of his seat and in the direct reach of the airbag.

SEAT BELT AIRBAG

In 2009, Toyota developed the first production rear-seat center airbag designed to reduce the severity of secondary injuries to rear passengers in a side collision. This system deploys from the rear center seat first appearing in on the redesigned Crown Majesta.[49] In late 2012 General Motors with supplier Takata introduced a front center airbag, it deploys from the driver's seat.[50]

IP TELEPHONY

Kavita

Department of computer science, S.B.M.N Engg. College, Asthal Bohar,Rohtak-124021(Haryana) INDIA
kavita.kathuria1990@gmail.com

If you've never heard of Internet Telephony, get ready to change the way you think about long-distance phone calls. Internet Telephony, or **Voice over Internet Protocol**, is a method for taking analog audio signals, like the kind you hear when you talk on the phone, and turning them into digital data that can be transmitted over the Internet.

How is this useful? Internet Telephony can turn a standard Internet connection into a way to place **free phone calls**. The practical upshot of this is that by using some of the free Internet Telephony software that is available to make Internet phone calls, you are bypassing the phone company (and its charges) entirely.

Above all else, Internet Telephony is basically a clever "reinvention of the wheel." In this article, we'll explore the principles behind Internet Telephony, its applications and the potential of this emerging technology, which will more than likely one day replace the traditional phone system entirely.

VOICE GATEWAY

The Internet Telephony network acts as a gateway to the existing PSTN network. This gateway forms the interface for transportation of the voice content over the IP network. Gateways are responsible for call origination, call detection, analog-to-digital conversion of voice, and creation of voice packets. Voice compression, echo cancellation, silence suppression, and statistics gathering are their optional features. The gateways must also perform some of the database services, such as phone number translations, host lookup, and signaling. Fig.1 shows the architecture of a typical gateway.

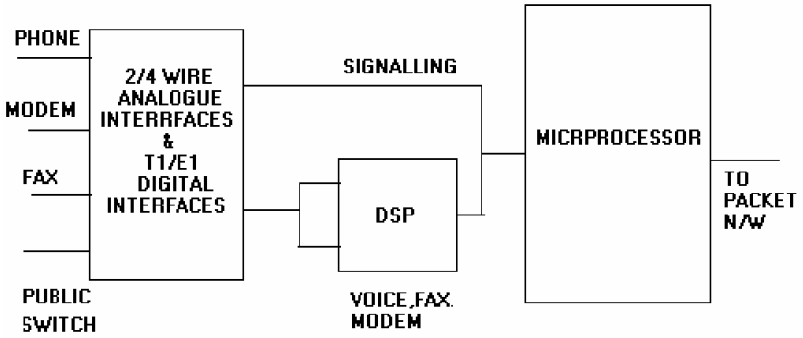


Figure 1 Architecture of a typical gateway

The functions like call origination, call detection, signaling, and phone number translations are performed by the microprocessor. Gateways exist in several forms; for example, the gateway could be a dedicated telecommunication equipment chassis, or even generic PC running Internet Telephony software.

A TYPICAL INTERNET TELEPHONY NETWORK

The IP network should ensure smooth delivery of voice and signaling information to the Internet Telephony elements. Since the IP network is to carry both voice and data, it must be able to prioritize the voice traffic. This prioritization is required for real-time Internet Telephony applications to ensure that voice traffic is unaffected by other network traffic. Without

prioritization, the voice packets may be bogged down by heavy data traffic like large file transfers using file transfer protocol (FTP).The voice packets are encapsulated with real-time protocol (RTP) and real-time control protocol (RTCP) for real-time transfer. The resource reservation protocol (RSVP) is used at the networking gateways (such as the routers) to reserve a particular amount of bandwidth for real-time applications (Internet Telephony, video multicasting, etc).

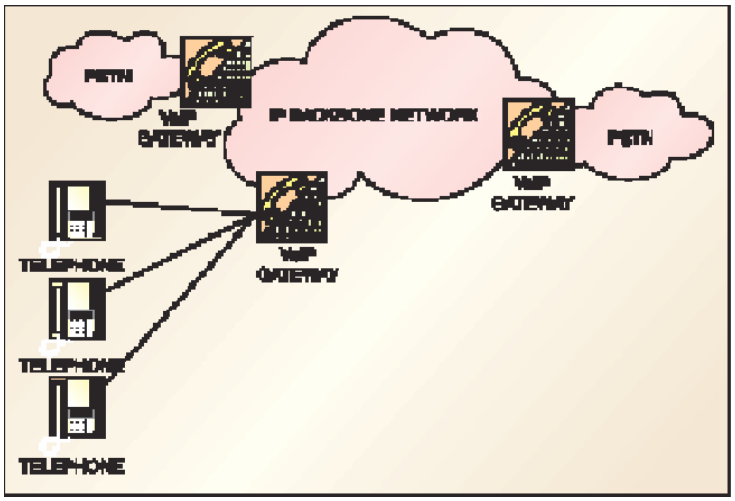


Figure 2 A typical full service internet telephony network

Unlike the PCM data streams in circuit switched telephony, Internet Telephony data travels over the networks in packets. In Internet Telephony digitized voice is bundled into IP packets and sent out into the network for delivery. Routers, switches, and other network equipment direct the packets to their destination IP address. This mode is called packet switched telephony. The transport of voice packets is affected by several factors, such as the amount of bandwidth available in the network connection, the delay that the packet experiences, and any packet loss or corruption that occurs. The ability of the network to deliver the voice packets quickly and consistently is referred to as Quality of Service (QoS).

APPLICATIONS

A wide variety of applications are enabled by the transmission of Internet Telephony networks.

- ✓ The first application, shown in Figure 3, is a network configuration of an organization with many branch offices (e.g., a bank) that wants to reduce costs and combine traffic to provide voice and data access to the main office. This is accomplished by using a packet network to provide standard data transmission while at the same time enhancing it to carry voice traffic along with the data.

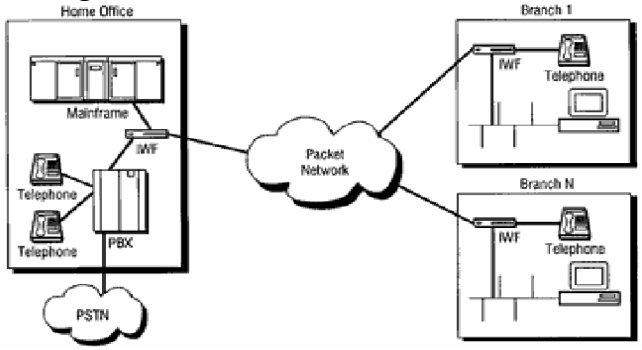


Figure 3. Branch office application

- ✓ A second Internet Telephony application, shown in Figure 4, is a trunking application. In this scenario, an organization wishes to send voice traffic between two locations over the packet network and replace the tie trunks used to connect the PBXs at the locations.

Figure 4. Interoffice trunking application

- ✓ A third application of Internet Telephony software is interworking with cellular networks, as shown in Figure 5. The voice data in a digital cellular network is already compressed and packetized for transmission over the air by the cellular phone. Packet networks can then transmit the compressed cellular voice packet, saving a tremendous amount of bandwidth.

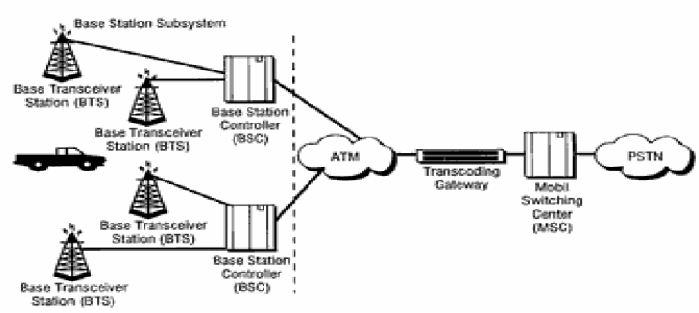


Figure 5. Interoffice trunking application

CONCLUSION

IP Telephone has grown in recent years because small business customers and consumers are clamoring for this technology because of its easy-to-use and sophisticated features that surpass those of traditional phones, its software upgrade potential, and its bandwidth efficiency. Examples of some cost-efficient residential IP Telephony services include Vonage, Packet8 and Skype.

EVALUATION OF FUTURE DIELECTRIC MATERIAL (HIGH-K GATE DIELECTRICS OF THIN FILMS) FOR MOS TECHNOLOGY

Jitender khurana

Department of Electronics and Communication, S.B.M.N Engineering college, Rohtak

ABSTRACT

The excellent dielectric properties of silicon dioxide (SiO2) have aided the evolution of microelectronics during the past decades. Reduced feature size improves the performance of an integrated circuit. However the performance of SiO2 as dielectric sets a limit on device scaling. In metal oxide field effect transistor (MOSFET) dielectric films with higher dielectric constant have better control over the channel electrons. A number of high dielectric materials are available to replace SiO2, but most of them have inherent disadvantages and incompatible with existing fabrication technology. Erbium based oxides have shown encouraging performance as high-k dielectric in MOS device.

Keywords: ***Dielectric, Fabrication, High-k, Leakage current, MOSFET, Silicon dioxide.***

1. INTRODUCTION

The scaling of device dimensions allows the integration of higher number of transistors on a chip. This scaling requires suitable dielectric material in a metal oxide field effect transistor (MOSFET). For decades silicon dioxide (SiO2) has been showing excellent performance with the reduction of device dimension. SiO2 is an excellent dielectric due to (i) the high quality interface between Si and SiO2, (ii) chemical and thermal stability at high temperature (~1000○C), (iii) good quality of insulation, (iv) the property of hard mask in different diffusion and doping process, and (v) high breakdown fields of 13 MV/cm. It is required to keep high capacitance density for channel formation in the sub-micron MOSFET with ultra thin SiO2 layer. The recent trend shows that the high leakage current will prevent the scaling of the SiO2 below 1nm for future applications. Therefore, thickness reduction of SiO2 gate layer below 1nm is a big challenge. Again defects are formed in the gate oxide at the SiO2/Si interface due to flow of charge carriers. If defect density reaches a certain threshold, this may cause quasi-breakdown on the gate layer. This is an important reliability issue of the transistor. An insulator with higher dielectric constant can be a solution. But the alternative insulator should have the following properties [1]: (i) chemical and electrical stability on silicon, (ii) uniform oxide thickness during fabrication, (iii) high breakdown voltage, (iv) thermal stability up to 1000○C, (v) pinhole free and negligible defects, (vi) low charge trapping and ionic impurities, (vii) high life time under normal operating conditions, (viii) low interface state density for high carrier mobility, (ix) small gate-leakage current (x) low hot-carrier degradation, (xi) low diffusivity of boron and phosphorous at typical processing conditions. Some of these properties depend on the material as well as on the processing technology. At first Cam bell et al. introduced TiO2 as the potential high-k gate dielectric [2]. Later various research groups work on the feasibility of other alternative high-k dielectric (e.g. Al2O3, ZrO2, Ta2O5, Er2O3, HfO2, ZrSixOy, Y2O3, and Ya2O3) for submicron MOSFET. All these high-k materials have some practical limitations. Recently binaries and ternaries of erbium (Er) show promising performance. In this paper we explain the various issues regarding the replacement of SiO2 by high-k dielectric which can fulfill the requirements of submicron MOSFETS. Section-II describes the factors that lead us to replace SiO2, section-III explains the criteria required for High-k dielectrics, section-IV

describes the fabrication challenges of high-k dielectric, section-V introduces some of the potential high-k dielectrics, and section-VI describes the performance issues of high-k dielectrics.

2. Challenges with Ultra-thin SiO2

The excellent material and electrical properties of SiO2 is the key to the success of the silicon based transistors. Thermal growth of SiO2 on Si is easy with a precisely controlled oxide thickness as well as a very high quality Si/SiO2 interface. Moreover, SiO2 has high resistivity, large bandgap, high melting and crystallization temperature, large electron and hole band offset, low defect density. The SiO2/Si interface is the heart of the CMOS gate stack structure. The scaling of the MOS-devices has become the driving force for the semiconductor industry to achieve the versatile functionality and better performance of the integrated circuit at a low cost [1]. In MOSFET the gate capacitance density will decrease with the reduction of the channel length and the gate area. The thin SiO2 faces several challenges with the scaling of the device, such as (i) increase in direct tunneling leakage current with decreasing gate oxide thickness, (ii) undesirable boron diffusion from the polysilicon gate through the oxide, (iii) poor reliability, (iv) high defect density, and (v) poor uniformity of the gate oxide. Therefore a new dielectric material is required to replace SiO2.

3. Desirable Criteria of High-k Dielectric

With the scaling of the MOS-device ultra-thin SiO2 suffers some unsolvable issues. Therefore, it is necessary to replace the SiO2 with a thicker layer of higher dielectric constant. Fig. shows the energy band gap variation with the dielectric constant. Since high-k dielectric is not as favorable as the native oxide (SiO2) some factors need to be considered while replacing SiO2 by other dielectric materials.

(i) Equivalent Oxide Thickness (EOT)
(ii) Energy Band Gap, Permittivity,and Barrier Height
(iii) Thermodynamic Stability
(iv) Alloy Crystallization
(v) Atomic Diffusion
(vi) High Quality Interface
(vii) Compatibility with Gate Electrode

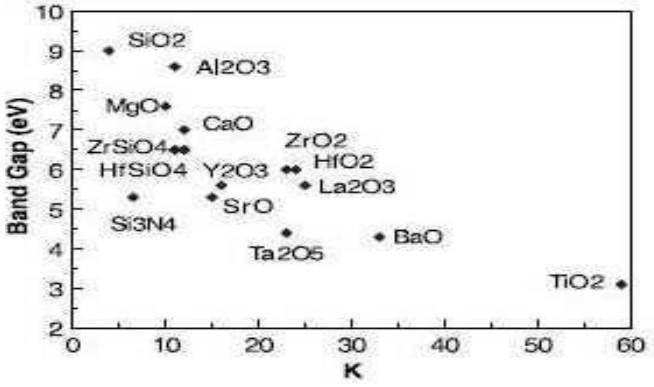


Fig. : Static dielectric constant vs. bandgap for candidate of high-k gate oxides, [3]

4. Deposition Techniques for High-k Dielectric

Deposition technique plays a major role to determine the dielectric film quality. The deposition process for high-k dielectric has to be compatible with the existing CMOS process technology. The widely used deposition techniques are physical vapor deposition (PVD), chemical vapor deposition (CVD), and MBE. However deposited oxide cannot be high quality like thermally grown oxide. Sputtering method is broadly available and can produce pure oxides. Sputtered oxides tend to have plasma-induced damage and they don't have good coverage. To produce highly pure and thin oxides, metal evaporation by electron beam can be applied. This technique has good control in case of small oxide thickness and it creates less damage than oxide sputtering. But it cannot be economical due to low throughput. Chemical vapor deposition (CVD) and atomic layer deposition (ALD) are the two preferred techniques in the commercial scale.

5. Deposition Techniques for High-k Dielectric

The potential high-k material should have some important properties in order to replace SiO2. First, the permittivity of the material should be much higher than 3.9, preferably greater than 12 [4]. Second, the metal oxide has to have both thermal (up to 1000°C) and chemical stability with silicon [4]. This requirement may eliminate some potential candidates such as Ta2O5, Nb2O5 [5].Third, the high-k material should have high enough band gap (> 5 eV) as well as high conduction band offset (1 eV) to prevent the leakage current [5]. A low defect at the Si/dielectric interface is required to have better mobility in the channel region. In this respect amorphous material is preferable over polycrystalline dielectric. Selection of high-k candidate is a challenging issue. There are a number of high-k dielectric materials such as Si3N4, TiO2, Al2O3, Er2O3, ZrO2, HfO2, Y2O3, La2O3, Gd2O3 etc. Among these, ZrO2 and HfO2 are probably the most promising. The rare earth oxides are also potential candidates though their permittivity increases slightly. Recently rare earth scan dates (e.g. GdScO3) have been introduced as high-k candidates, with permittivity of 20 which is higher than the permittivity of Gd2O3 [6].

5.1 Aluminum Oxide (Al2O3)

Al2O3 have high permittivity, high band gap, high band discontinuities, and good break down voltage. But at the high processing temperatures (~1000◦C) the mobility of the transistors degrades due to Al diffusion into the channel [7]. Moreover p-MOSFETs fail to function due to B diffusion through the Al2O3 layer to the Si channel. Al2O3 on Si shows a flat band voltage shift in the positive direction. This shift could arise from either damage associated with gate electrode deposition or further processing steps.

5.2 Titanium Oxide (TiO2)

TiO2 has been used as an alternative gate dielectric material for deep submicron MOSFET's by Campbell [8]. The dielectric constant of TiO2 is 80 [9]. The band gap of the material is 3.5 eV for amorphous films and 3.2 eV for crystalline films [10]. These band gaps are good for semiconductor but higher band gap is required to act as an effective insulator. Yan *et.al* shows that the leakage current through TiO2 is determined by the thermionic emission over a 1 eV barrier (which is the conduction band discontinuity) [11]**.** Therefore, TiO2 has low energy band offset with respect to Si. TiO2 has EOT of less than 10Aº. Transistors made with TiO2 shows near ideal behavior but they have challenges with mobility.

5.3 Zirconium Oxide (ZrO2)

ZrO2 is widely studied due to its dielectric constant ($\kappa \sim 25$) [12] as well as higher band gap (~5.8 eV). It is also thermodynamically stable with Si. However the crystallization temperature is about 500oC, which is low for ULSI processing. Lucovsky et al. has reported that

transition temperature can be improved by adding impurities into the film [13]. This is because they do pant atoms distorting the original ordered structure and therefore increase the entropy which in turn suppresses the crystallization process. Elements such Si, Al, and N are reported as effective do pant for this purpose [14]. Chui et al. have obtained 6–10 Aº EOT for ZrO2 on the Ge p-MOSFET.

5.4 Hafnium Oxide (HfO2)

HfO2 has been extensively studied due to its high dielectric constant and large energy band gap with high band offset. However, like ZrO2, HfO2 on Si substrate suffers from low crystallization temperature (~ 500oC).This crystallization temperature can be increased by incorporating Al2O3 with the HfO2 (HfxAl1-xO1-y). There is an interfacial layer at HfAl2O5/Si interface which decreases the interface defects and it then eventually reduces the leakage current. But it increases the EOT and belittles the high-k advantages.

5.5 Tantalum Pent oxide (Ta2O5)

Ta2O5 is a potential high-k candidate as it has high dielectric constant of 25 and reasonable band-gap of 4.4 eV. But due to poor thermal instability with Si and small electron band offset Ta2O5 is not popular for submicron MOSFET. But incorporation of Hf with Ta2O5 reduces the fixed charge density as well as leakage current. Addition of Zr with Ta2O5 increases the dielectric strength.

5.6 Erbium Oxide (Er2O3)

An effective relative dielectric constant in the range of 10– 14, a minimum leakage current density of 1 – 231028 A/cm2 at an electric field of 106 V/cm and break down electric field of 0.8– 1.73107 V/cm are demonstrated. The band gap of the material is 7.8 eV. These band gaps are good for semiconductor. The Er2O3 has low energy band offset with respect to Si. Er2O3 has EOT of less than 4.5 nm.

6. Challenges with High-k Dielectric

High-k dielectric gate oxide faces several challenges in MOS-devices. The major concerns are structural defects, mobility degradation, interface fixed charge, and do pant depletion in the poly-Si gate electrode.

(i) Structural Defect
(ii) Mobility Degradation
(iii) Threshold Voltage Control
(iv) Gate Electrode Selections

CONCLUSION

We have explained various issues that need to be consider while replacing SiO2 with high-k dielectric to meet the requirement of submicron devices. The main considerations are EOT, energy bandgap, barrier height, thermodynamic stability, crystallization, atomic diffusion, interface quality, and process compatibility. Different metal oxide can be used as high-k dielectric but they have some electrical and mechanical challenges during fabrication. These challenges can be solved significantly by using metal gate instead of poly-Si gate. It has been found that erbium based oxides are the most promising gate oxides.

REFERENCES

[1] S. Wolf, Silicon Processing for the VLSI Era: Deep-Submicron Process Technology, Sunset Beach, CA: Lattice Press, 2002.
[2] S. A. Campbell, D. C. Gilmer, X. Wang, M. T. Hsieh, H. S. Kim, W. L. Glatfelter, and J. H. Yan, "MOSFET Transistors Fabricated with High Permittivity TiO2 Dielectrics", IEEE Trans. Electron Dev.,Vol. 44, 1999 , p. 104.

[3] J. Robertson, “Band Offsets of Wide-band-gap Oxide and Implications for Future Electronic Devices”, J. Vac. Sci. Technol. B, Condense. Matter, Vol. 18, No. 3, 2000, pp. 1785-1791.
[4] J. Robertson, “High Dielectric Constant Oxides”, J. Appl. Phys., Vol. 28 , 2004, pp.265–291.
[5] K. J. Hubbard, D. G. Schlom, “Thermodynamic Stability of Binary Oxides in Contact with Silicon”, J. Mater. Res., Vol.11, 1996, p. 2757.
[6] S. Guha, E.P. Gusev, M. Copal, L-Å. Ragnarsson, and D.A. Buchanan, "Compatibility challenges for high-k materials integration into CMOS technology", MRS Bulletin, Vol. 27, 2002, pp.226-229.

NANO – RAM

Seema

Department of computer science, S.B.M.N Engg. College, Asthal Bohar,Rohtak-124021(Haryana) INDIA
seemakoshik16@yahoo.co.in

Nano-RAM is a proprietary computer memory technology from the company **Nantero**. It is a type of nonvolatile random access memory based on the position of carbon nanotubes deposited on a chip-like substrate. In theory, the small size of the nanotubes allows for very high density memories. Nantero also refers to it as **NRAM**

NRAM has a density, at least in theory, similar to that of DRAM. DRAM consists of a number of capacitors, which are essentially two small metal plates with a thin insulator between them. NRAM is similar, with the terminals and electrodes being roughly the same size as the plates in a DRAM, the nanotubes between them being so much smaller they add nothing to the overall size.

HISTORY

Nantero was founded in 2001, and headquartered in Woburn, Massachusetts. Due to the massive investment in flash semiconductor fabrication plants, no alternative memory has replaced flash in the marketplace, despite predictions as early as 2003 of the impending speed and density of NRAM. In 2005, NRAM was promoted as universal memory, and Nantero predicted it would be in production by the end of 2006. In August 2008, Lockheed Martin acquired an exclusive license for government applications of Nantero's intellectual property. By early 2009, Nantero had 30 US patents and 47 employees, but was still in the engineering phase. In May 2009, a radiation-resistant version of NRAM was tested on the STS-125 mission of the US Space Shuttle *Atlantis*.

Nantero raised a total of over $42 million through the November 2012 series D round. Investors included Charles River Ventures, Draper Fisher Jurvetson, Globespan Capital Partners, Stata Venture Partners and Harris & Harris Group. In May 2013, Nantero completed series D with an investment by Schlumberger. *EE Times* listed Nantero as one of "10 top startups to watch in 2013".

CHARACTERISTICS

- NRAM has a density, at least in theory, similar to that of DRAM.
- NRAM has terminals and electrodes roughly the same size as the plates in a DRAM, the nanotubes between them being so much smaller they add nothing to the overall size.
- NRAM appears to be limited only by lithography. This means that NRAM may be able to become much denser than DRAM, perhaps also less expensive. Unlike DRAM, NRAM does not require power to "refresh" it, and will retain its memory even after power is removed.
- NRAM can theoretically reach performance similar to SRAM, which is faster than DRAM but much less dense, and thus much more expensive.

Comparison with other non-volatile memory

Compared with other non-volatile random-access memory (NVRAM) technologies, NRAM has several advantages.

- NRAM reads and writes are both "low energy" in comparison to flash (or DRAM for that matter due to "refresh"), meaning NRAM could have longer battery life.
- It may also be much faster to write than either, meaning it may be used to replace both.

- NRAM is one of a variety of new memory systems, many of which claim to be "universal" in the same fashion as NRAM – replacing everything from flash to DRAM to SRAM.

An alternative memory ready for use is ferroelectric RAM (FRAM or FeRAM). FeRAM adds a small amount of a ferro-electric material to a DRAM cell. The state of the field in the material encodes the bit in a non-destructive format. FeRAM has advantages of NRAM, although the smallest possible cell size is much larger than for NRAM. FeRAM is used in applications where the limited number of writes of flash is an issue. FeRAM read operations are destructive, requiring a restoring write operation afterwards.

PHISHING

Kavita

Department of computer science, S.B.M.N Engg. College, Asthal Bohar,Rohtak-124021(Haryana) INDIA
kavita.kathuria1990@gmail.com

The convenience of online commerce has been embraced by consumers and criminals alike. Phishing, the act of stealing personal information via the internet for the purpose of committing financial fraud, has become a significant criminal activity on the internet. There has been good progress in identifying the threat, educating businesses and customers, and identifying counter measures. However, there has also been an increase in attack diversity and technical sophistication by the people conducting phishing and online financial fraud. Phishing has a negative impact on the economy through financial loses experienced by businesses and consumers, along with the adverse effect of decreasing consumer confidence in online commerce.

Phishing is an e-mail fraud method in which the perpetrator sends out legitimate-looking email in an attempt to gather personal and financial information from recipients. Typically, the messages appear to come from well known and trustworthy Web sites. Web sites that are frequently spoofed by phishers include PayPal, eBay, MSN, Yahoo, BestBuy, and America Online. A phishing expedition, like the fishing expedition it's named for, is a speculative venture: the phisher puts the lure hoping to fool at least a few of the prey that encounter the bait.

Phishing is the illegal attempt to acquire sensitive information such as usernames, passwords, and credit card details (and sometimes, indirectly, money), often for malicious reasons, by masquerading as a trustworthy entity in an electronic communication.

Along with an increase in the number of potential targets, there are three major factors that criminals have been able to take advantage of:

Unawareness of threat - If users are unaware that their personal information is actively being targeted by criminals, they may lack the perspective needed to identify phishing threats and may not take the proper precautions when conducting online activities.

Unawareness of policy - Phishing scams often rely on a victim's unawareness of organizational policies and procedures for contacting customers, particularly for issues relating to account maintenance and fraud investigation. Customers unaware of the policies of an online merchant are likely to be more susceptible to the social engineering aspect of a phishing scam, regardless of technical sophistication.

Criminals' technical sophistication - Criminals conducting phishing scams are leveraging technology that has been successfully used for activities such as spam, distributed denial of service (DDoS), and electronic surveillance. Even as customers are becoming aware of phishing, criminals have responded with technical tricks to make phishing scams more deceptive and effective.

PHISHING TRENDS

Social component – Criminals often use social engineering along with vulnerabilities in applications such as web browsers or email clients to trick users into installing malicious code on their computer.

Common infrastructure – We have observed the use of common tools and techniques for delivering phishing emails and distributing malware. These include the use of botnets, open mail relays, and compromised web sites to host phishing sites and malware.

The big picture - As countermeasures are implemented to thwart one method of stealing information, criminals still have additional opportunities available to them. It is important to understand the technical capabilities available to these criminals so that more effective measures for protecting customer information can be developed and law enforcement personnel tasked with tracking down and prosecuting criminals conducting phishing scams can be more effective.

Tackle Box

Just as with real fishermen, phishers today have a large tackle box of tools available to them. These tools serve a variety of functions, including email delivery, phishing site hosting, and specialized malware.

- Bots/Botnets
- Phishing Kits
- Technical Deceit
- Session Hijacking
- Abuse of Domain Name Service (DNS)
- Specialized Malware

PHISHING COUNTERMEASURES

Various solutions have been developed in response to phishing. These solutions target both technical and non-technical problem areas.

Widely Implemented Countermeasures

Although there are multiple recommendations for countering phishing, the following list contains the ones most commonly implemented today to either combat phishing directly or to mitigate phishing-capable threats such as malware.

- Awareness and Education
- Targeting Hosting Sites
- Web Browser Toolbars
- Strong Authentication and Authorization
- Virus, Spyware, and Spam Prevention

Recommendations

Though there has been an increase in the general public's awareness of phishing and has been success in reactive solutions to prevent phishing scams, countermeasures need to be designed with the big picture in mind. Based on the trends in the technical capabilities of phishing, the following recommendations provide high-level guidance for businesses, customers, and law enforcement to help them deal with the increasing technical capabilities of criminals conducting phishing scams.

- Vigilance
- Foresight

CONCLUSION

Phishing is a highly profitable activity for criminals. Over the past two years, there has been an increase in the technology, diversity, and sophistication of these attacks in response to increased user awareness and countermeasures, in order to maintain profitability.

These trends are important to understand as they show the ability of criminals to recognize and adapt to increasing awareness of and response to phishing. By properly understanding the continual evolution of technical capabilities used by those who commit phishing and online financial fraud in general, more effective countermeasures and more secure online commerce systems can be developed.

ENCRYPTION TECHNIQUE

Rajiv Sharma

*Computer Science Engineering Department, Shri Baba Mastnath Engineering College, Asthal Bohar, Rohtak, Haryana, India

rajivsharma.075@ymail.com

In cryptography, encryption is the process of encoding messages or information in such a way that only authorized parties can read it.Encryption does not of itself prevent interception, but denies the message content to the interceptor. In an encryption scheme, the message or information, referred to as plaintext, is encrypted using an encryption algorithm, generating ciphertext that can only be read if decrypted. For technical reasons, an encryption scheme usually uses a pseudo-random encryption keygenerated by an algorithm. It is in principle possible to decrypt the message without possessing the key, but, for a well-designed encryption scheme, large computational resources and skill are required. An authorized recipient can easily decrypt the message with the key provided by the originator to recipients, but not to unauthorised interceptors.

TYPES OF ENCRYPTION

SYMMETRIC KEY ENCRYPTION

In symmetric-key schemes, the encryption and decryption keys are the same. Thus communicating parties must have the same key before they can achieve secret communication.

PUBLIC KEY ENCRYPTION

In public-key encryption schemes, the encryption key is published for anyone to use and encrypt messages. However, only the receiving party has access to the decryption key that enables messages to be read. Public-key encryption was first described in a secret document in 1973; before then all encryption schemes were symmetric-key (also called private-key).

A publicly available public key encryption application called Pretty Good Privacy (PGP) was written in 1991 by Phil Zimmermann, and distributed free of charge with source code; it was purchased by Symantec in 2010 and is regularly updated.

Uses of Encryption have long been used by military and governments to facilitate secret communication. It is now commonly used in protecting information within many kinds of civilian systems. For example, the Computer Security Institute reported that in 2007, 71% of companies surveyed utilized encryption for some of their data in transit, and 53% utilized encryption for some of their data in storage.[7] Encryption can be used to protect data "at rest", such as files on computers and storage devices (e.g. USB flash drives). In recent years there have been numerous reports of confidential data such as customers' personal records being exposed through loss or theft of laptops or backup drives. Encrypting such files at rest helps protect them should physical security measures fail. Digital rights management systems, which prevent unauthorized use or reproduction of copyrighted material and protect software against reverse engineering (see also copy protection), is another somewhat different example of using encryption on data at rest.

Encryption is also used to protect data in transit, for example data being transferred via networks (e.g. the Internet, e-commerce), mobile telephones, wireless microphones,wireless intercom systems, Bluetooth devices and bank automatic teller machines. There have been numerous reports of data in transit being intercepted in recent years. Encrypting data in transit also helps to secure it as it is often difficult to physically secure all access to networks.

MESSAGE VERIFICATION

Encryption, by itself, can protect the confidentiality of messages, but other techniques are still needed to protect the integrity and authenticity of a message; for example, verification of a message authentication codes (MAC) or a digital signature. Standards for cryptographic software and hardware to perform encryption are widely available, but successfully using encryption to ensure security may be a challenging problem. A single error in system design or execution can allow successful attacks. Sometimes an adversary can obtain unencrypted information without directly undoing the encryption. See, e.g., traffic analysis, TEMPEST, or Trojan horse.

Digital signature and encryption must be applied to the cipher text when it is created (typically on the same device used to compose the message) to avoid tampering; otherwise any node between the sender and the encryption agent could potentially tamper with it. Encrypting at the time of creation is only secure if the encryption device itself has not been tampered with.

ROLE OF E-COMMERCE IN EDUCATIONAL SECTOR

Ritika khurana

Assistant Professor SBMN Engg. College

INTRODUCTION

Information technology is the key factor for the development of post industrial society. The Business in this modern era are networked and use information Technology to survive in a highly competitive environment. Information Technology, E-Commerce and their role in higher education in commerce discussed in this paper.

TECHNICAL ADVANCEMENT IN EDUCATION

The growing phenomenon of globalization, liberalization and privatization has been immensely influencing the higher education commerce in particular. The technological revolution has further provided new dimensions. E-commerce, e-finance, e-marketing, e-investment, e-banking, paperless trading and governance has been gaining importance all over the World. At the same time, the outsourcing business, call center activities, small business operation, IT based services etc, are expanding very fast.

The technological advancements must be integrated into the basic fabric of higher education in commerce. In fact, development of IT skills provides edge to commerce graduates in dealing with the changing scenario of trade, commerce and industry. Moreover, it will further help in creating new employment avenues in the market.

Importance of Information Technology

The continuous strife of business to increase productivity and efficiency, reduce the costs of their products and services, and use technology to continually innovate in order to expand and create new markets is not new. It is just that today, competition is much more severe than ever before. Technology is an enabler of change and a method, but change itself has to be driven by business drivers that take advantage of the technology.

For several business of today do not have sufficient time to strengthen themselves in this changing age. There are continuous changes in the market, in customer needs, in technology, in the system environments and also changes in the rules, regulations and legislations of governments. The challenge into the present business world is not only to survive competition, and use new technologies, but also to manage change in technology and in markets.

E-COMMERCE

E-Commerce is associated with buying and selling of information, products and services over computer communication networks. E-Commerce helps to conduct traditional commerce through new ways of transferring and processing information. Since, it is an information which is at the heart of any commercial activity. Information is electronically transferred from computer to computer, in an automated way.

Parts of E-Commerce

High-end-e-commerce application development like end-to-end shopping mall/storefront, web hosting services, web performance tuning, domain name registration, web-enabling mission-critical legacy applications, providing interfacing to enterprise applications like ERP,SCM,CRM, specialized workflow management software, IT infrastructure management, performance-tuning etc are important part of the e-commerce.

Further it Includes

Internet Service Providers

Content-mangers

The primary job of ISP is to

Manage a high-speed internet backbone to carry all the e-commerce data

Ensure access to their digital pipe through many access devices that include data modems, ADSL, cable modern, cell phones, palm tops & Web TV(digital taps) and

Manage lacks of customers

The infrastructure management is primarily technical & a strong background in Electronics & Communication engineering or computer networking is a must. Customer management is an area where liberal arts, commerce graduates, management degree holders & others can excel. Management an ISP node in remote areas would call for a combination of technical and business skills.

Much of Web design is about HTML, XML, Web and Database integration, Web-enabling and Perl and Java Script. Yet it calls for creativity and aesthetic appreciation to win customers, visual Design, Graphic design, Audio & Video mastery and an eye for beauty & aesthetics are must. Thanks to very powerful web design tools and creative skills that would dominate technical skills in Web design area. Web hosting itself is emerging as a vast area of business and is more of Infrastructure management than mere creation of Web pages.

E-Commerce Courses

The course on e-commerce is nothing but a set of courses include,

HTML,DHTML,JAVA, ASP,JSP,XML,FRONTPAGE

Oppourtunities for Commerce Students

Commerce students of tomorrow must need awareness will be well advised to develop a deep understanding of e-commerce. In fact, M.Com and MBA tomorrow will be M.Com (e-commerce) e-MBA with specialized courses on E-Marketing, E-Finance, E-HR and E-Production and E-Hospital management also.

With every business embracing e-business the demand for professionals who can address these issues would rise significantly and called as, over the years, they would not call themselves as e-commerce experts, they would be registration management experts, store-front developers, site management experts, web strategists, application reengineering experts, workflow experts, performance experts, payment systems experts or web-hosting experts! Such professionals would be the first IT professionals with years of experience and note that e-commerce experts who were suddenly "dressed-up" through a one year crash course on e-commerce from the street comer shops. On the whole, e-commerce is a huge opportunity. There is a place for everyone. The close links and synergistic environment have to be created between industrial activities and commerce education.

Conclusions

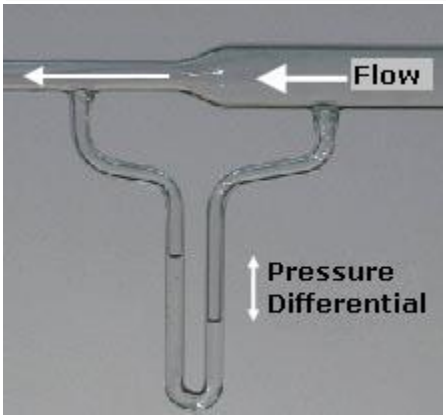
The skills, attitudes, training and values must be imparted to commerce students in such a way that suit the requirements of the industry. The influx of foreign universities in the country poses new challenges to the commerce education. The whole educational components required to be strengthened for facing the competition. The industrial requirements based curriculum should be developed to enhance employability of our commerce graduates. The students equipped with the new knowledge and skill will be able to deal with the changing business environment effectively.

BERNOULLI'S PRINCIPLE

Sandeep Kumar Jangra

*Mechanical Engineering Department, Shri Baba Mastnath Engineering College, Asthal Bohar, Rohtak, Haryana, India sandeepjangra095@ymail.com

This article is about Bernoulli's principle and Bernoulli's equation in fluid dynamics. For Bernoulli's theorem in probability, see law of large numbers. For an unrelated topic in ordinary differential equations, see Bernoulli differential equation.



A flow of air into a venturi meter. The kinetic energy increases at the expense of the fluid pressure, as shown by the difference in height of the two columns of water. In fluid dynamics, Bernoulli's principle states that for an inviscid flow of a nonconducting fluid, an increase in the speed of the fluid occurs simultaneously with a decrease in pressure or a decrease in the fluid's potential energy.[1][2] The principle is named after Daniel Bernoulli who published it in his book Hydrodynamica in 1738. Bernoulli's principle can be applied to various types of fluid flow, resulting in what is loosely denoted as Bernoulli's equation. In fact, there are different forms of the Bernoulli equation for different types of flow. The simple form of Bernoulli's principle is valid forincompressible flows (e.g. most liquid flows and gases moving at low Mach number). More advanced forms may in some cases be applied to compressible flows at higher Mach numbers (see the derivations of the Bernoulli equation).

Bernoulli's principle can be derived from the principle of conservation of energy. This states that, in a steady flow, the sum of all forms of energy in a fluid along a streamline is the same at all points on that streamline. This requires that the sum of kinetic energy, potential energy and internal energy remains constant.[2] Thus an increase in the speed of the fluid – implying an increase in both its dynamic pressure and kinetic energy – occurs with a simultaneous decrease in (the sum of) its static pressure, potential energy and internal energy. If the fluid is flowing out of a reservoir, the sum of all forms of energy is the same on all streamlines because in a reservoir the energy per unit volume (the sum of pressure and gravitational potential $\rho g h$) is the same everywhere.

Bernoulli's principle can also be derived directly from Newton's 2nd law. If a small volume of fluid is flowing horizontally from a region of high pressure to a region of low pressure, then there is more pressure behind than in front. This gives a net force on the volume, accelerating it along the streamline.

INCOMPRESSIBLE FLOW EQUATION

In most flows of liquids, and of gases at low Mach number, the density of a fluid parcel can be considered to be constant, regardless of pressure variations in the flow. Therefore, the fluid can be considered to be incompressible and these flows are called incompressible flow. Bernoulli performed his experiments on liquids, so his equation in its original form is valid only for incompressible flow. A common form of Bernoulli's equation, valid at any arbitrary point along a streamline, is:

$$\frac{v^2}{2} + gz + \frac{p}{\rho} = \text{constant}$$

where:

v is the fluid flow speed at a point on a streamline,

g is the value of acceleration due to gravity,

z is the elevation of the point above a reference plane, with the positive z-direction pointing upward – so in the direction opposite to the gravitational acceleration,

p is the pressure at the chosen point, and

ρ is the density of the fluid at all points in the fluid.

For conservative force fields, Bernoulli's equation can be generalized as:

$$\frac{v^2}{2} + \Psi + \frac{p}{\rho} = \text{constant}$$

where Ψ is the force potential at the point considered on the streamline. E.g. for the Earth's gravity $\Psi = gz$.

The following two assumptions must be met for this Bernoulli equation to apply:

The flow must be incompressible – even though pressure varies, the density must remain constant along a streamline; friction by viscous forces has to be negligible. In long lines mechanical energy dissipation as heat will occur. This loss can be estimated e.g. using Darcy–Weisbach equation.

By multiplying with the fluid density ρ, equation (A) can be rewritten as:

$$\tfrac{1}{2}\rho v^2 + \rho g z + p = \text{constant}$$

or:

$$q + \rho g h = p_0 + \rho g z = \text{constant}$$

where:

$$q = \tfrac{1}{2}\rho v^2$$

is dynamic pressure,

$$h = z + \frac{p}{\rho g}$$

is the piezometric head or hydraulic head (the sum of the elevation z and the pressure head) and

$$p_0 = p + q$$

is the total pressure (the sum of the static pressure p and dynamic pressure q).

The constant in the Bernoulli equation can be normalised. A common approach is in terms of total head or energy head H:

$$H = z + \frac{p}{\rho g} + \frac{v^2}{2g} = h + \frac{v^2}{2g},$$

The above equations suggest there is a flow speed at which pressure is zero, and at even higher speeds the pressure is negative. Most often, gases and liquids are not capable of negative absolute pressure, or even zero pressure, so clearly Bernoulli's equation ceases to be valid before zero pressure is reached. In liquids – when the pressure becomes too low – cavitation occurs. The above equations use a linear relationship between flow speed squared and pressure. At higher flow speeds in gases, or for sound waves in liquid, the changes in mass density become significant so that the assumption of constant density is invalid.

WATER SUPPLY & DISTRIBUTION SYSTEMS

Sonu Panchal

Department of Civil Engineering, SBMNEC, Asthal Bohar, Rohtak, Haryana, India; Email: sonu.007panchal@yahoo.com

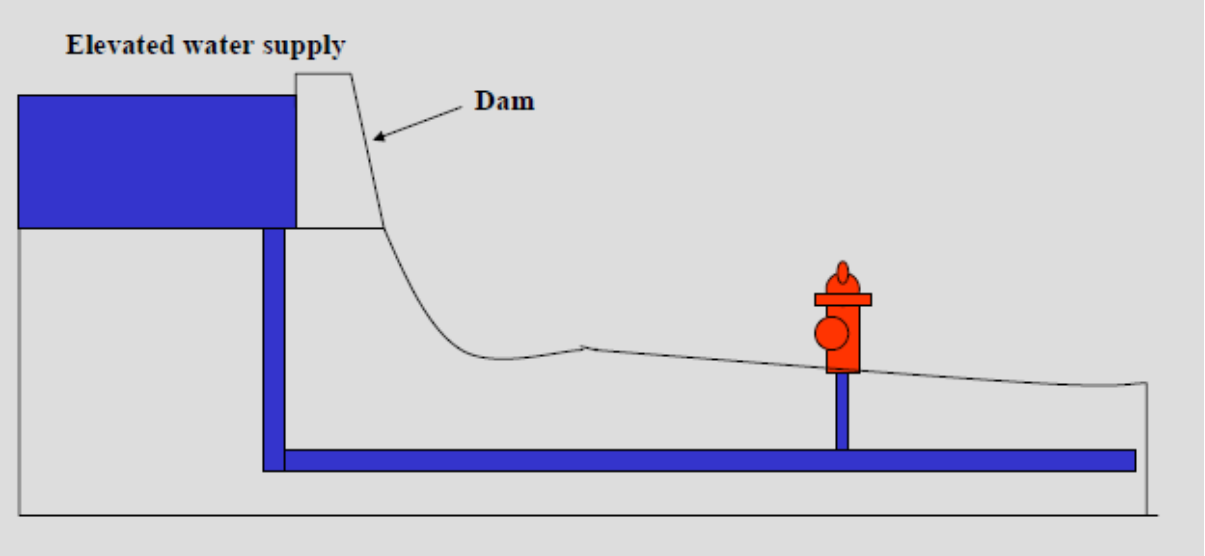
INTRODUCTION

Water supply is a critical determinant for communities. Distribution system is the system of water supply to convey the water to consumer with the same degree of purity and required pressure level. The distribution system consists of pipes of various sizes, Valves, Meter pumps, distribution reservoirs etc. Depending upon the methods of distribier the distribution system is classified as follows:-

(i) Gravity system
(ii) Pumping system
(iii) Dual system

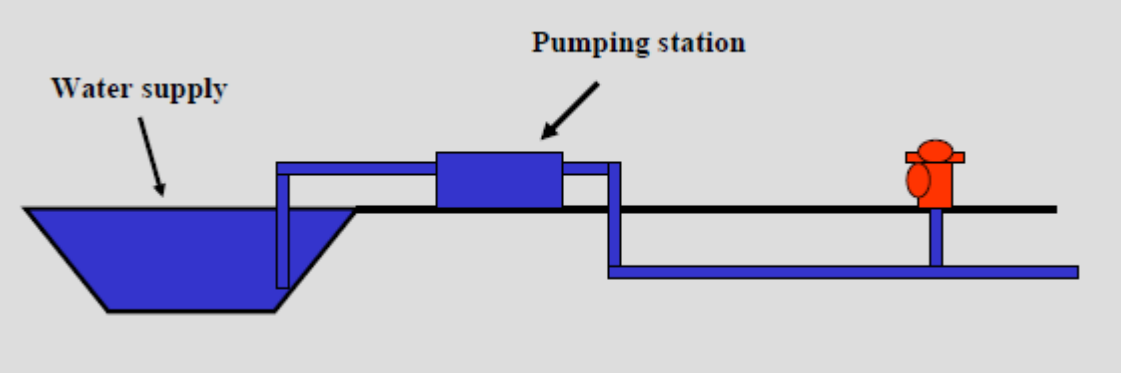
1.) GRAVITY SYSTEM:-

When the ground level, sufficiently high above the ground level is available this can be best utilized for the distribution system in maintaining pressure in pipes. The water flow in mains due to gravitational force. No pumping is required.



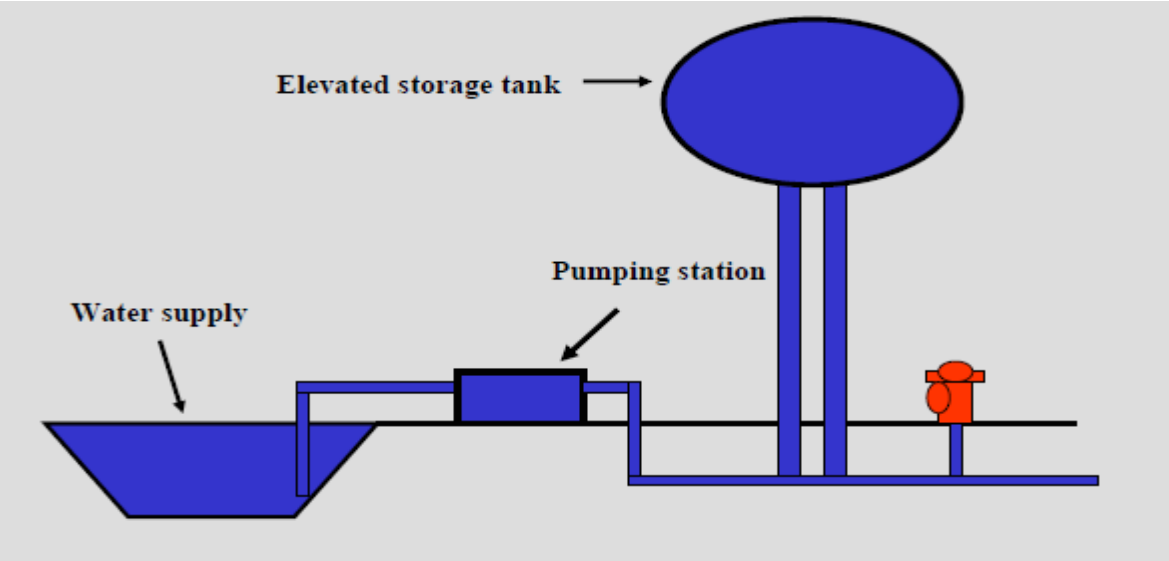
2.) PUMPING SYSTEM:-

In this system water is directly pumped in mains. Since the pump has to work at different rates in a day, the maintenance cost increases. This system should be avoided whenever possible



3.) DUAL SYSTEM:-

The pump is connected to mains as well to an elevated reservoir . in the beginning when the demand is low the water is stored in elevated reservoir , but when demand increases the rate of pumping, flow in the distribution system comes from both the pumping station as well as elevated reservoir. This system is more reliable and economical.



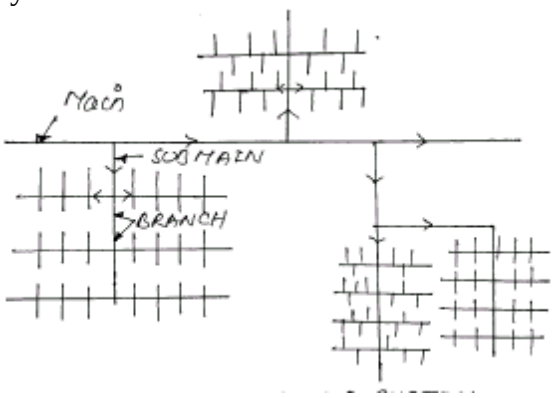
LAYOUTS OF DISTRIBUTION SYSTEM

Generally in practice there are four different systems of distribution which are used. They are:

1. Dead End or Tree system
2. Grid Iron system
3. Circular or Ring system
4. Radial system

1.) DEAD END OR TREE SYSTEM:

This system is suitable for irregular developed towns or cities. In this system water flows in one direction only into submains and branches. The diameter of pipe decreases at every tree branch.

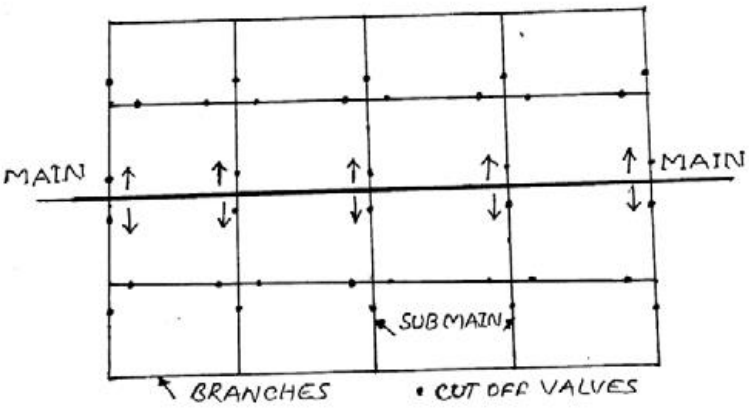


Dead End System

2.) GRID IRON SYSTEM

From the mains water enters the branches at all Junctions in either directions into

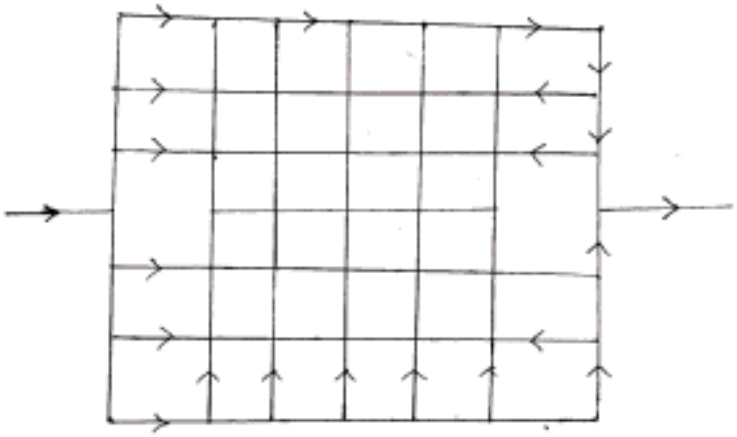
submains of equal diameters. At any point in the line the pressure is balanced from two directions because of interconnected network of pipes.



Grid – Iron Method

3.) CIRCULAR OR RING SYSTEM

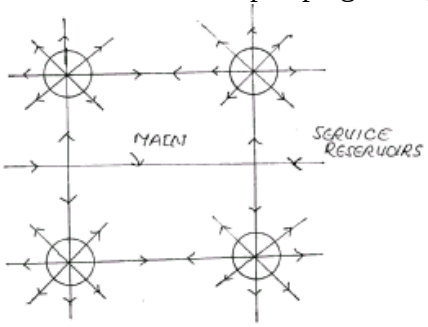
Supply to the inner pipes is from the mains around the boundary. It has the same advantages as the grid-Iron system. Smaller diameter pipes are needed. The advantages and disadvantages are same as that of grid-Iron system.



Circular of Ring System

4.) RADIAL SYSTEM:

This is a zoned system. Water is pumped to the distribution reservoirs and from the reservoirs it flows by gravity to the tree system of pipes. The pressure calculations are easy in this system. Layout of roads need to be radial to eliminate loss of head in bends.This is most economical system also if combined pumping and gravity flow is adopted**.**



Radial System

PROS AND CONS OF SOCIAL MEDIA IN THE CLASSROOM

Subham Gandhi[1], Ajay Madan[2]

[1]Associate Professor, [2]Assistant Professor SBMN Engg College, Asthal Bohar, Rohtak (HR)

There's an ongoing debate about the role social media playing in the education. Advocates point out the benefits that social media provides for today's digital learners while critics call for regulation and for removing social media from classrooms. Finding a middle ground has become a challenge. As an educational tool, social media enriches the learning experience by allowing students and teachers to connect and interact in new, exciting ways. Web sites such as Facebook, Twitter, and LinkedIn provide a platform where users can dialog, exchange ideas, and find answers to questions. These sites are designed to foster collaboration and discussion.

Despite these benefits, critics argue that there are serious risks to using social media in the classroom. What are these risks—and do they outweigh the potential for opportunity.

PROS

Educational Tool Today's students arrive on campus, fluent in Web and social networking technologies. Educators can leverage this knowledge to enrich the learning experience. With social media, instructors can foster collaboration and discussion, create meaningful dialogue, exchange ideas, and boost student interaction.

Enhance Student Engagement Social media is an effective way to increase student engagement and build better communication skills. Students who rarely raise a hand in class may feel more comfortable expressing themselves on Facebook, Twitter, or YouTube. Social networking platforms enable teachers to establish "back channels" that foster discussion and surface ideas that students are too shy or intimidated to voice out loud.

Improve Communication Among Students and Teachers Facebook and Twitter can enhance communication among students and teachers. Educators can answer students' questions via a Facebook page or Twitter feed, post homework assignments and lesson plans, send messages and updates, schedule or announce upcoming events, and share interesting Web sites and multimedia content. Students can use Twitter to get help from instructors or other students. A great way for instructors to give participation points in addition to in class participation is by having students tweet about something that was discussed in class.

Preparing Students for Successful Employment Students entering the workforce can use social networking sites to network and find employment. With LinkedIn, students can establish a professional web presence, post a resume, research a target company or school, and connect with other job seekers and employers. College career centers and alumni associations are using Twitter to broadcast job openings and internships. Students should follow businesses or professional organizations on Facebook and Twitter to stay updated on new opportunities and important developments in their field.

CONS

Social Media can be a Distraction A common complaint among educators is that social media is distracting in the classroom. These instructors maintain that tools like Facebook and Twitter divert students' attention away from what's happening in class and are ultimately disruptive to the learning process. With the possibility that the use of social media tools can be an invitation for students to goof off, instructors should make sure they won't be abused.

Cyberbullying While social networking sites provide a way for students and teachers to connect, they can be a weapon of malicious behavior--even on college campuses. In a study about cyberbullying at Indiana State University, researchers Christine Macdonald and Bridget Roberts-Pittman found that almost

22 percent of college students admit to being harassed online. Of this group, 25 percent report they were bullied through a social networking site. Instructors who use social media as part of their course activities should be aware of potential dangers and plan to intervene on minor incidents before they become more serious. "By intervening at minor behaviors, we can stop more severe negative behaviors," said Macdonald. "We must insist on civil and respectful behavior."

Discouraging Face-to-Face Communication Some educators are concerned that while real-time digital stream may create a safe harbor for students who are uncomfortable expressing themselves, students are missing valuable lessons in real-life social skills. Students may find themselves at a disadvantage during college admission or job interviews when they need to command attention and deliver a coherent message. At social gatherings and in personal relationships, they need to be able to effectively express themselves and connect with others.

Ultimately, while the debate continues over what role social media should play in the classroom, no one can argue the influence that social networking has on today's students. This tech-savvy generation conducts much of their life through social media channels. Not surprisingly, they're already using YouTube, Facebook, and Twitter as tools for learning and collaboration. They expect that their campuses will follow suit. With this in mind, it seems prudent for today's institutions to get on the social media train and find ways to successfully integrate these tools into the classroom.

Conclusion:

Social networking clearly has its pros and cons. With careful monitoring and usage, social media can be an effective form of communication in the classroom. It should be used to encourage discussion and collaboration, in addition to face to face communication. In today’s digital era we can’t ignore using social media in the classrooms, however, it needs to be monitored. Social media could boost student engagement and student's desire to come to class because it is something more familiar to them. But there are some serious repercussions using social media if not monitored closely by administration. The most obvious is cyberbullying. This is becoming more and more of a problem for young children today. Another disadvantage to social media in the classroom is that students may not fully develop their communication skills when talking to someone face-to -face. Things like eye contact and shaking hands goes out the window when our main focus is social media and that can affect our children down the road. Monitoring the correct use might be the key to insuring the use of the application is actually working toward the learning objective. Thus, more research is needed in this regard for the sake of future of students.

TO STUDY OF DISK BRAKE BY USING ANSYS SOFTWARE

Aditya Kaushik[1], Sumit[2]

[1,2]Asst. Prof., S.B.M.N.E.C., Asthal Bohar, Rohtak Email: Adityakaushik15@gmail.com
Engr.sumit1990@gmail.com

ABSTRACT

In this paper the thermo elastic phenomenon occurring in the disk brakes, the occupied heat conduction and elastic equations are solved with contact problems. The numerical simulation for the thermo elastic behavior of disk brake is obtained in the repeated brake condition. The computational results are presented for the distribution of heat flux and temperature on each friction surface between the contacting bodies. Also, thermo elastic instability (TIE) phenomenon (the unstable growth of contact pressure and temperature) is investigated in the present study, and the influence of the material properties on the thermo elastic behaviors (the maximum temperature on the friction surfaces) is investigated to facilitate the conceptual design of the disk brake system. Based on these numerical results, the thermo elastic behaviors of the carbon-carbon composites with excellent mechanical properties are also discussed.

I. INTRODUCTION

A disk brake consists of a cast iron disk bolted to the wheel hub and a stationary housing called caliper. The caliper is connected to some stationary part of the vehicle like the axle casing or the stub axle as is cast in two parts each part containing a piston. In between each piston and the disk there is a friction pad held in position by retaining pins, spring plates etc. passages are drilled in the caliper for the fluid to enter or leave each housing. The passages are also connected to another one for bleeding. Each cylinder contains rubber-sealing ring between the cylinder and piston.

When the brakes are applied, hydraulically actuated pistons move the friction pads in to contact with the rotating disk, applying equal and opposite forces on the disk. Due to the friction in between disk and pad surfaces, the kinetic energy of the rotating wheel is converted into heat, by which vehicle is to stop after a certain distance. On releasing the brakes the brakes the rubber-sealing ring acts as return spring and retract the pistons and the friction pads away from the disk.

In the course of brake operation, frictional heat is dissipated mostly into pads and a disk, and an occasional uneven temperature distribution on the components could induce severe thermo elastic distortion of the disk.

The thermal distortion of a normally flat surface into a highly deformed state, called thermo elastic transition. It sometimes occurs in a sequence of stable continuously related states s operating conditions change. At other times, however, the stable evolution behavior of the sliding system crosses a threshold whereupon a sudden change of contact conditions occurs as the result of instability. This invokes a feedback loop that comprises the localized elevation of frictional heating, the resultant localized bulging, a localized pressure increases as the result of bulging, and further elevation of frictional heating as the result of the pressure increase. When this process leads to an
accelerated change of contact pressure distribution, the unexpected hot roughness of thermal distortion may grow unstably under some conditions, resulting in local hot spots and leaving thermal cracks on the disk.

This is known as thermo elastic instability (TEI).The thermo elastic instability phenomenon occurs more easily as the rotating speed of the disk increases. This region where the contact load is concentrated reaches very high temperatures, which cause deterioration in braking performance. Moreover, in the course of their presence on the disk, the passage of thermally distorted hot spots moving under the brake pads causes low-frequency brake vibration.

The present investigation is aimed to study the given disk brake rotor of its stability and rigidity (for this Thermal analysis and coupled structural analysis is carried out on a given disk brake rotor and to investigate best combination of parameters of disk brake rotor like Flange width, Wall thickness and material there by a best combination is suggested.

II. RELATED WORK

S. V. Tsinopoulos Metal an advanced boundary element method was appropriately combined with the fast Fourier transform (FFT) to analyze general axis- symmetric problems in frequency domain elastodynamics. The problems were characterized by axis-symmetric geometry and non-axis-symmetric boundary conditions. Boundary quantities were expanded in complex Fourier series in the circumferential direction and the problem was efficiently decomposed into a series of problems, which were solved by the BEM for the Fourier boundary quantities, discretizing only the surface generator of the axis-symmetric body. Quadratic boundary elements were used and BEM integrations were done by FFT algorithm in the circumferential direction and by Gauss quadrature in the generator direction. Singular integrals were evaluated directly in a highly accurate way. The Fourier transformed solution was then numerically inverted by the FFT, provided the final solution. The method combines high accuracy and efficiency and this was demonstrated by illustrative numerical examples.

A. Floquet Metal determined of temperature distribution and comparison of simulation results and experimental results in the disc by 2D thermal analysis using axis-symmetric model.

The disc brake used in the automobile is divided into two parts; a rotating axis-symmetrical disc, and the stationary pads. The friction heat, which is generated on the interface of the disc and pads, can cause high temperature during the braking process. The influence of initial velocity and deceleration on cooling of the brake disc was also investigated. The thermal simulation is used to characterize the temperature field of the disc with appropriate boundary conditions.

A Finite-element method was developed for determining the critical sliding speed for thermo elastic instability of an axis-symmetric clutch or brake. Linear perturbations on the constant-speed solution were sought that vary sinusoidally in the circumferential direction and grow exponentially in time.

These factors cancel in the governing thermo elastic and heat-conduction equations, leading to a linear Eigen value problem on the two-dimensional cross-sectional domain for the exponential growth rate for each Fourier wave number. The imaginary part of this growth rate corresponds to a migration of the perturbation in the circumferential direction. The algorithm was tested against an analytical solution for a layer sliding between two half-planes and provided excellent agreement, for both the critical speed and the ,migration speed. Criteria were developed to determine the mesh re-finement required to give an adequate discrete description of the thermal boundary layer adjacent to the sliding interface. The method was then used to determine the unstable mode and critical speed in geometries approximating current multi-disc clutch practice.

A. E. Enderson Metal investigated the hot spotting in automotive friction system. When sliding occurs with significant frictional heating, thermo elastic deformation may lead to a transition from smoothly distributed asperity contact to a condition where the surfaces are supported by a few thermal asperities. This circumstance may be associated with a transition to a condition of severe wear because of the elevated contact pressure and temperature, and also because of production of tensile stresses. This second stress component may lead to heat checking whereupon the rough checked surface acts to abrade the mating material.

III. AXIS-SYMMETRIC ANAL YSIS

Due to the application of brakes on the car disk brake rotor, heat generation takes place due to friction and this thermal flux has to be conducted and dispersed across the disk rotor cross section. The condition of braking is very much severe and thus the thermal analysis has to be carried out. The thermal loading as well as structure is axis- symmetric. Hence axis-symmetric analysis can be performed, but in this study we performed 3-D analysis, which is an exact representation for this thermal analysis. Thermal analysis is carried out and with the above load structural analysis is also performed for analyzing the stability of the structure. According to given specifications the element type chosen is solid 90.Solid 90 is higher order version of the 3-D eight node thermal element (Solid 70). The element has 20 nodeswith single degree of freedom, temperature, at each node. The 20-node elements have compatible temperature shape and are well suited to model curved boundaries. The 20-node thermal element is applicable to a 3-D, steady state or transient thermal analysis.

STUDY FOR REPLACEMENT OF SAND BY FLY ASH FOR BETTER PACKING

V.K AHUJA , HOD (CIVIL ENGG.)

Engg.vkahuja@gmail.com **ph. 9255589865**

Abstract

The use of fly ash as replacement of sand is an economical solution for making green and denser concrete. The paper presents a concrete mix design procedure for partial replacement of sand with fly ash. Present method could produce additional compressive and flexural strength for concrete with partial replacement of sand with fly ash over control concrete, with higher slump. Addition of 0.5% super plasticizer could further improve compressive and flexural strength with higher slump over control concrete. Concrete with sand replaced by fly ash was also found to be economical without and with super plasticizer, when cost per N/mm2 was compared. The beneficial effect may be attributed to better packing, pozzolanic activity of fly ash and internal curing by fly ash as partial replacement of sand.

INTRODUCTION

It is a pressing need today for the concrete industry to produce concrete with lower environmental impact, the so-called green concrete. This can be achieved in three ways. The first one is by reducing the quantity of cement as one tonne of cement saved will save equal amount of CO2 to be discharged into atmosphere. Secondly by reducing the use of natural aggregates whose resources are limited and are exhausting very fast. It is also achieved by utilizing maximum possible waste materials like fly ash in concrete. This will reduce the requirement of landfill area and make system more sustainable. The World Bank has reported that by 2015 disposal of fly ash will require 1000 square kilometre area or one square meter of land per person. Also SiO2 and Al2O3 in fly ash react with the free lime available in concrete to form CSH and CAH gel. These gels provide extra cementing
material and also fill the pores in concrete making it possible to reduce the quantity of cement.

Fly ash is generally used as replacement of cement, as an admixture in concrete, and in manufacturing of cement. Concrete containing fly ash as partial replacement of cement poses problems of delayed early strength development. Concrete containing fly ash as partial replacement of fine aggregate will have no delayed early strength development, but rather will enhance its workability and strength. This higher workability and strength achieved gives scope for indirectly reducing the cement quantity in concrete. Earlier investigations in respect of development of strength of cement mortars with fly ash showed the 50% to 80% increase in 91 days strength. For better packing of concrete more quantity of particle size less than 75 micron is highly desirable.

COMPRESSIVE STRENGTH AND FLEXURAL STRENGTH OF CONCRETE

150 mm cubes were tested on seventh and twenty eighth day. 100 mm cubes were used to compare their strength with 150 mm cubes and extend the study long term effect up to 147 days. 3 number 100 mm cubes each were tested on 3, 7, 28, 56, 91 and 119 days of curing. One set of 3 cubes in each mix was tested after 28 days of air curing to know the internal curing due to fly ash in concrete. Compressive strength results are shown.

WORKABILITY

The slump and compacting factor were determined for fresh concrete to understand effect on workability. It is evident from the result that slump and compaction factor increases with the partial replacement of the sand with the fly ash and addition of the super plasticizer. Addition of

fly ash as replacement of sand has more pronounced lubricating effect and ball bearing action in the concrete. This concrete also has lesser voids hence more cement paste will be available for lubrication and hence concrete becomes more workable. This is also justified by the lower Surface Index Factor by Murdock . Increase in the slump was about 25 mm and 65 mm over the control concrete with the partial replacement of the sand with the fly ash without and with the super plasticizer, respectively.

.Cost per N/mm2 Strength

Decrease in the cost per N/mm2 was about 15% and 22% over
the control concrete with the partial replacement of the sand with the fly ash without and with the super plasticizer, respectively. This shows that partial replacement of sand with fly ash is economical over control concrete.

Internal Curing by Fly Ash

Fly ash used in present research work had water absorption of 16%. Hence available fly ash in concrete as replacement of sand could supply about 20 liters of water for internal curing. This should result in better hydration product, pore structure etc. along with reduced internal cracking. To check possible internal curing with partial replacement of sand with fly ash 100 mm cubes were air cured for 28 days after 119 days of pond curing.

CONCLUSIONS

1) Present mix design procedure clearly achieves lesser voids as indicated by higher pulse velocity, compressive and the flexural strength.

2) The compressive and the flexural strength of concrete mixes with partial replacement of sand by fly ash was found to be 15% higher without super plasticizer and 28% higher respectively with super plasticizer.

3) The compressive and the flexural strength of concrete mixes with the partial replacement of the sand by the fly ash by the minimum voids method could be higher than the replacement by the maximum density method. Hence the minimum voids method is preferable over the maximum density method for the partial replacement of the sand with the fly ash.

4) The maximum compressive and flexural strength could occur with the partial replacement of the sand with fly ash by the minimum voids method and the super plasticizer.

5) It could be finally concluded that fly ash could be very conveniently used as partial replacement of sand in structural concrete where its proportion and replacement of sand could be efficiently done by using minimum voids method for higher compressive strength, flexural strength and workability and lower voids at lower cost.

GREEN CHEMISTRY- NEW METHODS FOR ORGANIC SYNTHESIS AND APPLICATIONS: AN OVERVIEW

Sharwan K Dewan*,Vinay Batra[1]

* Formerly Prof.of Organic Chemistry , Deptt. Of Chemistry ,M.D.University,Rohtak.
1. Assistant Prof. S.B.M.N.Engg.College,Asthal Bohar,Rohtak. Email id: sharwankumardewan@yahoo.com; vb30393@gmail.com

ABSTRACT:
The principles of green chemistry guide firms in designing new products and processes in such a way that their impact on the environment is reduced. This article begins with an overview of green chemistry & organic reactions with past and present trends of formation .

Key words: Green Chemistry Atom Economy Synthetic Efficiency Sustainable Chemical Feed stocks, Green Solvents.

ORGANIC SYNTHESIS: INNOVATIONS AND NEW TECHNOLOGY

Organic chemistry chemicals are some of the important starting materials for a great number of major chemical industries. The production of organic chemicals as raw materials or reagents for other applications is a major sector of manufacturing polymers, pharmaceuticals, pesticides, paints, artificial fibers, food additives, etc. Organic synthesis on a large scale, compared to the laboratory scale, involves the use of energy, basic chemical ingredients from the petrochemical sector, catalysts and after the end of the reaction, separation, purification, storage, packaging, distribution etc. During these processes there are many problems of health and safety for workers in addition to the environmental problems caused by their use and disposition as waste. Green Chemistry with its 12 principles would like to see changes in the conventional ways that were used for decades to make synthetic organic chemical substances and the use of less toxic starting materials. Green Chemistry would like to increases the efficiency of synthetic methods, to use less toxic solvents, reduce the stages of the synthetic routes and minimize waste as far as practically possible. In this way, organic synthesis will be part of the effort for sustainable development. Green Chemistry is also interested for research and alternative innovations on many practical aspects of organic synthesis in the university and research laboratories of institutes. By changing the methodologies of organic synthesis health and safety will be advanced in the small scale laboratory level but also will be extended to the industrial large scale production processes through the new techniques. Another beneficiary of course will be the environment through the use of less toxic reagents, minimization of waste and more biodegradable by-products.

CHEMICAL SUBSTANCES AND REGULATIONS

In the last decades various health and safety organizations listed the number of chemical substances used for commercial reasons. In the beginning of the 1980s it was estimated that there were between 100-120.000 commercial chemicals identified by their CAS number, produced in quantities more than 100 kg.

The European Union in 1981 under the Dangerous Substances Directive (67/548/EEC) classified 100.000 existing chemicals which needed (such as the NIOSH, OSHA, EPA in the USA and the European Chemicals Bureau and under the 1967 Directive on Chemicals) regulation, labeling and testing for their properties (except cosmetics, medicines, foodstuffs, pesticides, radioactive materials, etc). From 1981 onwards the European Chemicals Bureau gathered data for another 20-25.000 chemical substances. It is estimated that every year 600-800 new chemicals enter the

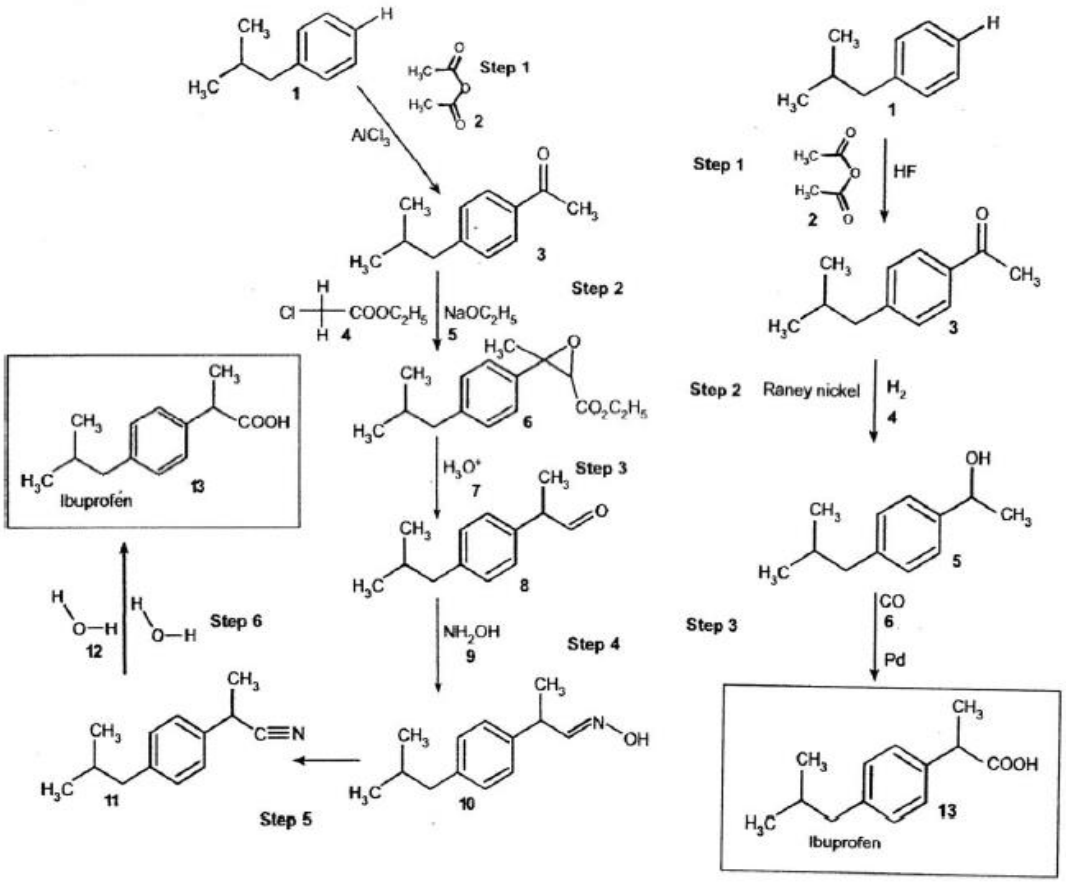
international market. The health and safety authorities concentrate on the 2.500-3.000 high volume chemicals which are produced in million of tones every year. But the new chemicals are covered by new more strict regulations and toxicity tests in order to be approved for commercial use. But the European system encountered many problems and in 2007 a new system REACH of registration and evaluation was established.

REACH (Registration, Evaluation, Authorisation and Restriction of Chemical substances) is the new European Community Regulation on chemicals and their safe use (EC 1907/2006). The aim of REACH is to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances. At the same time, REACH aims to enhance innovation and competitiveness of the European Union chemicals industry. Chemical industries all over the world are competing for innovation and safer products. Green Chemistry and Green Engineering provide the tools and alternative materials, processes and systems which will change not only the sustainability of the production of chemical materials, but also their environmental credentials by reducing toxicity and increase recyclability.

OLD AND NEW SYNTHESIS OF IBUPROFEN

Chemical industry is focusing from many years on some classic synthetic processes of important starting chemicals or crucial chemicals produced in high volume as intermediates in synthetic industrial reactions. The intention is to reduce the synthetic stages, to lower the energy use, to increase efficiency with higher yields and to minimize waste. Also, renewable starting chemicals away from the traditional petrochemical supplies of raw chemicals is another desired innovation.

Ibuprofen was synthesized in 1960 by the pharmaceutical company Boot (England) and sold under the commercial name Aspro, Panadol and Nurofen. The synthesis of Ibuprofen was performed in six steps with the production of secondary by-products and waste. The main problem according to the scientists at the time was that this synthesis had a very "poor atom economy". The initial synthesis, observed under the "green" principles, had many disadvantages.



The starting chemical could not be incorporated into the product, producing lots of by-products and waste. The six steps of the synthetic route was consuming chemicals and energy while lowering the yield of the final product.
In 1990 the company BHC after prolonged research on the subject discovered a new synthetic route with only three steps and increased efficiency. The atoms of the starting chemicals are incorporated into the products of the reactions and waste is minimised. In both synthetic routes the starting chemical is 2-methylpropylbenzene, which is produced from the petrochemical industry. The innovation in the new method was in the second step. A catalysts of Nickel (Raney nickel) was used thus decreasing substantially the steps of the synthesis.

In the old synthetic route, each step had a yield of 90% so that the final product came to be 40% yield compared to the starting chemical. This resulted in the increased production of by-products as waste. The drug was produced annually (only in Great Britain) in 3.000 tones and we understand that substantial amounts of chemicals were lost as waste. Energy also was lost by the low efficiency of the reaction method. In the "greener' method of three steps the final yield is 77%, whereas the Raney nickel catalyst (Nickel, CO/Pt) can be recycled and reused. In the old synthetic route, the AlCl3 used as a catalyst had to be thrown away as waste. The energy requirements of the second method were much lower than the first. The new synthetic route of Ibuprofen is a classic example of how Green Chemistry ideas can influence to the better the industrial synthetic methods, not only from the point of economic efficiency, but also from the point of more effective science and technology methods.

Green Chemistry Metrics- The Environmental factor E for Waste in Chemical Reactions

Green Chemistry introduced various general metrics to give quantitative meaning of chemical processes. The environmental **E-factor** was established as the indicator of mass waste per unit of product in the chemical industry. The E-factor can be made as complex and thorough or as simple as required. Assumptions on solvent and other factors can be made or a total analysis can be performed. The E-factor calculation is defined by the ratio of the mass of waste (kg) per unit of product in kilograms: **E-factor = total waste (kg) / product (kg).** The Green Chemistry metric is very simple to understand and to use. It highlights the waste produced in the process as opposed to the reaction, thus helping those who try to fulfil one of the twelve principles of green chemistry to avoid waste production. The environmental E-factors ignores recyclable factors such as recycled solvents and re-used catalysts, which obviously increases the accuracy but ignores the energy involved in the recovery.

Microwave Applications for Green Chemistry Synthesis

Microwave applications in organic synthesis is not something new. But it is interesting to realize the potential of this synthetic method with low energy requirements, less waste, no use of solvent. The principles of Green chemistry apply to most of the synthetic routes with microwave irradiation. Microwave-assisted eco-friendly organic synthesis have become a new trend with many applications in synthesising organic chemicals. Organic reactions under the microwave irradiation have many advantages compared to the conventional reactions which need very high temperatures. Microwave assisted reactions are "cleaner", last only very few minutes, have high yield and produce minimum waste. Microwave assisted organic synthesis has become an expanding field in synthetic research. New publications cover the many aspects of this "greener" technique and its practical applications. The scientific literature is full of new research papers on microwave reaction mechanisms and applications.

New "Green" Methods in Synthetic Organic Sonochemistry .

Ultrasound-assisted organic synthesis is another "green" methodology which is applied in many organic synthetic routes with great advantages for high efficiency, low waste, low energy requirements. **Sonochemistry** (in the region of 20 kHz to 1 MHz) has many applications due to its high energy and the ability to disperse reagent in small particles and accelerate reactions. Irradiation with high intensity sound or ultrasound, acoustic cavitation usually occurs (growth, and implosive collapse of bubbles irradiated with sound). Experimental results have shown that these bubbles have temperatures around 5000 K, pressures of roughly 1000 atm. These cavitations can create extreme physical and chemical conditions in otherwise cold liquids. Also, Sonochemical engineering is a new field involving the application of sonic and ultrasonic waves to chemical processing. Sonochemistry enhances or promotes chemical reactions and mass transfer. It offers the potential for shorter reaction cycles, cheaper reagents, and less extreme physical conditions. Existing literature on sonochemical reacting systems is chemistry-intensive, and applications of this novel means of reaction in environmental remediation and pollution prevention seem almost unlimited and is rapidly growing area.

CONCLSION:

To combine the technological progress with the safeguard of the environment is one of the challenges of the new millennium. Chemists will play a key role in the realization of the conditions for a sustainable development and green chemistry may be their winning strategy. Green chemistry addresses such challenges by inventing novel reactions that can maximize the desired products and minimize by-products, designing new synthetic schemes and apparati that can simplify operations in chemical productions and seeking greener solvents that are inherently environmentally and ecologically benign.

REFERENCES

1. Anastas PT, Warner JC. *Green Chemistry: Theory and Practice*. Oxford University Press, New York, 1998.
2. Warren D. *Green Chemistry. A Teaching Resource*. Royal Society of Chemistry, Cambridge, 2001.
3. Clark J, Macquarrie D. *Handbook of Green Chemistry and Technology*. Blackwell Publishing, Abingdon, Oxfordshire, 2002.
4. Poliakoff M, Licence P. Green Chemistry. *Nature* 450: 810-812, 2007.
5. Tundo P, Anastas PT (Eds). *Green Chemistry: Challenging Perspectives*. Oxford University Press, Oxford, UK, 2000.
6. Sheldon RA, Arends I. *Green Chemistry and Catalysis*. Wiley–VCH, Indianapolis, USA, 2006.
7. American Chemical Council. Global Business of Chemistry (www.amecicanchemistry.com/jobs/EconomicStatistics/Industry-Profile/Global-Business-of-chemistry)
8. Royal Society of Chemistry (RSC). Ibuprofen- a case study in green chemistry. RSC publications, Cambridge, UK (http://www.rsc.org/education/teachers/learnnet/ibuprofen/ibuprofen.pdf)
9. The BHC Company Synthesis of Ibuprofen. From Cann MC, Connelly ME. Real World Cases in Green Chemistry. American Chemical Society, Washington, DC, 2000. (http://alpha.chem.umb.edu/chemistry/orgchem/greensynthiboprufencasestudy.pdf
10. Anastas PT, Kirchhoff MM, Williamson TC. Catalysis as a foundational pillar of green chemistry. *Appl Catal A: General*, 221: 3-13, 2001.
11. Sato K, Aoki M, Noyori R. A "green" route to adipic acid: direct oxidation of cyclohexene with 30 percent hydrogen peroxide. *Science* 281:1646-1647, 1998.
12. Usui Y, Sato K. A green method of adipic acid synthesis: organic solvent- and halide-free oxidation of cyclohexanones with 30% hydrogen peroxide. *Green Chem* 5, 373-375, 2003.
13. Li H, Zhu W, He X, Pan J, Shu H, Guo J, et al. Green synthesis of adipic acid with hydrogen peroxide catalyzed by oxpoeroxo tungsten complexes. The 10th Annual Green Chemistry and Engineering Conference, June 26-30, 2006.
14. Draths CM, Frost JW. Environmentally compatible synthesis of adipic acid from D-glucose. *J Am Chem Soc* 116(1):399-400, 1994.
15. Draths CM, Frost JW. *Microbial catalysis. Synthesis of adipic acid from D-glucose*. ACS Symposium Series, vol. 577, Chapter 3, pp 32-45. ACS publications, Washington DC, Nov. 1994.

16. Draths KM, Frost JW. The Presidential Green Chemistry Challenge Awards Program. Summer of 1998 Award. EPA 744-R-98-001. US Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington DC, 1998, p. 3.
17. 1998 Academic Award. Green Chemistry. Dr. K. M. Draths and Prof. J.W. Frost (Michigan State University) (http://www.epa.gov/greenchemistry/pubs/pgcc/winners/aa98b.html)
18. Reed SM, Hutchison JE. Green Chemistry in the organic teaching laboratory: an environmentally benign synthesis of adipic acid. *J Chem Educ* 77:1627-1628, 2000.

FIXED POINT THEOREMS FOR COMPATIBLE MAPS IN METRIC SPACES

Indu Bala and Vinod Kumar

Department of Mathematics, Baba Mastnath University, Rohtak
Induvats11@gmail.com

ABSTRACT:

The aim of this paper is to prove a common fixed point theorem for compatible maps and weakly compatible maps in metric spaces, which generalizes the results of various authors.

Keywords and Phrases: Compatible mappings, metric spaces

AMS Subject Classification (2001): 47H10, 54H25

INTRODUCTION

In 1976, Jungck [2] proved a common fixed point theorem for commuting maps generalizing the Banach's fixed point theorem, which states that, 'Let (X, d) be a complete metric space. If T satisfies $d(Tx, Ty) \leq kd(x, y)$ for each $x, y \in X$ where $0 \leq k < 1$, then T has a unique fixed point in X'. This result was further generalized and extended in various directions by many authors. Further, Jungck [2] introduced more generalized commutativity, the so-called compatibility, which is more general than that of weak commutativity.

In 1986[2] introduced the notion of compatible mappings as follows:

The pair A, S is said to be compatible if $\lim_{n\to\infty} d(ASx_n, SAx_n) = 0$, whenever $\{x_n\}$ is a sequence in X such that $\lim_{n\to\infty} Ax_n = \lim_{n\to\infty} Sx_n = t$ for some $t \in X$.

2. Main Results.

Now we prove our main result.

Theorem 2.1. Let (X, d) be a complete metric space and *f*, g be self mappings of X satisfying the following conditions:

(2.1) $f(X) \subseteq g(X)$,

(2.2) *f* or g is continuous,

(2.3) $d(fx, fy) \leq \alpha\, d(fx, gy) + \beta\, d(gx, fy) + \gamma\, d(gx, gy)$, for every x, y in X where $\alpha, \beta, \gamma \geq 0$ and $0 \leq \alpha + 3\beta + 3\gamma < 1$.

Then *f* and g have a unique common fixed point in X provided *f* and g are compatible maps.

Proof. Let x_0 be an arbitrary point in X. By (2.1), one can choose a point x_1 in X such that $fx_0 = gx_1$, In general one can choose x_{n+1} such that $y_n = fx_n = gx_{n+1}$, n = 0,1,2,… .

From (2.3), we have

$$d(fx_n, fx_{n+1}) \leq \alpha\, d(fx_n, gx_{n+1}) + \beta\, d(gx_n, gx_{n+1}) + \gamma\, d(gx_n, fx_{n+1})$$

$$= \alpha\, d(fx_n, fx_n) + \beta\, d(fx_{n+1}, fx_n) + d(fx_n, fx_{n+1})$$

$$(1- \beta- \gamma)\, d(fx_n, fx_{n+1}) \leq 0.$$

This implies

$$d(fx_n, fx_{n+1}) \leq \frac{(\beta + \gamma)}{(1- 2\beta - 2\gamma)}\, d(fx_{n-1}, fx_n),$$

$$= qd(fx_{n-1}, fx_n), \text{ where } q = \frac{(\beta + \gamma)}{(1- 2\beta - 2\gamma)} < 1.$$

Continuing in the same way, we have

$$d(fx_n, fx_{n+1},) \leq q^n\, d(fx_0, fx_1).$$

Therefore, for all n, m $\in \mathbb{N}$, n < m, we have by rectangle inequality that

$$d(y_n, y_m) \leq d(y_n,y_{n+1}) + d(y_{n+1}, y_{n+2}) + d(y_{n+2}, y_{n+3}) + \ldots + d(y_{m-1}, y_m,)$$

$$\leq (q^n + q^{n+1} + \ldots + q^{m-1})\, d(y_0, y_1)$$

$$\leq \frac{q^n}{1-q}\, d(y_0, y_1).$$

Letting n, m $\to\infty$ we have $lim_{n\to\infty}$ d $(y_n,y_m) = 0$. Thus $\{y_n\}$ is a Cauchy sequence in X. Since (X, d) is complete metric space, therefore, there exists a point z $\in$ X such that $lim_{n\to\infty}$ $y_n = z$ and $lim_{n\to\infty}$ $y_n = lim_{n\to\infty}$ $fx_n = lim_{n\to\infty}$ $gx_{n+1} = z$.

Since the mapping f or g is continuous, for definiteness one can assume that g is continuous, therefore $lim_{n\to\infty} gfx_n = lim_{n\to\infty} ggx_n = gz$. Further, f and g are compatible, therefore, $lim_{n\to\infty} d\,(gfx_n, fgx_n) = 0$, implies $lim_{n\to\infty}$ $fgx_n = gz$.

From (2.3), we have

$$d(fgx_n, fx_n) \leq \alpha\, d(fgx_n, gx_n) + \beta\, d(ggx_n, gx_n) + \gamma\, d(ggx_n, fx_n).$$

Proceeding limit as n$\to \infty$, we have g z = z.

From(2.3), we have

$$d(fx_n, fz) \leq \alpha\, d(fx_n,gz) + \beta\, d(gx_n, fz) + \gamma d(gx_n, gz).$$

Taking limit as n$\to \infty$, we have z = fz. Therefore, we have gz = fz = z. Thus z is a common fixed point of f and g.

Uniqueness.

We assume that z_1 ($\neq$ z) be another common fixed point of f and g.

Then $d(z, z_1) > 0$ and

$d(z, z_1) = d(fz, fz_1)$

$\leq \alpha d(fz, gz_1) + \beta\, d(gz, fz_1) + \gamma d(gz, fz_1)$

$= (\alpha + \beta + \gamma)\, d(z, z_1)$

$< d(z, z_1)$,

a contradiction, therefore, $z = z_1$. Hence uniqueness follows.

This completes the proof of the theorem.

We now give an example to illustrate Corollary 2.1.

Example 2.1. Let $X = [-1, 1]$ and let d be the metric on $X \times X$ defined as follows:

$d(x, y) = |x - y|$ for all x, y in X.

Then (X, d) is metric space. Let us define $f(x) = \frac{x}{6}$ and $g(x) = \frac{x}{2}$. Here we note that, f is continuous and $f(X) \subseteq g(X)$. Also,

$d(fx, fy)) \leq q\, d(gx, gy)$,

holds for all $x, y \in X$, $\frac{1}{3} \leq q < 1$ and '1' is the unique common fixed point of f and g.

REFERENCES

[1] B. Fisher, Common fixed point of four mappings, *Bull Inst. Math. Acad. Scinica*, **9** (1983), 399.

[2] G. Jungck, Commuting maps and fixed points, *Amer. Math. Monthly*, **83** (1976), 261-263.

[3] G. Jungck, Compatible mappings and common fixed points, *Internat. J. Math. and Math. Sci.*, **9** (1986), 771-779.

[4] G. Jungck, Compatible mappings and common fixed points, (2) *Internat. J. Math. and Math. Sci.*, **11** (1988), 285-288.

[5] G. Jungck, P.P. Murthy & Y.J. Cho, Compatible Mappings of Type (A) and Common Fixed Points. *Math. Japonica*, **38**(2) (1993), 381-390.

[6] Kannan R, some results on fixed points, *Bull. Cal. Math. Soc.* **60**(1968) 71-76.

COST OF QUALITY

Ajay Sharma

*Civil Engineering Department, Shri Baba Mastnath Engineering College, Asthal Bohar, Rohtak, Haryana, India,
aajay.055@ymail.com

The fast growing Indian economy is reaching a point where quality becomes just as important as quantity. However, the quality concept is still somewhat vague to many people and too many companies. One way to make it more concrete is to calculate quality costs. Quality cost is a measure of how costly it is for the organization to lack in quality in any way. This way is easier to understand quality and to see which areas should be prioritized in the quality improvement work. This thesis makes an attempt to map out the quality cost of an Indian company. Based on the calculated quality costs areas of improvement potential are suggested to the management. These way the company's improvement efforts can be directed to where they make the best use. Successful running, sound economy and profitability of an organization is entirely depends upon effective control of non-quality costs generated in an organization. This analysis of quality cost data has been done by using pareto analysis and effects of different cost elements of quality costs. Quality cost contains conformance costs - Prevention costs and Appraisal costs, non-conformance costs – Internal failure costs and External failure costs. Total quality costs can be controlled resulting considerable savings. This thesis discuss how quality has an impact on the costs of goods and services in an organization

INTRODUCTION

A. WHAT IS QUALITY?

- Quality is simply about meeting customer requirements and current and future expectations (Dale and Oakland, 1991).
- The total composite product and service characteristics of marketing, engineering, manufacture, and maintenance through which the product and service in use will meet the expectations of the customer (Feigenbaum, 1991).
- The totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs (BS 4778, 1987)
- Fitness for use (Juran, 1993).
- Quality is a predictable degree of uniformity and dependability at low cost and suited to the market (Deming, 1986).
- Quality is the (minimum) loss imparted by the product to society from the time the product is shipped (Taguchi, 1985).

METHODOLOGY

Prior to the study the only costs collected and identified as quality costs were the costs of operating the quality control department, expenditure on warranty, and the costs of scrap and defective products. The research approach in this case study was to examine the company's operations against the model elements of BS 61431(the 1981 version of the Standard) and to put Costs on them. The company's quality costs for the first quarter of the current year in which the study was carried out (hereafter referred to as Year 1) were measured. Then, using these costs, a projected quality cost report was prepared for the full year. The work was carried out in the third quarter of Year 1, by which time all the first quarter transactions and accounting were complete. In this study a deliberately ingenuous approach was adopted to try to ensure that all the major obstacles to the collection of quality costs in the company were discovered. Before attempting to

gather costs, knowledge of the company‘s operations and practices was gained by studying the company‘s procedures and reports, supplemented by discussions with staff from quality control, inspection, personnel, work study, production and accounts departments. Attempts were then made to detect and measure costs against each of the cost elements listed in the BS 6143 guide1 (the 1981 version of the Standard).

Table 1.1 *corresponding sections in BS 6143 and ASO Quality Costs— What and How categorization of quality-related cost elements.*

BS6143	Elements
A1	Quality control and process control engineering
A2	Design and develop control equipment
A3	Quality planning by others
A4	Production equipment for quality -maintenance and calibration
A5	Test and inspection equipment — maintenance and calibration
A6	Supplier quality assurance
A7	Training
A8	Administration, audit, improvement
B1	Laboratory acceptance testing
B2	Inspection and test
B3	In-process inspection (non-inspectors)
B4	Set-up for inspection and test
B5	Inspection and test materials
B6	Product quality audits
B7	Review of test and inspection data
B8	On-site performance testing
B9	Internal testing and release
B10	Evaluation of materials and spares
B11	Data processing, inspection and test reports
C1	Scrap
C2	Rework and repair
C3	Troubleshooting, defect analysis
C4	Re-inspect, retest
C5	Scrap and rework: fault of supplier
C6	Modification permits and concessions
C7	Downgrading
D1	Complaints
D2	Product service: liability
D3	Products returned or recalled
D4	Returned material repair
D5	Warranty replacement

COMPANY QUALITY CONTROL AND ACCOUNTING SYSTEMS

The company, which is an approved supplier to the Indian Railway, has a comprehensive quality manual clearly setting out the responsibilities of quality, production, engineering and

other personnel for quality-related matters. The manual contains no reference to quality costs other than warranty. There was, however, a clear acknowledgement of the existence of quality costs in the company. The company accounting system divides the company into 21 indirect cost centre‘s, covering its manufacturing facilities. There are also 188 financial codes, of which, apart from the routine administrative codes applied to the quality control cost centre, only sales of scrap material, indirect materials, inspection equipment, research materials and warranty repairs were readily recognizable as being quality-related. Another potential source of quality cost information — labour bookings — was equally disappointing, having only _defective material‘as an obviously quality-related code, though it was learned later that bookings to _prototype‘might also contain some quality costs. The accounts department does, however, produce a monthly scrap report analyzed across production cost centre‘s and displaying material, lab our and overhead costs.

It is fair to say that, so far as quality-related costs are concerned, the accounting system lacked sophistication and the availability of data failed to meet expectations. Some idea of the situation may be gauged from the fact that only four of the 188 financial codes referred to quality-related matters, and perhaps even more telling, there was only one labour-booking code for work concerned with defective products. As a result, the costing relied a great deal on estimates. The extent of estimation was such that only 50 per cent of the total quality costs were derived from data specifically noted in accounts under headings identifiable as being quality-related.

MODULATION FORMATS IN OPTICAL COMMUNICATION SYSTEM

Jitender Khurana

Prof., S. B.M.N. Engineering College Rohtak,Haryana,India

ABSTRACT

The objective of this study is to analyse the performance of dispersed managed RZ system, different modulation formats and to study the different compensation techniques at high bit rate. The dispersed managed system is a promising way to transmit data in optical communication networks. The performance of 10 Gbps optical communication system with the dispersion managed return-to-zero (RZ) pulse has been reported The return-to-zero (RZ) pulse is efficient for long-distance, high-bit-rate, wavelength division multiplexed (WDM) transmission dispersion-managed systems. In RZ pulse, the power is transmitted only for fraction of bit period. In this thesis, predictions are made by varying the dispersion parameter of single mode fiber in optical communication system. It has been reported that the performance of the system is improved with increase in the value of dispersion parameter. Using the different types of modulation formats, it is predicted that the novel modulation formats enhance the overall performance of the optical communication systems at high bit rate. The performance of non-return-to-zero (NRZ), carrier suppressed return-to-zero (CSRZ) and do binary modulation format at 10 Gb/s for the optical communication system is analyzed.

I INTRODUCTION

Fiber-optic communication is a method of transmitting information from one place to another by sending light through an optical fiber. Fiber-optic communication systems have revolutionized the telecommunications industry and played a major role in the advent of the Information Age. Because of its advantages over electrical transmission, the use of optical fiber has largely replaced copper wire communications in the developed world. Optical fiber is the most common type of channel for optical communications; however, other types of optical waveguides are used within communications gear, and have even formed the channel of very short distance (e.g. chip-to-chip) links in laboratory trials.

The main benefits of fiber are its exceptionally low loss, allowing long distances between amplifiers or repeaters and its inherently high data-carrying capacity, such that thousands of electrical links would be required to replace a single high bandwidth fiber. Another benefit of fiber is that even when are alongside each other for long distances, fiber cables experience effectively no crosstalk, in contrast to some types of electrical transmission lines With the explosive growth in demand for capacity in national, regional, and even metropolitan optical networks, high bit rate fiber transmission have recently become an essential part of state-of-the-art communications. Modern optical networks a re now primarily based on 2.5 Gb/s and 10 Gb/s channels. 40 Gb/s channels have begun to be implemented in new product offerings [1]. In addition to increases in data rate per channel, the number of channels per fiber is also increased through wavelength division multiplexing (WDM) or dense WDM (DWDM) to further improve overall capacity .High-bit rate transmission is attractive for several reasons. First, it potentially enables lower capital expenditure by sharing transmitter/receiver cost between more data sources or users. Second, it eases wavelength management by reducing the number of WDM channels. Wavelength management, such as reconfigurable optical add/drop multiplexing, is essential to making optical networks transparent, scalable, and flexible, which ultimately reduces the operational expenditure of such networks. Thirdly, high spectral efficiency can be achieved in a WDM system that has a common channel grid through the use of high bit rate.

Amplitude Shift keying

Amplitude-Shift-Keying (ASK) known as"On-Off"-keying (OOK) is the technique of modulating the intensity of the carrier signal is shown in figure. In the simplest form, a source is

switched between on and off states. The ASK modulation is characterized by the relation between the signal levels in on and off states called extinction ratio (ER). The ER value is dependent on the approach used for the signal generation: direct or external modulation of the laser source. In case of external modulation, the ER is limited by the extinction ratio of the external modulator. Typical ER values vary between 8-12 dB depending on the signal bit rate in use. The ASK-based modulation formats are characterized by simple signal generation and detection, due to which all currently deployed optical transmission systems employ ASK-based modulation formats. In the following section various ASK-based modulation formats is discussed. Due to the use of different modulation methods for generation of these formats, they posses different signal shapes (e.g. return-to-zero or non return-to-zero) and spectral characteristics, resulting in different transmission.

Frequency Shift Keying

Frequency Shift Keying (FSK) is realized by switching the laser light frequency between two frequency values as shown in figure. In FSK, the optical signal envelope remains unchanged and the complexity of signal generation and detection increases compared to ASK modulation. FSK modulation is characterized by the modulation index. By the variation of modulation index, different FSK based modulation format can be realized. The differences between FSK formats are reflected in the optical signal spectra, whereby a smaller modulation index.

Phase Shift Keying

Phase Shift Keying (PSK) uses the phase of the signal to encode information. Optical PSK signals posses a narrow spectrum and a constant signal envelope as shown in figure, which enables improved nonlinear tolerance, but on the other hand the PSK signals are sensitive to a phase modulation induced by multi-channel effects, which can result in decoding errors at the receiver side. At the same time, PSK-based modulation enables improved receiver sensitivity (up to 6 dB) compared to ASK-formats. Especially interesting method of PSK modulation is differential PSK (DPSK). In DPSK signals, the information is encoded in the phase change between two successive bits. Basically, PSK signals only allow coherent detection, which require a local oscillator at the receiver to compare the phase of transmitted with the phase of the local signal, making the feasibility of this modulation more difficult. Also, a phase-locked-loop (PLL) is required to synchronize the local oscillator to the received signal. Pure PSK modulation is rather inapplicable for the system implementation, but some special binary and multilevel variants of PSK like DPSK or differential quaternary PSK (DQPSK) allow the use of direct detection methods. DQPSK enables a further improvement of the code efficiency using 4 different phases, where the signal symbol rate is half of that in DPSK case. The DQPSK bit stream must be differentially encoded using a digital pre-coder. The signal detection in DPSK formats can be made using MZI interferometer based configurations which enable a reduced detection complexity compared to coherent detection. In spite of increased realization complexity of PSK modulation, recently presented DPSK and DQPSK system are as good lternatives to ASK-based modulation formats in future high speed WDM systems.

Polarization Shift Keying

\Polarization Shift Keying (PolSK) is the most exotic modulation format among all already presented. The optical PolSK signals are generated by switching the signal polarization between two orthogonal states of polarization. The PolSK is characterized by a Constant signal envelope enabling an improved nonlinear tolerance, an improved sensitivity (3 dB) compared to ASK-based modulation, and enable a better utilization of the system bandwidth by the use of orthogonal polarization as an additional degree of freedom. The drawbacks of PolSK are an

increased complexity of signal generation and detection, as well as, the sensitivity to polarization disturbances in the transmission line, whose impact increases with an increased channel data rate.

II PERFORMANCE OF OPTICAL SYSTEM WITH DIFFERENT MODULATION FORMATS

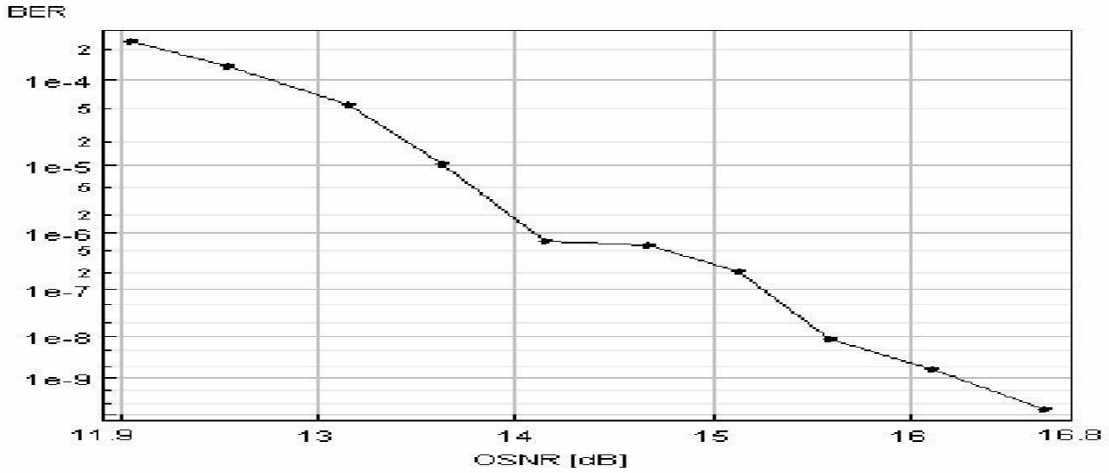
The performance of NRZ, CSRZ and doubinary modulation format at 10 Gb/s for the optical communication system at 10 Gb/s is analyzed. The performance evaluation of the modulation format has been analyzed in terms of the bit error rate against the accumulate dispersion and optical signal to noise ratio. The dispersion tolerance of the modulation formats has been analyzed. It is observed that doubinary modulation format provides the maximum dispersion tolerance. It is shown that CSRZ has the lowest bit error rate BER value. It is reported that CSRZ modulation format has the edge over NRZ and doubinary modulation format. The performance of the NRZ, CSRZ and doubinary has been observed which shows that CSRZ is better for long optical communication system at 10 Gb/s. The analysis indicates that the AGV is a bottleneck for the flexible manufacturing cell. There are on average a large number of parts waiting for transport by the AGV. Currently AGV utilization is 100%. The addition of a second AGV is a logical solution to the problem of excessive utilization, but due to cost inefficiencies it was not considered as a viable alternative.

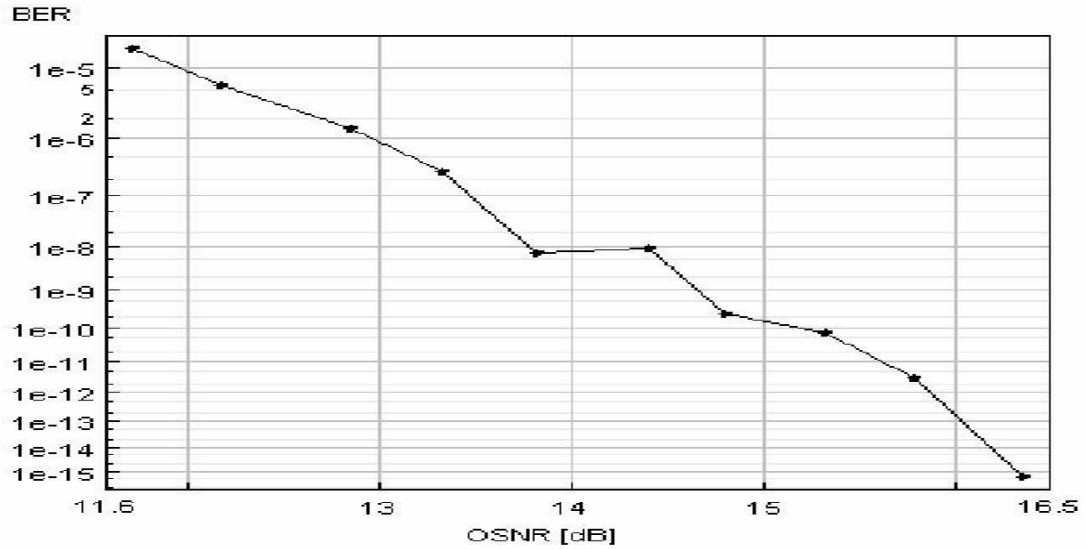
The optical communication systems are used as high speed long haul communication system. Due to high data rates, limitation due to dispersion and nonlinearities in the optical communication system has been of great concern as these parameters limits the overall efficiency of the system. An optical modulation format is the method used to impress data on an optical carrier wave for transmission over optical fiber. The ideal modulation format for long haul, high speed and WDM transmission links is the one that has a narrow spectral width, low susceptibility to fiber nonlinearity, large dispersion tolerance and good transmission performance and has a simple and cost-effective configuration for generation. In Inensity-modulated direct-detection (IM/DD) systems, there are two possible modulation formats, non return-to-zero (NRZ), tin which a constant power is transmitted during the entire bit period, and return-to-zero (RZ), in which power is transmitted only for a fraction of the bit period. Most commercial systems use the NRZ modulation format .The non-return-to-zero (NRZ) has been the most dominant modulation format in intensity modulated-direct detection fiber-optical communication systems for the last years. The reasons for using the NRZ in the early days of fiber-optical communication as it is not sensitive to laser phase noise, requires a relatively low electrical bandwidth for transmitter and receivers compare with the RZ and the simplest configuration of transmitter and receiver. The NRZ pulses has a narrow optical spectrum .The reduced spectrum width improves the dispersion tolerance but it has the effect of intersymbol interference. The RZ pulse occupies just a part of the bit slot, so it has a duty cycle smaller than 1 and a broad spectrum. The RZ pulse shape enables an increased robustness to fiber nonlinear effects and to the effect of polarization mode dispersion (PMD). Due to its broader spectrum, the RZ pulse has a reduced dispersion tolerance and spectral efficiency. The RZ achieves a 1-2 dB advantage in optically pre-amplified receiver sensitivity compared to the NRZ .Carrier suppressed RZ pulse is a special form of the RZ pulse where the carrier is suppressed. The difference between the CSRZ and conventional RZ is that the CSRZ signal has a p phase shift between adjacent bits. The CSRZ signal is far less sensitive to fiber nonlinear effects and provides better robustness against transmission impairments. Optical duobinary format s a very interesting modulation format, which offers high spectral efficiency and chromatic dispersion tolerance. In the duobinary

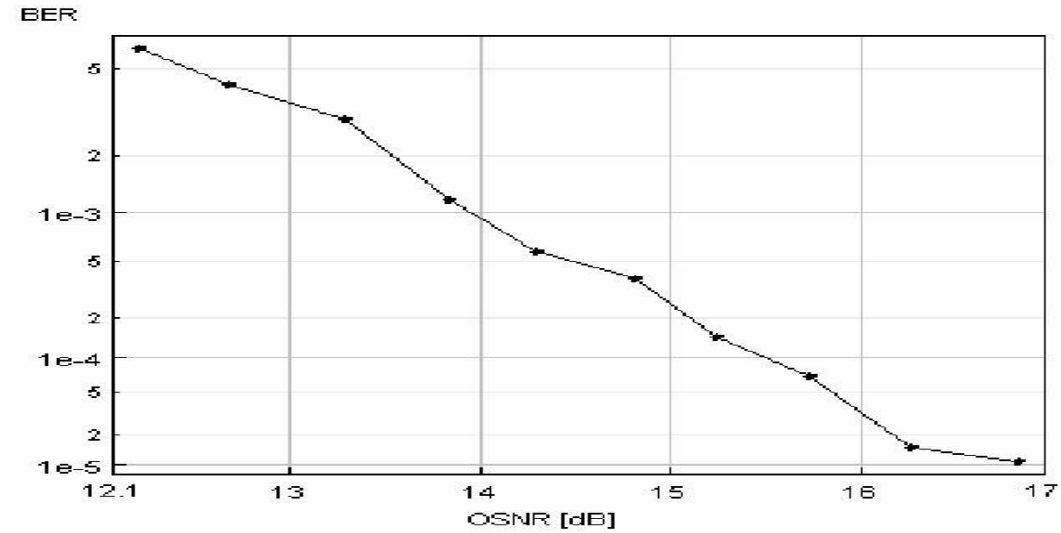
format, the optical phases of "1" bits that are separated by an odd number of "0s" differ by p radians. The optical spectrum of the duobinary signal is very compressed as compared to many other binary formats. The LPF duobinary has recently received significant attention. One reason for this is that duobinary can be easily created using simple low-cost techniques. So different types of modulation techniques are used these days to enhance the performance of optical communication system. Each modulation format has its own advantages and disadvantages. Depending upon the required application, the modulation format is used.

III RESULT AND DISCUSSION

In previous section, various component and parameters used in simulation setup are discussed. Using some of these components, the bit error rate (BER), optical signal to noise ratio and eye-diagrams is measured at the receiver end is measured. The measurement component







used are Q estimator to measure Q-factor, average eye opening values and timing jitters, BER estimator to measure to measure bit error rate (BER), electrical scope to measure eye diagrams and optical probe to measure optical spectrums the performance of NRZ, CSRZ and doubinary modulation format at 10 Gb/s for the optical communication system at 10 Gb/s is analyzed. The performance evaluation of the modulation format has been analyzed in terms of the bit error rate against the accumulate dispersion and optical signal to noise ratio. The dispersion tolerance of the modulation formats has been analyzed. It is observed that doubinary modulation format provides the maximum dispersion tolerance. It is shown that CSRZ has the lowest bit error rate BER value. It is reported that CSRZ modulation format has the edge over NRZ and doubinary modulation format. The performance of the NRZ, CSRZ and doubinary has been observed which shows that CSRZ is better for long optical communication system at 10 Gb/s. The optical communication systems are used as high speed long haul communication system. Due to high data rates, limitation due to dispersion and nonlinearities in the optical communication system has been of great concern as these parameters limits the overall efficiency of the system. An optical modulation format is the method used to impress data on an optical carrier wave for transmission over optical fiber. The ideal modulation format for long haul, high speed and WDM transmission links is the one that has a narrow spectral width, low susceptibility to fiber nonlinearity, large dispersion tolerance and good transmission performance and has a simple and cost-effective configuration for generation. In Intensity-modulated direct-detection (IM/DD) systems, there are two possible modulation formats, non return-to-zero (NRZ), in which a constant power is transmitted during the entire bit period, and return-to-zero (RZ), in which power is transmitted only for a fraction of the bit period. Most commercial systems use the NRZ modulation format. The non-return-to-zero (NRZ) has been the most dominant modulation format in intensity modulated-direct detection fiber-optical communication systems for the last years. The reasons for using the NRZ in the early days of fiber-optical communication as it is not sensitive to laser phase noise, requires a relatively low electrical bandwidth for transmitter and receivers compare with the RZ and the simplest configuration of transmitter and receiver. The NRZ pulses has a narrow optical spectrum .The reduced spectrum width improves the dispersion tolerance but it has the effect of intersymbol interference. The RZ pulse occupies just a part of the bit slot, so it has a duty cycle smaller than 1 and a broad spectrum. The RZ pulse shape enables an increased robustness to fiber nonlinear effects and to the effect of polarization mode dispersion (PMD). Due to its broader spectrum, the RZ pulse has a reduced dispersion tolerance and spectral efficiency

The above figures show the graphs for BER vs. OSNR for the NRZ, CSRZ and doubinary modulation format. It can be seen from all the three graphs that the value of BER is decreased with increase in the OSNR value. The value of BER for the NRZ, CSRZ doubinary modulation format at OSNR value of 16 is 91e−,141e−,51e− respectively. The

CSRZ modulation format has the best BER value from the entire different modulation format at. a given value of OSNR where as doubinary has the worst BER value. Hence the doubinary system requires a high input power to achieve the desired BER value which limits the performance of the doubinary modulation format to some extent. It is observed that the CSRZ provides a good performance at high bit rate. The CSRZ modulation can be used for long distance communication system at high bit rates.

IV CONCLUSION

In this chapter, the performance of NRZ, CSRZ and doubinary modulation format at 10 Gb/s for the optical communication system is analyzed. It is observed that the CSRZ modulation

format has the edge over the NRZ and doubinary modulation format. It is shown that the CSRZ has the lowest BER value. It is reported that the Doubinary modulation format provides the higher dispersion tolerance among the three modulation formats. The doubinary modulation format can be recommended for long distance communication systems at high bit rates but its performance are limited by the low OSNR value. It is observed that the NRZ modulation format has the worst performance in terms of dispersion tolerance. It is reported that the NRZ modulation format has a better OSNR value than the doubinary modulation format. The NRZ modulation format can be used for small distance communication system a high bit rates. It is concluded that the CSRZ modulation format is best for the long distance optical communication system due to its low value of BER and tolerance to the dispersion at high bit rates. That is, production output is maximized, long-term percentage mixes are met, and the average time a part spends in the manufacturing cell is minimized.

REFERENCES

[1] P. Hofmann, E. E. Basch, S. Gringeri, R. Egorov, D. A. Fishman, and W. A. Thompson, "DWDM Long Haul Network Deployment for the Verizon GNI Nationwide Network," Proc. Optical Fiber Communication Conf. (OFC „05), Vol. 2, (2005).

[2] B. Wedding and B. Franz, "Unregenerated optical transmission at 10 Gbit/s via 204 km of standard single mode fiber using a directly modulated laser diode,"Electronics Letters, 29(4):402–403, February 1993.

[3] B.Wedding, B. Franz, and B. Junginger, "10-Gb/s optical transmission up to 253 km via standard singlemode fiber using the method of dispersion-supported transmission," Journal of Lightwave Technology, 2(10):1720–1727, October 1994.

[4] M. Rhode, C. Caspar, N. Heimes, M. Konitzer, E. J. Bachus, and N. Hanik, " Robustness of DPSK direct detection transmission format in standard fiber WDM systems," Electronics Letters, 26(17):1483–1484, August 2000.

[5] C. Wree, J. Leibrich, and W. Rosenkranz, "RZ-DQPSK format with high spectral efficiency and high robustness towards fiber nonlinearities," European Conference on Optical Communication (ECOC), 4(9.6.6), September 2002.

[6] A. Carena, V. Curri, R. Gaudino, N. Greco, P. Poggiolini, and S. Benedetto, " Polarization modulation in ultra-long haul transmission systems: A promising alternative to intensity modulation," European Conference on Optical Communication (ECOC), 1:429–430, September 1998.

[7] M.I.Hayee and A.E.Willner, "NRZ versus RZ in 10-40-Gb/s dispersion-managed WDM transmission systems,"IEEE Photonics Technology Letters, 2003.

[8] H. Sunnerud, M. Karlsson, and P. A. Andrekson, "A comparison between NRZ and RZ data formats with respect to PMD-induced system degradations," IEEE Photonics Technology Letters, 13(5):448–450, May 2001.

[9] P. J. Winzer and A. Kalmar, "Sensitivity enhancement of optical receivers by impulsive coding," J. Lightwave Technol., vol. 17, pp.171–177, Feb. 1999.

[10] G. Castanon and T. Hoshida, "Impact of dispersion slope in NRZ, CSRZ, IMDPSK and RZ formats on ultra high bit-rate systems," European Conference on Optical Communication (ECOC), 4(9.6.1), September 2002.

[11] K. Yonenaga and S. Kuwano, "Dispersion-tolerant optical transmission system using duobinary transmitter and binary receiver," Journal of Lightwave Technology, 15(8):1530–1537, August 1997.

[12] C. X. Yu, S. Chandrasekhar, L. Buhl, A. Gnauck, S. Radic, X.Wei, and X. Liu, "10.7 Gbit/s transmission over

>200 km of standard singlemode fiber using forward error correction and duobinary modulation," Electronics Letters, 39(1):76–77, January 2003.

FIREWALL (COMPUTING)

Rajiv Sharma

*Computer Science Engineering Department, Shri Baba Mastnath Engineering College, Asthal Bohar, Rohtak, Haryana, India

rajivsharma.075@ymail.com

In computing, a firewall is a network security system that controls the incoming and outgoing network traffic based on an applied rule set. A firewall establishes a barrier between a trusted, secure internal network and another network (e.g., the Internet) that is assumed not to be secure and trusted. Firewalls exist both as software to run on general purpose hardware and as a hardware appliance. Many hardware-based firewalls also offer other functionality to the internal network they protect, such as acting as a DHCP server for that network.

Many personal computer operating systems include software-based firewalls to protect against threats from the public Internet. Many routers that pass data between networks contain firewall components and, conversely, many firewalls can perform basic routing functions.The term firewall originally referred to a wall intended to confine a fire or potential fire within a building. Later uses refer to similar structures, such as the metal sheet separating the engine compartment of a vehicle or aircraft from the passenger compartment.

Firewall technology emerged in the late 1980s when the Internet was a fairly new technology in terms of its global use and connectivity. The predecessors to firewalls for network security were the routers used in the late 1980s:

- Clifford Stoll's discovery of German spies tampering with his system[4]
- Bill Cheswick's "Evening with Berferd" 1992 in which he set up a simple electronic "jail" to observe an attacker[4]
- In 1988, an employee at the NASA Ames Research Center in California sent a memo by email to his colleagues[5] that read, "We are currently under attack from an Internet VIRUS! It has hit Berkeley, UC San Diego, Lawrence Livermore,Stanford, and NASA Ames."
- The Morris Worm spread itself through multiple vulnerabilities in the machines of the time. Although it was not malicious in intent, the Morris Worm was the first large scale attack on Internet security; the online community was neither expecting an attack nor

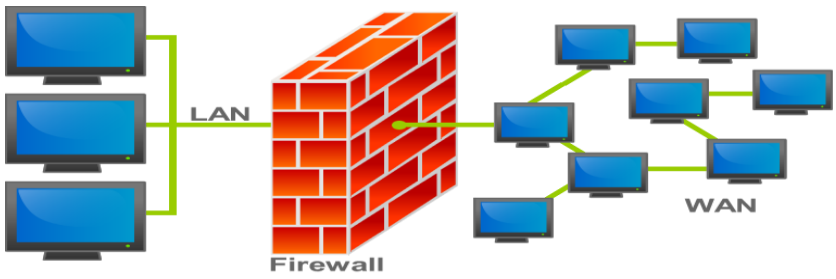


Fig. 1

FIRST GENERATION: PACKET FILTERS : The first paper published on firewall technology was in 1988, when engineers from Digital Equipment Corporation (DEC) developed filter systems known as packet filter firewalls. This fairly basic system was the first generation of what is now a highly involved and technical internet security feature. At AT&T Bell Labs, Bill Cheswick and Steve Bellovin were continuing their research in packet filtering and developed a working model for their own company based on their original first generation architecture.[7]Packet filters act by inspecting the "packets" which are transferred between computers on the Internet. If a packet matches the packet filter's set of filtering rules, the packet filter will drop (silently discard) the packet or reject it (discard it, and send "error responses" to the source).

This type of packet filtering pays no attention to whether a packet is part of an existing stream of traffic (i.e. it stores no information on connection "state"). Instead, it filters each packet based only on information contained in the packet itself (most commonly using a combination of the packet's source and destination address, its protocol, and, for TCPand UDP traffic, the port number). TCP and UDP protocols constitute most communication over the Internet, and because TCP and UDP traffic by convention uses well known ports for particular types of traffic, a "stateless" packet filter can distinguish between, and thus control, those types of traffic (such as web browsing, remote printing, email transmission, file transfer), unless the machines on each side of the packet filter are both using the same non-standard ports.[8]

Packet filtering firewalls work mainly on the first three layers of the OSI reference model, which means most of the work is done between the network and physical layers, with a little bit of peeking into the transport layer to figure out source and destination port numbers.[9] When a packet originates from the sender and filters through a firewall, the device checks for matches to any of the packet filtering rules that are configured in the firewall and drops or rejects the packet accordingly. When the packet passes through the firewall, it filters the packet on a protocol/port number basis (GSS). For example, if a rule in the firewall exists to block telnet access, then the firewall will block the TCP protocol for port number 23.

SECOND GENERATION: "STATEFUL" FILTERS: From 1989–1990 three colleagues from AT&T Bell Laboratories, Dave Presetto, Janardan Sharma, and Kshitij Nigam, developed the second generation of firewalls, calling themCircuit-level gateways. Second-generation firewalls perform the work of their first-generation predecessors but operate up to layer 4 (transport layer) of the OSI model. This is achieved by retaining packets until enough information is available to make a judgement about its state.[12] Known as stateful packet inspection, it records all connections passing through it and determines whether a packet is the start of a new connection, a part of an existing connection, or not part of any connection. Though static rules are still used, these rules can now contain *connection state* as one of their test criteria.Certain denial-of-service attacks bombard the firewall with thousands of fake connection packets in an attempt to overwhelm it by filling its connection state memory.

THIRD GENERATION: APPLICATION LAYER: Marcus Ranum, Wei Xu, and Peter Churchyard developed an Application Firewall known as Firewall Toolkit (FWTK). In June 1994, Wei Xu extended the FWTK with the Kernel enhancement of IP filter and socket transparent. This was known as the first transparent Application firewall, released as a commercial product of Gauntlet firewall at Trusted Information Systems. Gauntlet firewall was rated one of the number 1 firewalls during 1995–1998.The key benefit of application layer filtering is that it can "understand" certain applications and protocols (such as File Transfer Protocol (FTP), Domain Name System (DNS), orHypertext Transfer Protocol (HTTP)). This is useful as it is able to detect if an unwanted protocol is attempting to bypass the firewall on an allowed port, or detect if a protocol is being abused in any harmful way. As of 2012, the so-called next-generation firewall (NGFW) is nothing more than the "widen" or "deepen" inspection at application-stack. For example, the existing deep packet inspection functionality of modern firewalls can be extended to include i) Intrusion prevention systems (IPS); ii) User identity integration (by binding user IDs to IP or MAC addresses for "reputation"); and/or iii) Web Application Firewall (WAF). WAF attacks may be implemented in the tool "WAF Fingerprinting utilizing timing side channels" (WAFFle).

OPEN SUN DRYING OF CORN KERNELS

Sandeep Kumar Jangra

*Mechanical Engineering Department, Shri Baba Mastnath Engineering College, Asthal Bohar, Rohtak, Haryana, India sandeepjangra095@ymail.com

In this Article an attempt has been made to determine the convective heat transfer coefficient of corn kernels under open sun drying mode. The experiments were conducted in the month of June 2013 for open sun drying of corn kernels in the climatic conditions of Rohtak (28° 40': 29 05'N 76° 13': 76° 51'E). The corn kernels werwe dried from initial moisture content 43 % dry basis. Experimental data were used to evaluate the values of constants (C and n) in the Nusselt number expression by using linear regression analysis and consequently convective heat transfer coefficients were determined. The average value of convective heat transfer coefficient was found to be 3.91 W/m^2 °C for corn kernels. The experimental error in terms of percent uncertainty has also been evaluated.

Keywords: Corn kernels; Convective heat transfer coefficient; Open sun drying.

NOMENCLATURE

A_t	area of circular wire mesh tray, m^2
C	constant
C_v	specific heat of humid air, J/kg °C
g	acceleration due to gravity, m/s^2
Gr	Grashof number $= \beta g X^3 \rho_v^2 \Delta T / \mu_v^2$
h_c	convective heat transfer coefficient, W/m^2 °C
$h_{c,av}$	average convective heat transfer coefficient, W/m^2 °C
K_v	thermal conductivity of humid air, W/m °C
m_{ev}	moisture evaporated, kg
n	constant
Nu	Nusselt number $= h_c X / K_v$
Pr	Prandtl number $= \mu_v C_v / K_v$
$P(T)$	partial vapor pressure at temperature T, N/m^2
Q_e	rate of heat utilized to evaporate moisture, J/m^2 s
t	time, s
T_c	corn kernel surface temperature, °C
T_e	temperature just above corn kernel surface, °C
$\overline{T}_c$	average corn kernel surface temperature, °C
$\overline{T}_e$	average temperature of humid air, °C
T_i	average of corn kernel surface and humid air temperature, °C
ΔT	effective temperature difference, °C
X	characteristic dimension, m

Greek symbols

β	coefficient of volumetric expansion, 1/ °C
γ	relative humidity, %

γ average relative humidity, %

λ latent heat of vaporization, J/kg

μ_v dynamic viscosity of humid air, kg/m.s

ρ_v density of humid air, kg/m^3

INTRODUCTION

Corn is a popular food throghout the world in many forms. It is used in breakfast cereals in the western world (as corn flake) and it is a grain that can be eaten raw off the cob.

Open sun drying is the most primitive methods of corn kernels drying. Corn kernels drying involves a heat and mass transfer phenomenon in which heat energy supplied to the corn kernels surface is utilized in two different ways: (i) to increase the corn kernels temperature in the form of sensible heat and (i) to vaporize the moisture present in corn kernels through provision of the latent heat of vaporization. The removal of moisture from the interior of the corn kernels takes place due to induced vapor pressure difference between the corn kernel and surrounding medium. The moisture from the interior diffuses to the corn kernels surface to replenish the evaporated surface moisture.

The convective heat transfer coefficient is an important parameter in drying rate simulation since the temperature difference between the air and corn kernel varies with this coefficient. Sodha et al presented a simple analytical model based on simultaneous heat and mass transfer at the product surface and included the effect of wind speed, relative humidity, product thickness, and heat conducted to the ground for open sun drying and for a cabinet dryer. Miketinac. studied the drying of thin layer of barley and formulated five models simulating the process of simultaneous heat and mass transfer. Depending upon the form of drying model the heat transfer coefficient was found to vary between 43 and 59 W/m^2 ^{o}C. Goyal and Tiwari [3] have studied heat and mass transfer in product drying systems and have reported the values of convective heat transfer coefficient for wheat and gram as 12.68 and 9.62 W/m^2 ^{o}C, respectively, by using the simple regression and 9.67 and 10.85 W/m^2 ^{o}C respectively, for same products while using the multiple regression technique. Anwar and Tiwati studied the open sun drying of some crops (green chillies, green peas, white gram, onion flakes, potato slices and cauliflower) and found the values of convective heat transfer coefficients which were to vary from 3.71 – 25.98 W/m^2^{o}C. Togrul have determined the convective heat transfer coefficients of some crops dried under open sun conditions which were found to vary with a range of 0.768 to 3.292 W/m^2 ^{o}C. Akpinar determined the convective heat transfer coefficient of various agricultural products, namely, mulberry, strawberry, apple, garlic, potato, pumpkin, eggplant, and onion under open sun drying. The convective heat transfer coefficient of these crops was found to vary from crop to crop with a range of 1.136 – 11.323 W/m^2^{o}C. Togrul determined the convective heat transfer coefficient of apricots in open sun drying conditions which were found to vary from 0.0374 to 2.046 W/m^2^{o}C. Dilip Jain studied the solar drying of Indian minor fish species, such as prawn (Macrobrachium lamarrei) and carp (chelwa) (Oxygaster bacaila). The convective mass transfer coefficients were found to vary from 8.958 to 0.402 μms^{-1} for prawn and from 7.613 to 0.320 μms^{-1}for chelwa fish. Jaishree Akhilesh Prasad [9] studied the drying of *Tinospora cordifolia (herb), Curcuma longa L. and Zingiber officinale (spices)* in open sun drying mode. The maximum values of convective heat transfer coefficient were found to be 3.9, 3.4 and 3.3 W/m^2^{o}C for *T. cordifolia, C. longa L. and Z. officinale* under open sun drying, respectively. Studied the drying of papad in open sun and indoor forced convection drying modes. The convective heat transfer coefficients of papad were found to be 3.54 and 1.56 W/m^2 ^{o}C under open sun drying and indoor forced convection drying modes respectively. Sahdev the open sun drying of vermicelli of different diameters and found the convective heat transfer coefficient to be 5.61 and 4.13 for vermiceli of diameter 2 mm and 1.25 mm respectively.

In the present research paper, the convective heat transfer coefficient has been found by determining the values of the constants (C and n) in the Nusselt number expression for corn kernels dried

under open sun drying mode. This value would be helpful in designing a dryer to dry corn kernels to its optimum storage moisture level of about 16 %.

MATERIALS AND METHODS

EXPERIMENTAL SET-UP AND PROCEDURE

A circular shaped wire mesh tray of diameter 150 mm was used to accommodate the corn kernels. A digital weighing balance (Smart, Aqua Series) of 6 kg capacity having a least count of 0.1g was used to measure the mass of moisture evaporated. A non-contact (infra-red thermometer) thermometer (Raytek-MT4) having a least count of 0.2 ^{o}C with an accuracy of ± 2% on a full scale range of -1 to 400 ^{o}C was used to measure the corn kernels surface temperature. An eight channel digital temperature indicator (0-200^{o}C, least count of 0.1 ^{o}C) with a calibrated thermocouple was used to measure the ambient temperature. A digital hygrometer (model Lutron HT-315) was used to measure the relative humidity and temperature of air just above the corn kernels surface.

Experiments were conducted in the month of June 2013 for open sun drying mode in the climatic conditions of Rohtak (28^{o} 40': 29 05'N 76^{o} 13': 76^{o} 51'E). The corn kernels were kept on the weighing balance using the wire mesh tray. A digital hygrometer was kept just above the corn kernels surface with its probe facing downwards towards the corn kernels surface to measure the humidity and temperature of the air. Every time it was kept on 1 minute before reading the observations. All the observations were recorded at every 10 minute time intervals. The whole unit was kept in open sun at a place with negligible wind velocity. The difference in weight directly gave the quantity of water evaporated during that time interval. Average values of corn kernels surface temperature , exit air temperature and relative humidity were calculated from the two consecutive values for that time interval and were used in the calculations. The photograph of the experimental set up under open sun drying mode is shown in Figure 1.

Figure 1: A photograph of experimental set-up for open sun drying mode.

SAMPLE PREPARATION : Corn cobs were purchased from the local market and its grains (corn kernels) were separated from it. The corn kernels of 72.0 grams were used for open sun drying mode.

THERMAL MODELING

The convective heat transfer coefficient for open sun drying mode can be calculated using the expression for Nusselt number as [12, 10]:

$$Nu = \frac{h_c X}{K_v} = C(Gr \Pr)^n$$

or

$$h_c = \frac{K_v}{X} C(Gr \Pr)^n \qquad (1)$$

The rate of heat utilized to evaporate moisture is given as [13].

$$Q_e = 0.016 h_c [(T_c - T_e) + \gamma (P_c - P_e)] \qquad (2)$$

On substituting h_c from equation (1), equation (2) becomes

$$Q_e = 0.016 \frac{K_v}{X} C(Gr \Pr)^n [(T_c - T_e) + \gamma (P_c - P_e)] \qquad (3)$$

The moisture evaporated is determined by dividing equation (3) by the latent heat of vaporization (λ) and multiplying by the area of the tray (A_t) and time interval (t)

$$m_{ev} = \frac{Q_e}{\lambda} t A_t = 0.016 \frac{K_v}{X\lambda} C(Gr \Pr)^n [(T_c - T_e) + \gamma (P_c - P_e)] A_t \qquad (4)$$

Let $0.016 \frac{K_v}{X\lambda} [(T_c - T_e) + \gamma (P_c - P_e)] A_t = Z$

$$\frac{m_{ev}}{Z} = C(Gr \Pr)^n \qquad (5)$$

Taking logarithm on both sides of equation (5)

$$\ln\left[\frac{m_{ev}}{Z}\right] = \ln C + n \ln(Gr \Pr) \qquad (6)$$

This is the form of a linear equation,

$$Y = mX_0 + C_0$$

Where

$$Y = \ln\left[\frac{m_{ev}}{Z}\right], \qquad m = n, \; X_0 = \ln(Gr \Pr), \qquad C_0 = \ln C$$

Thus, $C = e^{C_0}$

By using the data of Table 1, the values of Y and X_0 were evaluated for different time intervals and then the constants C and n were obtained from the above equations. The values of constants C and n were further used to evaluate convective heat transfer coefficient from Equation (1). The physical properties of humid air, i.e., specific heat (C_v), thermal conductivity (K_v), density (ρ_v), viscosity (μ_v) and partial vapor pressure were calculated using the following expressions [4, 10]:

$$C_v = 999.2 + 0.1434 T_i + 1.101 \times 10^{-4} T_i^2 - 6.7581 \times 10^{-8} T_i^3 \qquad (7)$$

$$K_v = 0.0244 + 0.7673 \times 10^{-4} T_i \qquad (8)$$

$$\rho_v = \frac{353.44}{T_i + 273.15} \quad (9)$$

$$\mu_v = 1.718 \times 10^{-5} + 4.620 \times 10^{-8} T_i \quad (10)$$

$$P = \exp\left[25.317 - \frac{5144}{T + 273.15}\right] \quad (11)$$

Where

$$T_i = \frac{\overline{T}_c + \overline{T}_e}{2}$$

The values of constants C and n have been determined by linear regression analysis by using measured data of the corn kernels and exit air temperature, exit air relative humidity and moisture evaporated during a certain time period. The following linear regression formulae have been used to calculate *C* and *n*

$$n = \frac{N_o \Sigma X_0 Y - \Sigma X_0 \Sigma Y}{N_o \Sigma X_0^2 - (\Sigma X_0)^2} \quad (12)$$

and

$$C_0 = \frac{\Sigma X_0^2 \Sigma Y - \Sigma X_0 \Sigma X_0 Y}{N_o \Sigma X_0^2 - (\Sigma X_0)^2} \quad (13)$$

The experimental error were also calculated in terms of % uncertainty (internal + external).The following equations were used to evaluate % uncertainty [14]

$$U = \frac{\sqrt{\sigma_1^2 + \sigma_2^2 + \sigma_3^2 \ldots + \sigma_n^2}}{N} \quad (14)$$

Where σ is the standard deviation and is given as

$$\sigma = \sqrt{\frac{\Sigma (X_i - \overline{X}_i)^2}{N_0}} \quad (15)$$

Where X_i is the moisture evaporated and $(X_i - \overline{X}_i)$ is the deviation of the observations from the mean. N and N_o are the number of sets and number of observations in each set, respectively.

The % uncertainty was determined using the following expression.

$$\%\,\text{internal uncertainty} = \frac{U}{\text{Average of total number of observations}} \times 100$$

EXPERIMENTAL RESULTS AND DISCUSSION

The values of observations recorded for open sun drying mode are recorded in Tables 1 for corn kernels.

Table 1: Observations for corn kernels under open sun drying mode

Drying time (min.)	Wt (gms)	T_c (C)	T_e (C)	γ (%)	m_{ev} (gm)	$\overline{T}_c$ (C)	$\overline{T}_e$ (C)	$\overline{\gamma}$ (%)
0	72.0	34.2	34.4	0.5648	-	-	-	-
10	71.1	33.9	33.1	0.5219	0.0009	34.1	33.75	0.5434

20	69.5	34.8	34.7	0.5199	0.0016	34.4	33.92	0.5209
30	68.2	32.9	32.5	0.5206	0.0013	33.9	33.61	0.5203
40	67.6	33.6	34.7	0.5498	0.0006	33.3	33.58	0.5352
50	65.2	33.2	34.4	0.5626	0.0024	33.4	34.55	0.5562
60	64.2	35.2	34.9	0.5341	0.0010	34.2	34.68	0.5484
70	63.5	36.6	37.8	0.4885	0.0007	35.9	36.35	0.5113
80	62.6	37.8	38.2	0.4793	0.0009	37.2	37.96	0.4839
90	62.0	36.8	36.5	0.5085	0.0006	37.3	37.33	0.4939
100	61.2	37.0	38.1	0.4776	0.0008	36.9	37.32	0.4931
110	59.4	37.2	37.0	0.4953	0.0018	37.1	37.57	0.4865
120	58.8	36.9	36.5	0.5021	0.0006	37.1	36.76	0.4987
130	58.2	38.0	37.1	0.4888	0.0006	37.5	36.80	0.4955
140	57.8	37.9	38.2	0.4714	0.0004	38.0	37.64	0.4801
150	57.1	36.0	37.9	0.4857	0.0007	37.0	38.06	0.4786
160	56.4	36.8	37.7	0.4779	0.0007	36.4	37.82	0.4818
170	55.9	37.0	37.2	0.4757	0.0005	36.9	37.43	0.4768
180	55.1	37.0	38.9	0.3718	0.0008	37.0	38.06	0.4238
190	54.5	41.6	41.5	0.3820	0.0006	39.3	40.20	0.3769
200	54.1	42.8	44.1	0.3552	0.0004	42.2	42.78	0.3686
210	53.6	41.8	42.2	0.3520	0.0005	42.3	43.16	0.3536
220	52.7	38.6	39.7	0.4130	0.0009	40.2	40.96	0.3825
230	51.8	34.8	37.5	0.4738	0.0009	36.7	38.59	0.4434
240	50.9	31.0	31.9	0.4845	0.0009	32.9	34.69	0.4792
250	50.3	33.2	33.2	0.4628	0.0006	32.1	32.52	0.4737

The average of corn kernel surface temperature $(\overline{T}_c)$, exit air temperature $(\overline{T}_e)$ and exit air relative humidity $(\overline{\phi})$ were used to calculate the physical properties of the humid air which were further used to evaluate the values of Grashof number and Prandtl number. The values of 'C' and 'n' in equation (1) were obtained by simple linear regression analysis, and, thus the values of h_c were determined as tabulated in Table 2.

Table 2: Values of C, n and the convective heat transfer coefficients

	C	n	h_c (W/m^2 ^{o}C)	$h_{c\,avg}$ (W/m^2 ^{o}C)
corn kernels	0.99	0.24	2.45 – 5.16	3.91

The variation of convective heat transfer coefficient with respect to time for open sun drying mode is shown in Figures 2.

An estimate of internal uncertainty was carried out for experimental observations. The external uncertainty has also been calculated by taking into account the errors which occurred during measurements of mass evaporated, temperatures and relative humidity which were considered by taking the least count of all the measuring instruments. The value of percent uncertainty (internal+external) was found to be within 40%.

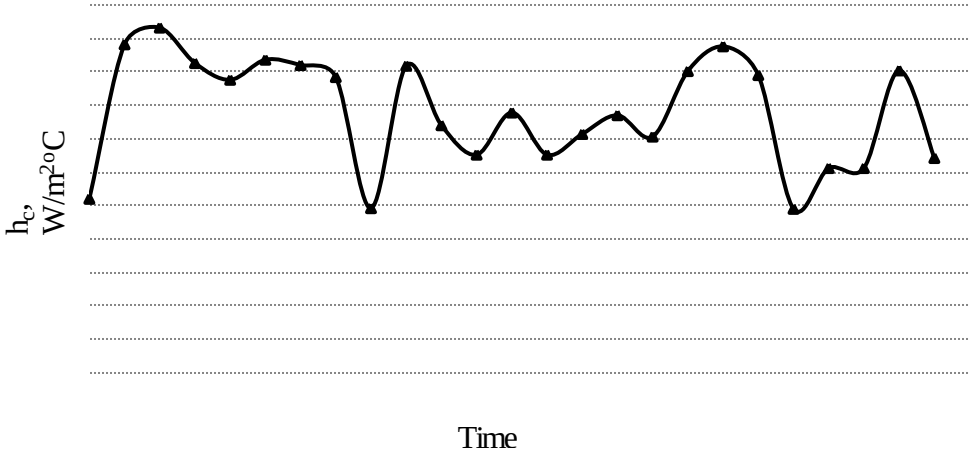


Figure 2: h_c vs time for corn kernels under open sun drying mode.

CONCLUSION

The convective heat transfer coefficients for corn kernels under open sun drying mode was determined using the values of the constants, 'C' and 'n' in the expression of Nusselt number by using the linear regression technique. The average value of convective heat transfer coefficient under open sun drying mode has been found to be 3.91 W/m^2 °C. The experimental error for open sun drying has been found to be within 40 %.

CLOUD COMPUTING

Seema

Department of computer science, S.B.M.N Engg. College, Asthal Bohar,Rohtak-124021(Haryana) INDIA
seemakoshik16***@yahoo.co.in***

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Cloud computing is a computing term or metaphor that evolved in the late 1900s, based on utility and consumption of computer resources. Cloud computing involves application systems are executed within the cloud and operated through internet enabled devices. Purely cloud computing do not rely on the use of cloud storage as it will be removed upon users download action. Clouds can be classified as public, private and hybrid.

Figure 1

Cloud computing[] relies on sharing of resources to achieve coherence and economies of scale, similar to a utility (like the electricity grid) over a network. At the foundation of cloud computing is the broader concept of converged infrastructure and shared services.

Cloud computing, or in simpler shorthand just "the cloud", also focuses on maximizing the effectiveness of the shared resources. Cloud resources are usually not only shared by multiple users but are also dynamically reallocated per demand. This can work for allocating resources to users. For example, a cloud computer facility that serves European users during European business hours with a specific application (e.g., email) may reallocate the same resources to serve North American users during North America's business hours with a different application (e.g., a web server). This approach should maximize the use of computing power thus reducing environmental damage as well since less power, air conditioning, rack space, etc. are required for a variety of functions. With cloud computing, multiple users can access a single server to retrieve and update their data without purchasing licenses for different applications.

The term "moving to cloud" also refers to an organization moving away from a traditional CAPEX model (buy the dedicated hardware and depreciate it over a period of time) to theOPEX model (use a shared cloud infrastructure and pay as one uses it).

The present availability of high-capacity networks, low-cost computers and storage devices as well as the widespread adoption of hardware virtualization, service-oriented architecture, and autonomic and utility computing have led to a growth in cloud computing. Companies can scale up as computing needs increase and then scale down again as demands decrease

Cloud vendors are experiencing growth rates of 50% per annum.

HISTORY OF CLOUD COMPUTING: The origin of the term cloud computing is unclear. The expression cloud is commonly used in science to describe a large agglomeration of objects that visually appear from a distance as a cloud and describes any set of things whose

details are not inspected further in a given context.[12] Another explanation is that the old programs to draw network schematics surrounded the icons for servers with a circle, and a cluster of servers in a network diagram had several overlapping circles, which resembled a cloud.

In analogy to above usage the word cloud was used as a metaphor for the Internet and a standardized cloud-like shape was used to denote a network on telephony schematics and later to depict the Internet in computer network diagrams. With this simplification, the implication is that the specifics of how the end points of a network are connected are not relevant for the purposes of understanding the diagram. The cloud symbol was used to represent the Internet as early as 1994, in which servers were then shown connected to, but external to, the cloud.

References to cloud computing in its modern sense appeared early as 1996, with the earliest known mention in a Compaq internal document**.** The popularization of the term can be traced to 2006 when Amazon.com introduced the Elastic Compute Cloud

THE 1950

The underlying concept of cloud computing dates to the 1950s, when large-scale mainframe computers were seen as the future of computing, and became available in academia and corporations, accessible via thin clients/terminal computers, often referred to as "dumb terminals", because they were used for communications but had no internal processing capacities. To make more efficient use of costly mainframes, a practice evolved that allowed multiple users to share both the physical access to the computer from multiple terminals as well as the CPU time. This eliminated periods of inactivity on the mainframe and allowed for a greater return on the investment. The practice of sharing CPU time on a mainframe became known in the industry as time-sharing. During the mid 70s, time-sharing was popularly known as RJE (Remote Job Entry); this nomenclature was mostly associated with large

CHARACTERISTICS

Cloud computing exhibits the following key characteristics:

- **Agility** improves with users' ability to re-provision technological infrastructure resources.
- **Cost** reductions claimed by cloud providers. A public-cloud delivery model converts capital expenditure to operational expenditure. This purportedly lowers barriers to entry, as infrastructure is typically provided by a third party and does not need to be purchased for one-time or infrequent intensive computing tasks. Pricing on a utility computing basis is fine-grained, with usage-based options and fewer IT skills are required for implementation (in-house). The e-FISCAL project's state-of-the-art repository contains several articles looking into cost aspects in more detail, most of them concluding that costs savings depend on the type of activities supported and the type of infrastructure available in-house.
- **Device and location independence** enable users to access systems using a web browser regardless of their location or what device they use (e.g., PC, mobile phone). As infrastructure is off-site (typically provided by a third-party) and accessed via the Internet, users can connect from anywhere.
- **Maintenance** of cloud computing applications is easier, because they do not need to be installed on each user's computer and can be accessed from different places.
- **Multitenancy** enables sharing of resources and costs across a large pool of users thus allowing for:
  - **centralization** of infrastructure in locations with lower costs (such as real estate, electricity, etc.)
  - **peak-load capacity** increases (users need not engineer for highest possible load-levels)

    - **utilisation and efficiency** improvements for systems that are often only 10–20% utilised.
- **Performance** is monitored, and consistent and loosely coupled architectures are constructed using web services as the system interface.
- **Productivity** may be increased when multiple users can work on the same data simultaneously, rather than waiting for it to be saved and emailed. Time may be saved as information does not need to be re-entered when fields are matched, nor do users need to install application software upgrades to their computer.
- **Reliability** improves with the use of multiple redundant sites, which makes well-designed cloud computing suitable for business continuity and disaster recovery.
- **Scalability and elasticity** via dynamic ("on-demand") provisioning of resources on a fine-grained, self-service basis in near real-time (Note, the VM startup time varies by VM type, location, OS and cloud providers, without users having to engineer for peak loads.
- **Security** can improve due to centralization of data, increased security-focused resources, etc., but concerns can persist about loss of control over certain sensitive data, and the lack of security for stored kernels. Security is often as good as or better than other traditional systems, in part because providers are able to devote resources to solving security issues that many customers cannot afford to tackle. However, the complexity of security is greatly increased when data is distributed over a wider area or over a greater number of devices, as well as in multi-tenant systems shared by unrelated users. In addition, user access to security audit logs may be difficult or impossible. Private cloud installations are in part motivated by users' desire to retain control over the infrastructure and avoid losing control of information security.

STONE DUST IN THE DESIGN OF HIGH PERFORMANCE CONCRETE

V.K AHUJA , HOD (CIVIL ENGG.)

Engg.vkahuja@gmail.com ph. 9255589865

ABSTRACT

This research evaluated the suitability of stone dust in the design and production of High Performance Concrete (HPC). HPC mix was designed, tested, costed and a comparison of concrete classes used in the market (Class 25, 30 and 35) done using Cost Benefit Analysis (CBA). The cost benefit was analyzed using Internal Rate of Return (IRR) and Net Present Value (NPV). Laboratory tests established the properties concrete obtained from the design mix. Compressive strength, slump, and modulus of elasticity were tested and analyzed.

INTRODUCTION

More than 40 years have passed since High Performance Concrete was realized; high-strength concrete itself has been enhanced in terms of performance and placeability through a lot of useful developments. Use of stone dust will also enhance environmental conservation particularly where river sand use will be reduced.

OBJECTIVES

1) Evaluate the suitability of stone dust (quarry waste) in production of High Performance Concrete (HPC).

2) To compare the cost of HPC (Class 80) production against costs of traditional Class 25, 30, and 35 MPa.

THE LITERATURE REVIEW

High performance concrete (HPC) is defined as concrete whose strength and durability is greater than those of "normally" obtained concrete (Addis, 2001) [2]. According to United States of America Strategic Highway Research Program on high performance concrete, HPC is defined as having 4 hour compressive strength of greater than or equal to 17.2 Megapscals (Mpa), 24 hour compressive strength of greater than 34.5 Mpa and 28 day compressive strength of greater than 68.9 Mpa

MATERIALS SELECTION

Stone dust was collected from Athi River crushing plant for testing after stock pile sampling. Ordinary Portland cement (CEM 42.5) and admixture Sika® ViscoCrete®-HE, a water reducer and super plasticizer obtained from the local dealers were used in the design for concrete manufacture.

COST BENEFIT ANALYSIS

The cost of production of HPC (Class 80) was calculated based on optimum design mix obtained from the laboratory tests. This cost was compared with the costs of Class 25, 30, and 35 as available in the market. Further Cost Benefit Analysis (CBA) was undertaken to evaluate the benefit accrued as a result of increased lettable space over the investment incurred. CBA determines the soundness of the investment/decision (justification/ feasibility). It provides a basis for comparing concrete classes. Total costs comparisons expected for each option against the total expected benefits, to see whether the benefits outweigh the costs, and by how much.

SUMMARY

Quarry dust obtained from Mlolongo quarry graded between 75 μm to 19 mm with a relative density of 2.389 Kg/m2 make good high strength concrete of over 80 N/mm2 at a water cement ratio of 0.32. The concrete manufactured used Sika® ViscoCrete®-HE admixture which is a plasticizer and water reducer to minimize the water requirement and achieve the required slump. Stone dust is much cheaper than both course aggregate and sand and

therefore minimize the cost of concrete which has high cement volume per tonne (780 kg/m3 from the mix design). Design of structures using high strength concrete reduces significantly the structural member sizes, steel reinforcement and increase the available usable space in the structure. The limitations for reduced structural members are modulus of elasticity particularly for slender columns and shear reinforcements for foundation footing and heavily loaded beams. There is significant return on investment when high strength of concrete is used for structural members (in the case of construction of 10 storey structure, the IRR was 3%). Use of HPC present additional advantages; in the case where the client has a small space and needs bigger floor area or in the case where the floor areas have big spans.

CONCLUSIONS

From the research the following conclusion can be made:

- Manufacture High strength concrete (HPC) using locally available stone dust is possible with strengths of over 80 kN/mm2 with a Modulus of Elasticity of 49.4 Gpa achieved using stone dust obtained from MlolongoQuarries.
- Use of High strength concrete significantly reduces structural members (columns sizes, beam depths). The sizes are however limited by modulus of elasticity particularly for slender columns and shear reinforcement for heavily loaded columns and foundation pads.
- There is also significant reduction in the total weight of reinforcement steel when high strength concrete is used.
- The benefits accrued from letting extra space created from the smaller column sizes are significant and present a business case when life cycle costs of the structure are considered. This is important for clients
  who have smaller development space and want to maximize it or for structure that have bigger floor spans.

HDMI IS DEAD. INTRODUCING HDBASET NETWORKING

Arvind Batra

Asstt. Prof., Baba Mastnath Engg. College, Asthal Bohar, Rohtak-124001 E-Mail : Batra_Arvind@rediffmail.com

HDMI is dead. How can we say this? Because we have seen the future and it is HDBaseT. HDBaseT technology runs over STANDARD Cat5e/6 cable and implements something it calls 5Play, an unrivaled feature-set that converges full uncompressed HD video, audio, 100BaseT Ethernet, and various control signals. Oh, it also transmits up to 100W of power - that's enough to drive a 37-inch TV. And it can extend up to 100 meters passively. HDBaseT has the bandwidth to support the highest video resolutions such as full HD 1080p as well as 3D and 2Kx4K formats. HDBaseT is the first to provide all-in-one connectivity, making it possible for a single-connector TV to receive power, video/audio, Internet and control signals from the same cable.

Think HDMI has a chance? Think again.

We were fortunate enough tp speak first hand with Ariel Sobelman, President of the HDBaset Alliance. He filled us in on the missing details and answered our questions regarding the future of HD BaseT.

What makes HDBaseT so odd is that it is sending more info than HDMI over a set of 8 wires within a standard Cat5e or Cat6 cable. How can it do this? Well, it uses much lower frequency modulated packets. These are not IP packets like you find in Gigabit Ethernet. Since they run on such low frequency, they are not subjected to typical EM (electromagnetic) interference. That means you can sit the cables in front of microwave or a cell phone and there are no problems with signal degradation.

5Play - Why You Should Be Impressed

Sure, HDBaseT replaces HDMI with a standard Cat5e or Cat6 cable... but is that really impressive? No, what's REALLY impressive is that HDBaseT's protocol allows you to literally NETWORK your sources and displays just like you do your home data network. They call it 5Play. Want to watch your living room Blu-ray in your bedroom? Check. How about your bedroom's cable box in your theater room? Check. Theater room's Xbox 360 in your children's room? Check? How about allowing three televisions to watch the Superbowl from your single Dish Network set top box at the same time? Check. Check. Check.

HDBaseT enables a network of sources - such as digital video recorders (DVR), Blu-ray disc players, game consoles, PCs and mobile devices — to be connected directly to displays in multiple locations. It allows users an independent yet fully compatible experience. HDBaseT LAN-based technology makes it possible to cut out the assortment of cables for audio, video, connecting CE devices. IR, networking... it's all there. At this year's CES show, LG did a demo where they sent three different sources to three different displays and switched them at will using an HDBaseT hub (and remember, when A/V receivers pick this up everything will be switched via GUI software).

So What's Next?

The demand for in-home converged distribution of HD multimedia content and the lack of adequate existing technologies are driving the industry toward an HD digital connectivity standard such as HDBaseT. Put plainly, HDMI, with its myriad of internal wires and impossibly difficult terminations, simply can't cut it. You really can't terminate it in the field and the more they add to the spec, the shorter the cable runs become until they need active components on either side just to make it work. Installers, in general, can't stand HDMI and are going to latch onto HDBaseT like you can't believe.

Consumers, on the other hand are familiar with Cat5e and more and more are running the lines in their houses for networking. At the very least they've all plugged in a desktop, laptop, or router to get onto the Internet. It;s comfortable, it's familiar.

It's lightweight and locks into a jack without falling out for heaven's sake!

Through development of the HDBaseT 1.0 digital connectivity specification, the HDBaseT Alliance addresses consumer needs and high market demand. HDBaseT increases the transfer distance of uncompressed HD multimedia content, expanding distribution, simplifying installation and ultimately lowering overall system cost.