

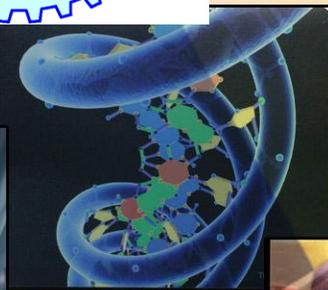
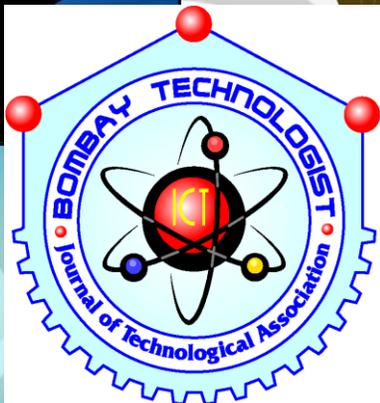
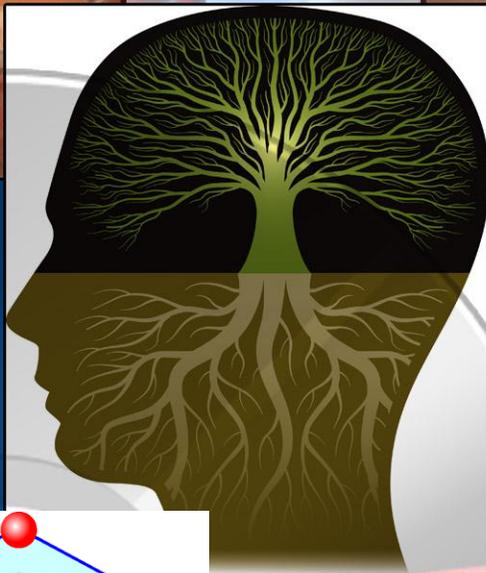
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INSTITUTE OF CHEMICAL TECHNOLOGY

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May 1, 2012

Message

While writing this message, I am immensely pleased to announce that the Govt of Maharashtra has accorded the Elite Status and Centre of Excellence to ICT, which will usher us into new era which will see the creativity of our students and faculty blossoming. One such activity is the Bombay Technologist, which has been in existence for decades now as a mouthpiece of the Technologist Association which was the students body started during Professor K. Venkataraman's tenure as the Director in 1950s. Venkataraman was internationally well known for his contributions to synthetic organic chemistry, including dyestuff, intermediates and pharmaceuticals. So many of his students and faculty used to publish articles in the Bombay Technologist. He developed the library culture in ICT.

Over the years, tremendous progress has taken place in collection and compilation of information and students seem to be more used to short cuts rather than in depth analysis of technical subjects. Of course, some of them spend hours in writing the review articles. This issue is no different and is more focussed on 'nano' in different areas due to wide acceptance of this term and its perceived benefits. One of the aspects of writing review papers is to understand the subject, critically dissect it, bring out the strength and weakness in the state-of-the art and provide future directions. In this regard, the articles written by the students have definite weakness. However, this being the training ground for future researchers, their contributions are most welcome. My personal belief is to include some of the best Posters which the Ph D students had prepared during last year in the Bombay Technologist will be a step in the right direction. Next year's issue is thus already on the board.

I am sure that the Editorial Board has taken lot of pains in collecting articles and my congratulations to one and all.

(G.D. Yadav)

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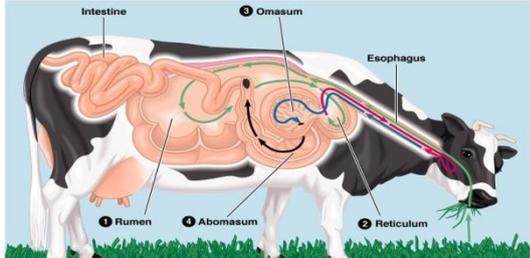
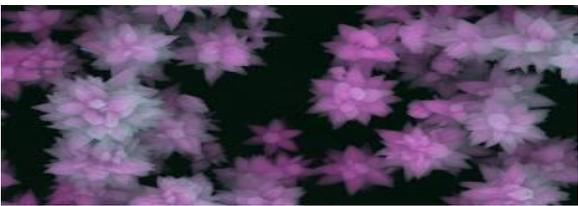
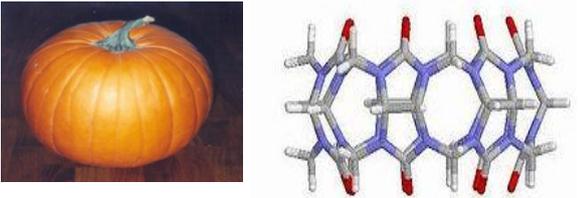
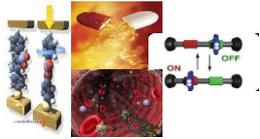
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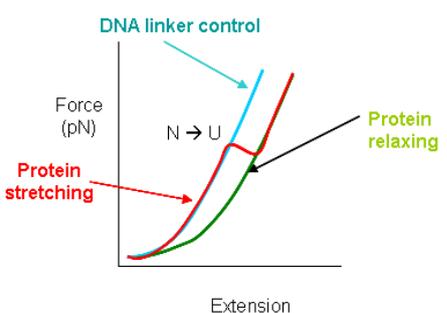
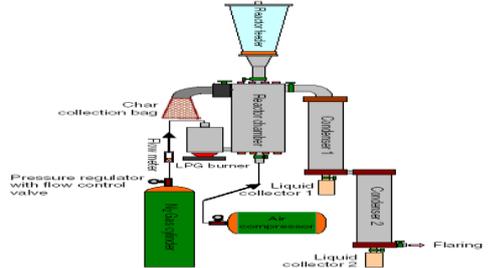
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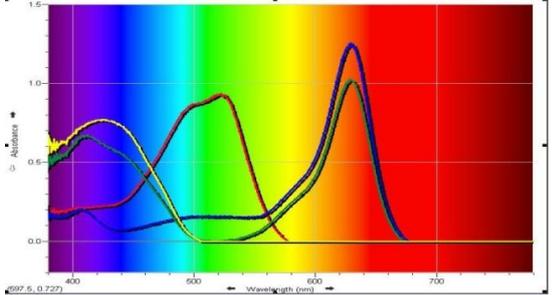
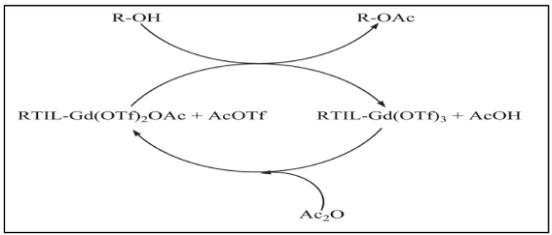
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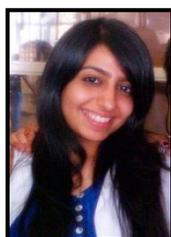
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ORAL DRUG DELIVERY SYSTEMS IN RUMINANT ANIMALS



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Abstract:

Ruminant animals like cattle, sheep, goat, etc. are commercially the most essential group of animals and are widely kept by human beings all over the world. With an increase in variety and popularity of products obtained from these species, their health also becomes an important consideration. Ruminants are animals with a distinct digestive system. The unique anatomy and physiology of these animals provides many challenges for their drug delivery. Animals, either large or small are difficult to handle and thus drug administration becomes a hassle for the caretaker and hurtful for the animal. However, the process of rumination along with their unusual four compartmental stomachs offers opportunities for controlled and sustained release delivery of drugs in these animals. This reduces the number of doses and makes the administration of a large variety of drugs possible. Taking advantage of this opportunity many formulations have been developed. However, there still remains tremendous scope for better and more efficient drug delivery systems for ruminants. This article talks about ruminant animals, their healthcare, devices used for drug administration, various oral formulations administered to them, with special emphasis to intraruminal devices- their mechanism and delivery.

1. INTRODUCTION:

The animals of commercial importance are mainly cattle, swine and poultry; hence the control of diseases which directly or indirectly affect the production in these animals is very important. The veterinary market is the “poor

cousin” to its human counterpart. 30.5 billion US dollars were spent in 2001 on R&D by research based pharmaceutical companies. Of this amount, only an estimated US \$0.6 billion (2%) were spent on pharmaceuticals for veterinary use. Nevertheless, the veterinary

pharmaceutical industry continues to thrive within a population of diverse species. The vast range of animal species and the corresponding anatomical and physiological differences, challenges the development of veterinary pharmaceutical formulations. ^{[1], [2]}

2. RUMINANTS:

2.1. An introduction to ruminants

The word "ruminant" comes from the Latin "ruminare", which means "to chew over again". Physiologically, a ruminant is a mammal of the order Artiodactyla that digests plant-based food by initially softening it within the animal's first stomach, then regurgitating the semi-digested mass, now known as cud, and chewing it again. The process of rechewing the cud to further break down plant matter and stimulate digestion is called "ruminating". There are about 150 species of ruminants which include both domestic and wild species including cattle, goats, sheep, giraffes, bison, moose, yaks, water, buffalo, deer, camels, wildebeest, antelope, etc., the most important ones being the domestic food animals in this class. ^[3]

2.2. Digestive system of ruminants

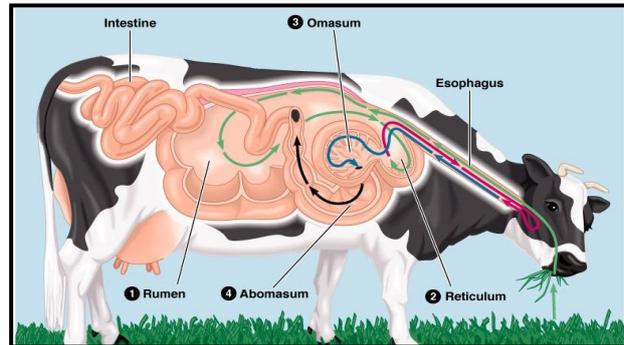


Figure 1: Ruminant digestive system.

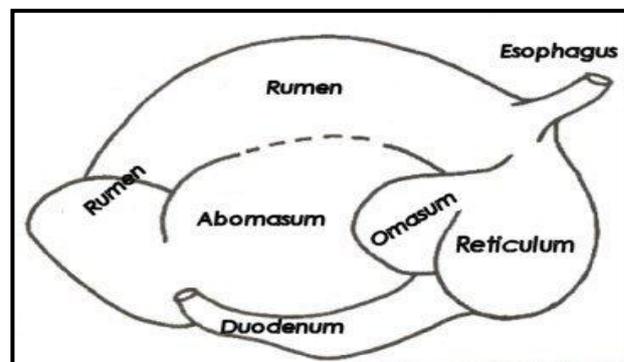


Figure 2: Ruminant Compartmental Stomach.

Ruminants have a four-compartment stomach. The four parts of the stomach are a fore-stomach (rumen, reticulum, and omasum) and abomasum. The function of the abomasum is similar to that of the stomach of other mammals. The compartments of the fore-stomach are the primary sites of microbial digestion of the feed. Fibre, especially cellulose and hemi-cellulose, is primarily broken down into the three volatile fatty acids by microbes (bacteria, protozoa, and fungi) in the reticulo-rumen region. Protein and non-structural carbohydrate (pectin, sugars, and starches) are also fermented.

After rumination and microbial digestion, the ruminal content (in the form of a suspension of small particles) passes through the omasum into the abomasum. The abomasum is the sole part of the gastrointestinal tract that secretes gastric juices. The pH is variable, but much lower than the rumen and is generally around a value of 3. Cattle produce about 100-190L of saliva per day. Continuous inflow provides extra fluid for the fermentation and a strong pH buffering of the digesta to optimise the microbial activity. Particles greater than 2mm (cattle) or 1mm (sheep) tend to be excluded from passage through the reticular-omasal orifice; this material is recycled through the rumination process. The abomasum is a true, glandular stomach, which secretes acid and functions in a manner similar to the stomach of a monogastric. Ingesta are finally subjected to the ruminant's own digestive enzymes. [16], [6], [3], [7].

2.3. Young Ruminants

At birth, the rumen and reticulum are not yet functional. When the lamb or calf sucks its mother's milk, the milk passes directly into the abomasum. The oesophageal groove was the pathway that allowed this to occur. The groove closed when the calf drank the milk. Thus the abomasum in calves is like the human stomach and not the ruminant stomach until they reach maturity. [3]

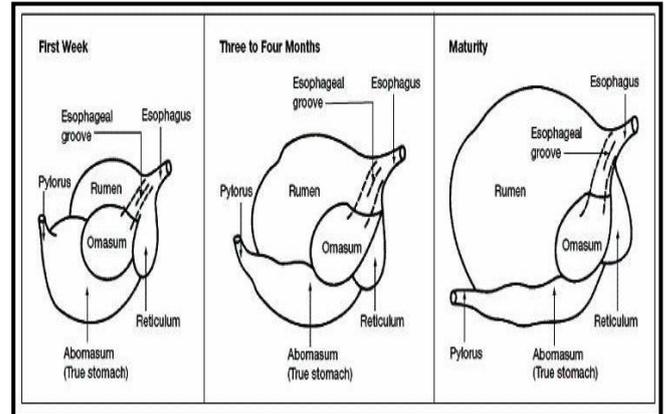


Figure 3: Development of the ruminant stomach compartments from birth to maturity.

3. ORAL FORMULATIONS FOR RUMINANT ANIMALS:



Figure 4: Oral formulations including boluses, pellets, granules, drenches

3.1. Solids

3.1.1. Conventional Oral Boluses:

Boluses are tablets or caplet-like products that are formulated with very large quantities of drug to be administered once daily. They are 4 inches long weighing 40g for large animals or 2 inches long for smaller ruminants. [8]

3.1.2. Sustained Release Oral Boluses: Rumen Retention Devices.

These are devices that remain in the reticulorumen for prolonged periods due to their density or geometry. These devices are formulated for zero buoyancy and its resulting lodging in the reticulum prevents regurgitation.^[12]

3.1.3. Granules and Pellets

These are formulations to be mixed either in the feed or in water. The formation of pellets by pelletisation is an agglomeration process that converts fine powders to granules of bulk drugs and excipients into small, free flowing, spherical and semi spherical units, referred to as pellets.^{[8],[21]}

3.1.4. Capsules for calves

Milk caused closure of the esophageal groove in calves and the milk passes directly into the abomasum. The main component of milk that caused this action is sodium bicarbonate. This effect continues and is effective in calves of upto 2 years of age. Thus in calves of upto 2 years of age these components can be added in capsules in order to close the groove and thus allowing the drug to pass directly to the abomasum.^[3]

3.2. Liquid

3.2.1. Drenches: These are liquid formulations that are intended to be delivered to the back of the tongue, forcing the animal to swallow the medication.^{[8],[12]}

3.2.2. Syrups, solution, suspensions^[8]

3.3. Semi-solids: Pastes and gels

4. SPECIAL DELIVER DEVICES FOR SOLID LIQUID AND SEMI-SOLID ORAL DOSAGE FORMS:

For effective drug delivery it is essential that the drug reaches its targeted site, disintegrates and thus displays the desired effect. Other than the physical and chemical parameters of the drugs it is important for the dosage form reach the site correctly. Administration of drugs in animals requires technique to avoid discomfort to the animal, hassle to the farmer and damage to the dosage form. Thus special devices for administration to ruminants help make this process more efficient and less strenuous.

4.1. For Solid Oral Medication



Figure 5: Various types of balling guns.

4.1.1. Conventional Oral Bolus Delivery Device

4.1.2. Sustained Release Oral Bolus Delivery Devices

Both conventional and sustained release oral boluses are delivered with the help of a balling gun. A balling (or bolling gun) is used to administer the bolus dosage form to large animals. The bolus is inserted to the base of

the tongue, and is delivered. After the bolus is placed in the pharynx it is allowed to be swallowed by a reflex action, and then passed into the ruminal sac. ^[12]

4.2. For Liquid Oral Medication

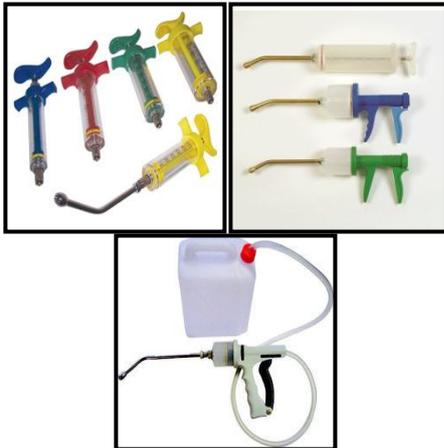


Figure 6: Various drenching devices.

4.2.1. Oesophageal Delivery: Most commonly used oesophageal delivery devices are stomach tubes of varying length, internal and external diameters, and composition.

4.2.2. Drenching Devices: Oral liquid medications are administered to cattle, sheep and goats using a method called drenching. Drenching can be done by using drenching syringes or drenching guns.

4.2.1.1. Drenching Syringes

4.2.1.2. Drenching Guns

4.2.1.2.1. Single-Dose Gun

4.2.1.2.2. Multi-Dose Gun

4.2.1.2.3. Automatic Gun

4.3. For Semisolid Oral Medications



Figure 7: Devices for semi-solid dosage forms

4.3.1. Single Dose Syringes.

4.3.2. Multiple Dose Syringes.

[2], [12]

5. INTRARUMINAL BIOACTIVE DELIVERY:

Ruminants possess a unique digestive system. Using the high metabolic potential of the symbiotic microflora of the rumen, ruminants are capable of digesting plant material and obtaining nutrients and energy from this process. Because of the ruminal fermentation, the most bioactives are not stable in the harsh ruminal environment. Major developments in nutritional and veterinary science, which increased substantially productivity of monogastric farm animals, could not be applied directly to ruminants. Rumen fermentation may also destroy or modify nutrients and drugs used to prevent or treat disease. For example, glucose and starch given orally to prevent or help treat ketosis is largely hydrolyzed to short-chain fatty acids. Some potent growth promoters require an effective

oral delivery system to deliver the active agent to the absorption site in the small intestine of the host animal. Thus, it was well recognized very early that there was a need for a rumen-stable delivery system to improve the bioavailability of a bioactive by protecting it from the ruminal digestion. [5], [16].

6. INTRARUMINAL DEVICES- PRINCIPLE:

The formulation of protected bioactive can be delivered in the rumen in a controlled manner and over a long period of time. Their stomachs have four compartments. Of these compartments, the rumen is the largest. It has two small openings: Esophagus & Omasum which allow substances in and out of the rumen. Long term delivery devices can be housed in this large compartment if a suitable method to prevent them from: Regurgitating & moving them into the remainder of the tract. This is possible by producing devices that prevent rumination. Such a device should be a sufficiently high density device so that it is heavy enough to resist the movement out of the rumen; or expandable devices so that when taken in, it increases in size thus not allowing it to leave the rumen. [5], [6] [16]

7. INTRARUMINAL DEVICES & THEIR FUNCTIONING:

Rumino-reticulum devices can be classified into several categories depending upon their release profile: sustained release; controlled but continuous release; pulsed release; novel

release patterns. Intraruminal devices are solid preparations that deliver the bioactive at required release rate and over required period of time. There are several main design features that are required for any intraruminal devices: A size and shape making them capable of being readily administered orally; Reliability of long term retention in the rumen; a controlled and long term release of the bioactive.

Theoretically there should be no limit to the duration of retention and release, but in practice the device lifetime should match the health condition for which it is designed. For example, treating an infection might need only days or weeks of exposure, an antiparasite drug might be needed for the duration of the grazing season, while a nutrient might be needed for 365 days a year. In practice, most current commercial products have a lifetime of around 100 days, and another device is re-administered if longer term treatment is required.

7.1. Ruminal retention

To avoid regurgitation during rumination, intraruminal devices have to be properly designed. This can generally be achieved either by increasing the density (high density devices) or modifying geometrical parameters of the device. Both approaches can also be combined in a single device.

7.2. Bioactive release mechanism

Various physical and/or chemical processes can be used to release the bioactive from ruminal devices. The simplest mechanism is the erosion of a bolus due to the permanent agitation of the ruminal contents. Another approach uses simple diffusion of a water-soluble bioactive out of the matrix, while an even more sophisticated process relies on osmosis as the release controlling process. All of these types of device can be referred to as “passive” release systems. On the other hand, there are “active” release mechanisms whereby some force is generated to mechanically force bioactive from the device. [6], [7], [16]

8. DIFFERENT INTRARUMINAL DEVICES:

8.1. Dispersed Matrix Systems

A dispersed matrix device is defined to be one in which the active species is dispersed within non-biodegradable polymer matrix. Under these conditions drug is released via diffusion processes and the release rates follow the square root of time law. The device is in the form of a large sheet that can be rolled up to form a cylinder. This rolled up device is constrained by a water soluble tape that dissolves following device administration. The device unrolls following removal of the tape. Under these circumstances the unrolled device will have dimensions that are greater than

those of the oesophageal channel thereby preventing device regurgitation.

8.1.1. Paratect flex:

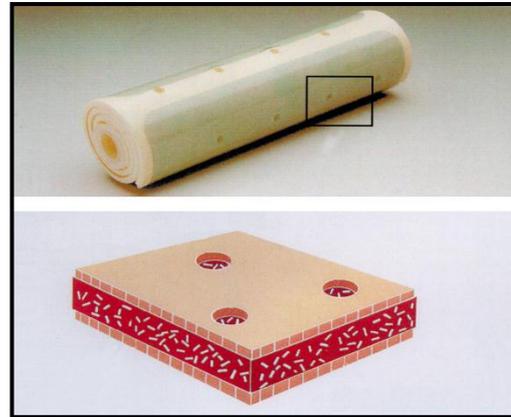


Figure 8: paratect flex.

It is a slow release device and takes over 90 days to release its drug content. It is a triaminate sheet that is rolled into a cylindrical shape for easy administration and is retained in this form by a water soluble adhesive bandage. In the ruminal Fluid, the band dissolves and allows it to assume its expanded form to prevent regurgitation. The active escapes through the holes in the sheet from the middle layers. The ruminal environment controls its release. [7] [12]

8.2. Continuous controlled release

8.2.1. Laby device:

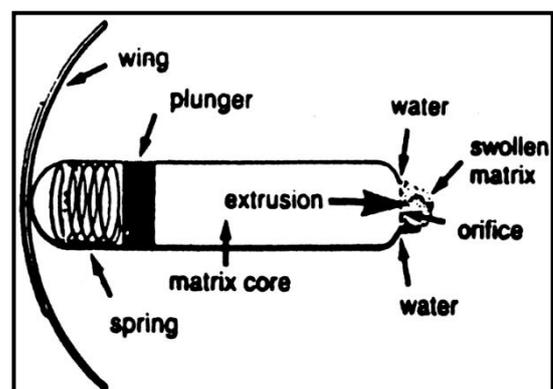


Figure 9: laby device.

It consists of a hollow cylinder capped at both ends. One of its end is closed and serve to help constrain a spring which acts as a piston. The polymeric wings attached to the cylinder expand and serve as a means to retain drug delivery device within the rumen. The density of the erodible composition helps to determine the target location of the device in the Reticulorumen. It dissolves or abrades due to mechanical action of rumen. [6], [7]

8.2.2. IVOMECS SR Bolus:

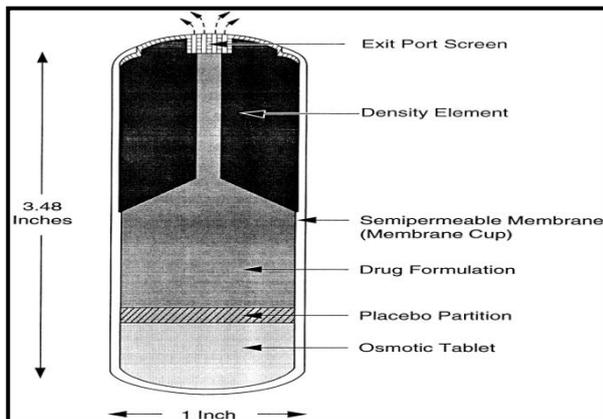


Figure 10: IVOMECS SR Bolus

It delivers ivermectin for full grazing season. It is a continuous controlled release bolus. It consists of a membrane cup (semipermeable membrane) that contains an osmotic table, partition layer, drug layer and a densifier. The drug can be in the form of a suspension @31-35C or it can be a fluid. Densifier made of sintered iron fillings ensures retention. The entry of water through osmosis results in the swelling of the osmotic table by imbibitions. The osmotic table swells due to entry of water, and thus pushes the drug content while

swelling through the exit port, slowly and continuously over about 135 days. Temperature in the rumen allows flow of the drug suspension. Concentration of the ruminal fluids controls the release. [6], [7], [18]

8.2.3. Erodible glass bolus: The Elemental Bolus.



Figure 11: The elemental bolus.

The elemental bolus is a continuous controlled release type of bolus. They are unique in that they are made of compressed glass. As the glass dissolves the copper, cobalt and selenium ions are released into the rumen. The bolus dissolves completely so there is no remaining residue. This is a great advantage of this bolus. The provision of a continual source of copper ions in the rumen is another unique feature of elemental boluses. The copper ions are available around the clock to bind to thiomolybdates and ensure they are passed out of the body rather than be absorbed to exert their toxic effect. Selenium ions are continually available in the rumen from the dissolving elemental boluses and are available for rumen microbes to convert into

selenomethionine and selenocystine which can be absorbed by the animal as organic selenium. A lack of selenium has been shown to increase the incidence of retained foetal membranes (placentas) and endometritis. Selenium deficiency can also reduce immunity and ability to fight infections such as mastitis and pneumonia. Elemental boluses are for use in ruminating cattle weighing over 100 kg. The expected period of protection is four to six months - six months in pasture fed conditions but the boluses will dissolve faster when supplements or concentrates are fed resulting in the rumen being more acidic. Administering to dairy cows at drying off will protect through mating. The boluses may crack if warmed too quickly. Thus it must be at room temperature (15 to 20°C) prior to administration. With an excellent retention rate, elemental boluses offer peace of mind from knowing each animal is getting the required daily dose. [22]

8.3. Pulsatile Systems

Boluses which release multiple doses at pre-programmed intervals have been termed pulsatile or intermittent release systems. The major impetus for the development of these systems has been the desire to have systems which better mimic current practices of multiple doses of immediate release products given at specific time intervals.

8.3.1. Castex device:

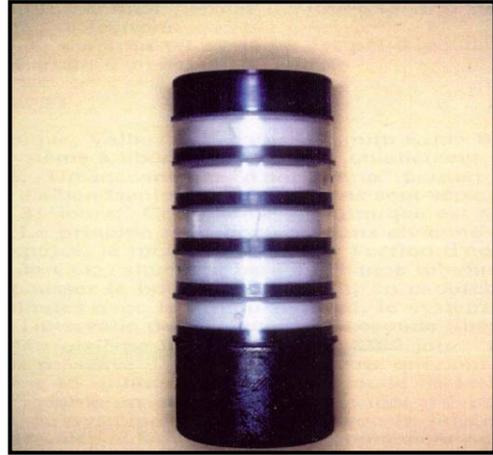


Figure 12: Castex device.

It is a pulsatile system that intermittently releases the drug at regular intervals. One end of this device remains closed while the other end slowly starts disintegrating because of the rumen environmental conditions. It is made of iron which acts as the “density element” allowing the device to be retained in the rumen. The central core is made of a magnesium alloy with the drug. The galvanic coupling allows the ruminal fluid to act as a conductor for the release of electrons and thus the disintegration of the core. It is pH dependent. It allows for the release of 5-6 tablets every 21- 23 days. [5], [6], [7]

8.3.2. Vandamme system:

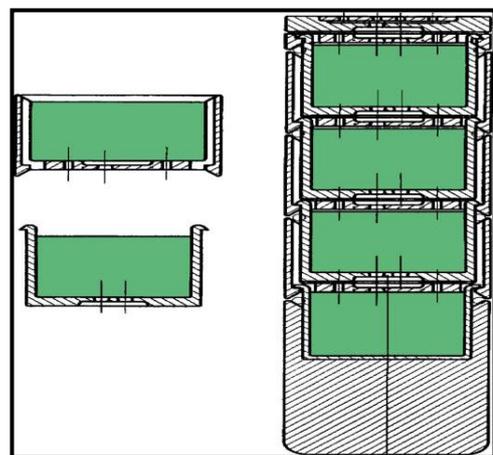


Figure 13: Vandamme system.

The vandamme system, also a pulsatile system contains series of compartments containing an antihelminthic drug, bound to each other with a biodegradable monofilament located in the centre of the device. The closed end is made of iron which acts as the “iron density element” which ensures that the device is retained. The biodegradable microfilament when exposed to the rumen fluid allows drug release in intervals. Thus the release of the drug depends on the ruminal environment. Depending on the nature of the monofilament, the device can release the drug after a long (86 days) or short (21 days) period. [6], [7].

8.3.3. The Electronic Bolus:



Figure 14: the electronic bolus.

The E-Bolus is an intermittent release Reticulo-ruminal device (RRD) that releases three therapeutic doses of the anthelmintic albendazole separated by 31 day intervals. Timing for the device is controlled by a custom integrated circuit, and power is provided by alkaline watch batteries. The drug, contained in each of the three adjacent

tubes is expelled at once by the action of a gas generator situated at the bottom of each tube. After immersion in the conductive ruminal fluid for a continuous 10 minute period a sensed by two conductive rubber electrodes, the device turns itself on, shuts off the external sensor and begins counting for 31 days. After this time, logic on the chip routes battery energy to the first gas generator, which releases gas, predominantly carbon dioxide sufficient to expel the medication and a protecting rubber stopper. The device then resets, counts an additional 31 days, routes energy to the second gas generator, whereupon the second dose is released on day 62 and this is repeated for the last release on day 93. Accuracy is provided by a quartz crystal, so that precision of release is within 15 min for the final release. An impervious casing of polypropylene protects the drug and electronics from ruminal fluid and the device operates independently of any changes within the rumen environment. [12], [5]

8.4. Controlled bioactive delivery using ART

Not yet commercially available, is another plunger driven system, Active Rumen Technology. It uses a galvanic cell to release up to 160 ml of hydrogen. Elevated pressure resulted causes the plunger to extrude bioactive formulation. Previous work has demonstrated the feasibility of linear and

reproducible release of placebo formulation out of an ART device over an extended period of time. The Active Rumen Technology may have a number of advantages over existing controlled-release technologies: The gas cell occupies a very small volume in the device so a larger bioactive payload is possible; Gas production rate is independent of the ruminal environment; there is a potential to modulate the bioactive release rate by remote control. [16]

8.5. Other approaches to ruminal delivery

- a. A pH sensitive polymer coating is used where a ph difference between abomasum and rumen is considered for effective coating.
- b. An increased amount of protein that bypass the rumen fermentation process may be used.

- c. Coating with substances that is less soluble than the active.
- d. Substances inert in the rumen e.g. Copper oxide, are in the rumen and are a source of copper ions in the abomasum.
- e. Increase in temperature in the rumen decreases the rate of degradation of bioactive.
- f. Coating with lipids protects the bioactive from degradation in the rumen. However they have poor post ruminal absorption rates.

During production of Pellets and granules for ruminal animals, the fine powders are microencapsulated with materials that are inert to the rumen environment to increase their strength. [1], [6], [7], [16], [20]

Type of device	Name	Company	Active
Matrix device.	Spanbolet	Smithkline	Sulfomathazine
Diffusion device	Paratect.	Pfizer	Antihelminthic agent- morantel.
Laby device.	Rumensin	Elanco	To reduce subclinical ketosis.
Osmotic pump.	Alzet 2ML4.	Merck	Ivomec- anti parasitic.
Castex	Repidose	Coopers.	Oxfendazole.

device	5
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Table 1: Various Intraruminal devices.

9. APPLICATIONS OF RUMINANT HEALTH CARE:

Like humans, animals need supplementary nutrients and pharmaceuticals that help to maintain good health and prevent or combat diseases. While the medication of humans is aimed to improve quality of life, intervention with bioactives in ruminants is primarily aimed to increase their production. Thus, all the approaches in medication and/or supplementation using bioactives or feed

additives to ruminants have an economical motivation. The factors that can influence the animal production include: Nutritional deficiency, Infectious diseases, Parasites (internal and external), Metabolic disorders, Controlling reproduction and Manipulating animal growth. These factors when taken care of help in the improvement of animal health thus increasing human benefits.^[16]

10. CONCLUSION:

The development of specialized dosage forms to treat a variety of animals thus results in the need for efficient administration devices. The advent of

controlled release implantable devices and rumen retention devices has hastened the need for the development of product specific administration devices. Innovation in the administrative device area will continue to satisfy the needs of the veterinary drug formulator and drug user to provide the tools that will permit precise administration of the desired drug to the animal in need of treatment. The ruminant animal is particularly amenable to the application of new systems, and one can expect new technologies to be applied to RRDs as the success of the current market introductions becomes apparent.

The foregoing account has demonstrated that a large number of intraruminal boluses have been designed using a variety of technologies that range from uncomplicated i.e., erodible systems to more complex eg. Osmotic systems. Each of the technologies has specific benefits and drawbacks. Each of these technologies has shown commercial products that have shown to be highly beneficial to the practice of animal husbandry. While current technologies represent a major advance over immediate release systems it is clear that more work needs to be done to

develop systems which provide better control of release rate at lower costs.

The oral drug delivery system for ruminant animals provides major challenges and opportunities which hopefully will be achieved in the near future.

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Zinc Oxide (ZnO) Nanoparticles: A Versatile Metal Oxide

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Abstract

In recent years, various metal oxide nanoparticles have gained significant importance due to their characteristic properties. Nano Zinc Oxide is the most important of all the metal oxide nanoparticles because of its varied properties. This paper focuses on methods of synthesis and characterization of ZnO nanoparticles, its properties, advantages over other materials of similar properties and applications in various fields. Also, various methods to stabilize the ZnO nanoparticles have been discussed.

Keywords: ZnO nanoparticles, ZnO capping agents, Photoluminescence.

1. Introduction

The nanoparticle synthesis of controlled size, size distribution, shape and surface state is recognized to be of prime importance as their properties are essential for successful application.

Among all nanomaterials, nanoparticles of metal oxides are very attractive as their unique characteristics make them the most diverse class of materials with properties covering almost all aspects of solid-state physics, materials science and catalysis. Indeed, the crystal chemistry of metal

oxides, i.e. the nature of the bonding, varies from highly ionic to covalent or metallic.

Besides catalysis, metal oxides represent therefore an essential constituent in technological applications such as magnetic storage, gas sensing, and energy conversion. As a wide band gap semiconductor, ZnO has found many applications such as transparent electrodes in solar cells, varistors, electro- and photoluminescence devices, chemical sensors, catalysts, UV absorbers and anti bacterials. Semiconductor nanoparticles have

attracted much interest because of their size-dependent optical and electrical properties.

The properties of nanoparticles depend on the particle size as well as several other factors: structures, shapes, and surface states of the particles. For these applications, the nanoparticles need to be dispersed homogeneously in different matrices and a number of new synthesis strategies have been developed in order to prevent particle agglomeration and to increase the stability of ZnO nanoparticles dispersions. The wide range of applications of ZnO nanoparticles is possible because of its three key advantages^[3]:

1. It is a semiconductor with a direct wide band gap of 3.37 eV and a large excitation binding energy of 60 MeV. It is an important functional oxide, exhibiting excellent photocatalytic activity.
 2. Because of its non-central symmetry, ZnO is piezoelectric, which is a key property in building electrochemical coupled sensors and transducers.
 3. Finally, ZnO is biosafe, biocompatible and can be used for biomedical applications without coating.
- With these three unique characteristics, ZnO is one of the most important

nanomaterial in future research and applications.

Many methods have been proposed for the synthesis of ZnO nanoparticles:

1. **Physical methods:** Vapor Phase Oxidation, Thermal Vapor Transport and Condensation (TVTC) or Chemical Vapor Deposition (CVD)
2. **Chemical methods:** Supercritical Precipitation, Sol-gel synthesis or Microemulsion.
3. Ultrasound assisted synthesis of semiconductor ZnO nanoparticles.

Most of the above methods like Vapour phase oxidation, Chemical vapour deposition [CVD], Supercritical precipitation require very high temperatures for synthesis, long reaction time, use of toxic and highly sensitive compounds and employ extremely sophisticated apparatus. Additionally, in case of vapour phase oxidation, the ZnO nanoparticles undergo cluster cluster interaction to form aggregates which is undesirable. Critical control over partial pressure of oxygen for Vapour phase deposition is required. Control over gas flow rates in Vapour phase deposition and CVD is equally essential. Compared to

these techniques Sol-gel synthesis results in higher yield and is easier.

Ultrasound assisted Acoustic Cavitation technique is a recently developed simple, green, and cost-effective approach. It has evident advantages due to good compositional control, good homogeneity of liquid precursors, low equipment cost, and lower crystallization temperature. Thus, Sol-gel technique and Ultrasound assisted Acoustic Cavitation are the most preferred methods for synthesis of ZnO nanoparticles.

1.1. Sol gel Synthesis^{[7], [8]}

Sol-gel technique is an effective method for synthesis of nanoparticles with visible fluorescence at low cost. The ZnO nanoparticles resulting from sol-gel method show sharp and clear visible emission, which accounts for the fact that the ZnO nanoparticles have high concentration of surface defects, small diameter, amorphous in nature and well protected by ligands or shells.

The traditional sol-gel route of preparing ZnO nanoparticles involves hydrolysing zinc acetate in ethanol, which requires refluxing zinc acetate in absolute ethanol for 3 hrs, followed by reacting it with LiOH under sonication. The as-prepared

ZnO nanoparticles are not very stable because the small acetate groups cannot protect the ZnO sufficiently. As a result, the emission color of the obtained colloids turns rapidly from blue to green within a few minutes and then slowly from green to yellow within several days.

Thus, another method used involves dissolving $\text{Zn}(\text{Ac})_2 \cdot 2\text{H}_2\text{O}$ and $\text{LiOH} \cdot \text{H}_2\text{O}$ together in triethylene glycol (TEG) at room temperature in beakers by stirring. The concentration of zinc is fixed at 0.1 M, while the molar ratio of $[\text{LiOH}]:[\text{Zn}]$ is varied as 1, 1.5 and 2 respectively. The solutions are exposed to air and stirred for a month. For thermal analyses and IR spectrum measurements, excess ethyl acetate is added into each TEG solution to precipitate the white ZnO gel. The gel is washed with ethyl acetate and centrifuged, followed by drying in a vacuum oven at 100°C .

In this technique the molar ratio of $[\text{LiOH}]:[\text{Zn}]$ (designated as R), plays a key role in determining the emission colour and particle size of the nanoparticles. For R values between 0.1-10 ZnO colloids are transparent and quiet stable for at least a week. Also, for $R < 0.5$ – the ZnO luminescence is rather weak, for $R > 1.8$ – ZnO nanoparticles do not precipitate but

exhibit strong blue emission while for $R > 2$ – the solution turns gradually yellow, indicating a red shift and some unknown reactions.

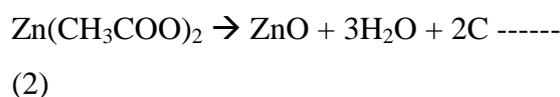
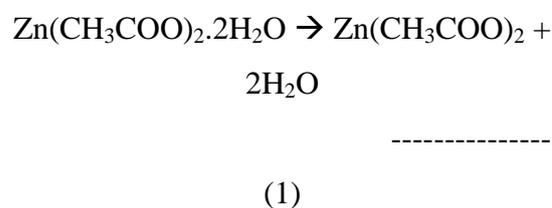
1.2. Ultrasound Assisted Acoustic Cavitation Technique

During sonication, ultrasonic longitudinal waves are radiated through the reaction solution causing alternating high- and low-pressure regions in the liquid medium. Millions of microscopic bubbles form and grow in the low-pressure stage, and subsequently collapse in the high-pressure stage. Hot spots that are localized regions of extremely high temperatures, as high as 5000K, and pressures of upto 1800 atm can occur from the collapsing bubbles, and cooling rates can often exceed 10^{10} Ks^{-1} . The energy released from this process, known as ‘Cavitation’, would lead to enhanced chemical reactivity and accelerated reaction rates.

This is a novel and very simple method to prepare extremely pure nanocrystallites of ZnO with hexagonal structure using aqueous solution of zinc acetate dehydrate in absolute ethanol as a capping agent with the help of ultrasound irradiation in normal laboratory conditions at room temperature (27°C). Zinc acetate dehydrate, thiophenol and absolute ethanol are the precursors

used. The proposed mechanism is as follows:

Zinc acetate can easily be dissolved in water and adding thiophenol solution would cap the dissolved zinc acetate colloids by the help of ultrasonic irradiation. The formation of the ZnO nanoparticles can be proposed employing the following thermal decomposition:



The sonication time is a key parameter to control the shape and morphology of the nanostructure. Increased sonication time, leads to deterioration of nanoparticles^[4].

2. Characterization techniques for ZnO nanoparticles

X-ray diffraction technique, Transmission electron microscopy, Scanning electron microscopy, UV-Vis spectroscopy,

Photoluminescence measurements are the general characterization techniques for ZnO nanoparticles synthesized by any method.

2.1. X-Ray Diffraction

Figure 1 shows the XRD pattern of nano-ZnO^[12]. All the peaks of the (100), (002), (101), (102), (110), (103), (200), (112), (201), (004), and (202) reflections can be indexed to the hexagonal wurtzite structure of ZnO. These match well with those in the JCPDS card (Joint Committee on Powder Diffraction Standards, Card No. 89-1397). The strong intensity and narrow width of ZnO diffraction peaks indicate high crystallinity.

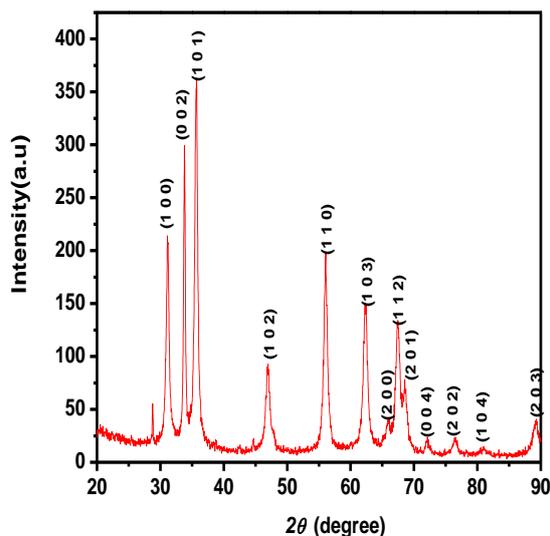


Figure 1^[12]: XRD Pattern of ZnO nanoparticles

2.2. TEM Images

The TEM image of ZnO nanoparticles synthesized by Sol gel method is as seen in **Figure 2**. It illustrates that the three ZnO samples (R=1, 1.5, 2) have similar particle sizes (about 3-4 nm) but their dispersion degrees differ significantly. The ZnO (R = 2) particles are uniform and monodispersed, while ZnO (R = 1) particles aggregate heavily^[7].

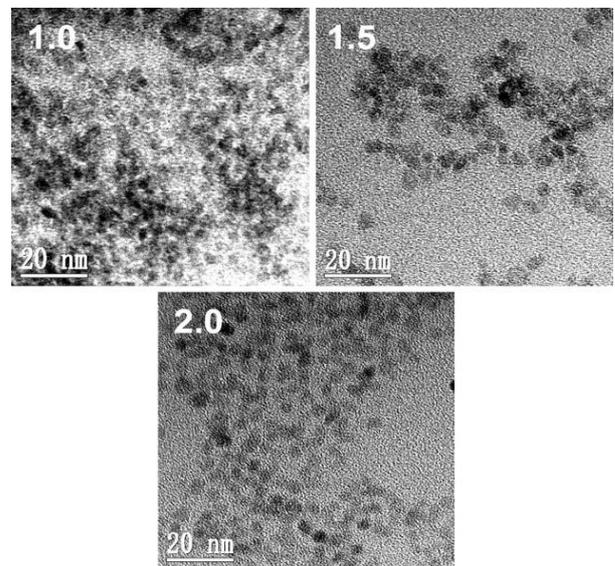


Figure 2^[7]: TEM images of ZnO nanoparticles synthesized by Sol-gel technique

Figure 3 shows the TEM image of ZnO nanoparticles synthesized by Ultrasonic cavitation. It can be seen that the uniform nanocrystalline ZnO particles have sphere shapes with weak agglomeration.

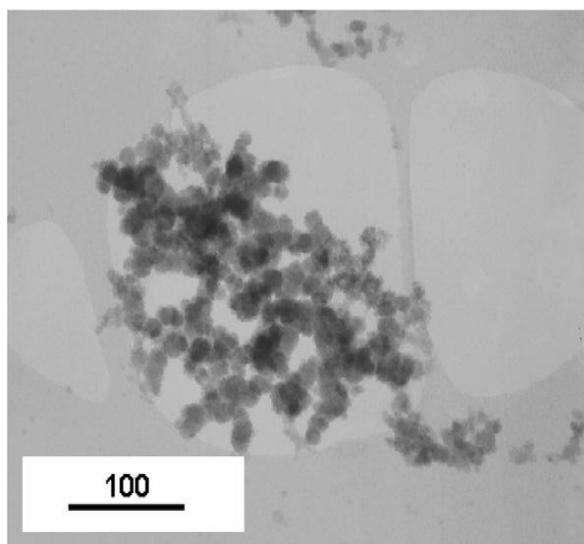


Figure 3^[6]: TEM image of ZnO nanoparticles synthesized by Ultrasound Assisted Acoustic Cavitation Technique

2.3. UV-VIS spectroscopy (for sol-gel technique)

Figure 4 indicates the UV-VIS absorption spectrum for nano-ZnO for sol-gel synthesis. These nanoparticles absorb strongly in the region 250-350 nm. Their excitation peaks come into the region of 320-340 nm and emission peaks has redshifting from 480 nm to 540 nm indicating heavy aggregation^[7].

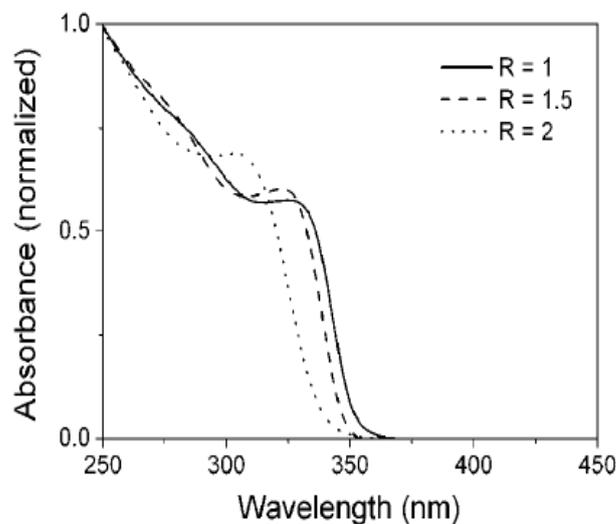


Figure 4^[7]: UV-Vis Spectrum

3. Stabilization of ZnO nanoparticles

ZnO nanoparticles tend to undergo spontaneous growth and aggregation as seen from TEM images and UV-VIS absorption spectrum. To avoid this, various attempts have been made some of which are: employing ligands, coating ZnO with polymers and protecting ZnO with inorganic shells such as SiO₂ or ZnS. The Ligands used could be either organic or inorganic. Organic ligands can easily detach from the ZnO surface due to weak bonding whereas the inorganic ligands are porous in nature. Thus, the protection provided by either of the ligands is insufficient and the ZnO nanoparticles coated with them are unstable in water. As a result, the most preferred strategy is coating ZnO with polymers wherein the

polymerization is initiated at the surface of the ZnO nanoparticles. As the polymerization continues more cross-linking occurs forming a tight shell around the ZnO core. Due to presence of cross link sites this shell is difficult to remove and provides better protection to the ZnO nanoparticles.

ZnO based polymer nanocomposite can be prepared by both Physical as well as Chemical methods. Physical methods involve simple mixing of nanoparticles in polymer solutions or polymer melt. The bonding between polymer and nanoparticles is based on static interactions, Van der Waal's forces or simple Lewis acid-base interactions. Whereas, chemical reactions include bonding via formation of chemical bonds to produce more stable products because of strong interaction between polymer and nanoparticles.

The advantages of chemical methods over physical methods are:

- (i) The products are homogeneous, usually transparent.
- (ii) Their composition is not destroyed by solvent washing, i.e., the products can be isolated from the reaction system by non-solvent methods or centrifugation–redispersion treatment.
- (iii) There is no significant phase separation (ZnO aggregation or polymer crystallization) under TEM or AFM observation.
- (iv) IR spectra show the signals of chemical bonds between polymers and ZnO nanoparticles.
- (v) The decomposition temperature of the products are higher than the polymers themselves^[8].

Thus, it can be concluded that, stronger the interaction between polymer and nanoparticles, the more stable nanocomposites will be formed.

3.1. Physical mixtures of polymers and ZnO nanoparticles:

Polymers like Polyvinylpyrrolidone (PVP), Polyaniline (PAni), Polyvinylalcohol (PVA), Polyethyleneoxide (PEO), Polyethyleneglycol (PEG) have been used so far for formation of polymer nanocomposites. However, this process resulted in decreased photoluminescence and increased UV emission. When ZnO nanoparticles are incorporated into an already luminescent polymer like Poly(phenylene vinylene) (PPV), a charge separation into electrons and holes arising from the PPV chains takes place at the polymer-nanoparticle interface. This

phenomenon results into quenching of polymer fluorescence^[8].

In conclusion, the various drawbacks associated with this process are:

1. Many polymers are able to quench ZnO visible emission through passivating the ZnO nanoparticle surface;
2. Polymers such as PEO, PVA and PMMA cannot suppress ZnO nanoparticle aggregation effectively;
3. Some polymers such as PVP and PPV themselves have fluorescence so as to interfere with ZnO emission, resulting in undesirable effects.

To overcome these difficulties various chemical modifications are employed to improve ZnO visible emission.

3.2. Chemical hybrids of polymers and ZnO nanoparticles

On the basis of structural differences, the chemically synthesized polymer– ZnO nanocomposites are divided into four types:

1. The first type involves grafting of polymer on ZnO surface as independent organic ligand. It resembles a “hair on head structure” and hence the name. It is synthesized by hydrolyzation of zinc salts or ligand

exchange. The two disadvantages associated with this type are:

- a. Due to large volume of polymers, the degree of ligand exchange is low.
 - b. Exchanging the organic groups of the ZnO surfaces by polymer ligands often destroys the ZnO luminescence.
2. The second structure resembles an olive with one core and a thin orbicular shell of crosslinked polymer ligand. It is synthesized strictly by ATRP initiated on nanoparticle surface. The polymeric ligands on ZnO surface are cross-linked by ATRP to form a tight shell around ZnO.
 3. The third structure resembles watermelon with a polymer forming a microsphere (100nm – 10nm) comprising of many ZnO nanoparticles inside. This structure is obtained by emulsion or solution polymer and occurs as a suspension in water.
 4. The fourth structure is obtained by Bulk polymerization. In this case the polymer is formed by bulk polymerization with the ZnO nanoparticles in the reaction medium. It is very large and can be cast into various forms^[8].

The method of preparation of polymer ZnO nanocomposites has profound effect on the final properties of ZnO. The surface state, dispersity, crystallinity and purity of

ZnQD could be changed during preparation. So, the resulting polymer ZnO nanocomposites with the same compositions would exhibit quite different optical properties.

3.3. Inorganic shell (SiO₂)

Organic compounds such as long chain aliphatic thiols or amines are used as capping agents for passivating the surfaces of unstable nanoparticles to prevent their aggregation and improve compatibility with the organic matrix. The strategies to control the particle sizes include encapsulating an organic capping agent on the nanoparticle surfaces such as alkylthiols, polymer micelles or using coordinating solvent such as dimethyl sulfoxide, N,N'-dimethylformamide and tri-n-octylphosphine oxide. However, in spite of this modification there is still some aggregation of nanoparticles observed which seriously affects the photoluminescence.

This problem can be overcome by a new method which involves modification of ZnO nanosurfaces to promote the stability of colloid suspensions and nanocomposites simultaneously preserving its luminescent properties.

As seen in **Figure 5** surface of the nanoparticles is stabilized by the

absorption and hydrolysis of an unsaturated aliphatic silane, 3 (trimethoxysilyl)propyl methacrylate (TPM), via a mild sol-gel reaction. The colloidal ZnO nanoparticles are first dispersed in 2-hydroxyethyl methacrylate (HEMA) monomers and then thermally polymerized to form a stable nanohybrid film. Besides, the unsaturated chain of TPM on the ZnO nanoparticles can be polymerized with 2-hydroxyethyl methacrylate, making the particles uniformly dispersed in the poly(2-hydroxyethyl methacrylate) (PHEMA) matrix^[9].

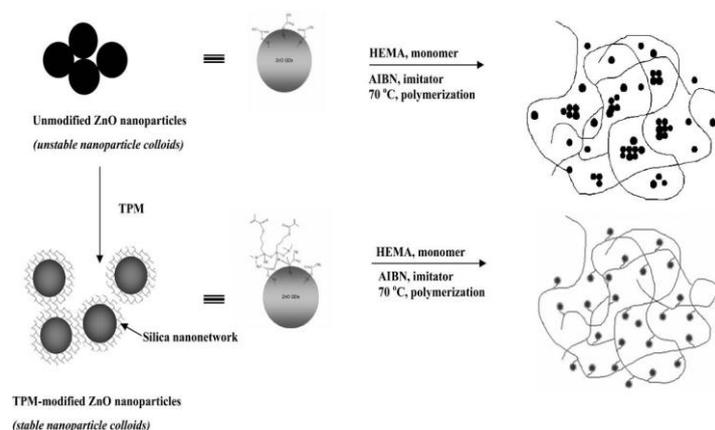


Figure 5^[9]: Stabilization of ZnO nanoparticles using inorganic shell (SiO₂)

The TPM modified ZnO nanoparticles have high dispersion stability in organic solutions and have very little tendency to aggregate even over long periods of time. The room temperature PL measurements indicate that this method preserves the

superior luminescence of ZnO in both the initial solutions as well as the nanohybrid films.

4.1. Properties

a. Photoluminescence in ZnO

Photoluminescence [PL] is a phenomenon in which a substance absorbs photon (electromagnetic radiation) resulting in excitation to higher energy state and then it returns to a lower energy state by emission of this photon. This transition occurs in a very short period of time typically in the order of 10 nanoseconds. The photoluminescent ZnO nanoparticles are non-toxic, cheap and very stable under ambient conditions towards sunlight, water and air.

The photoluminescence of ZnO nanoparticles has two components: One is the photo-generated electron recombination with holes in the valence band or in traps near the valence band. This process produces UV light of about 370 nm because the ZnO band gap is 3.37 eV at room temperature. The other component is visible emission (also called deep level emission) related with oxygen vacancies. Two popular mechanisms for the ZnO visible emission that have been

suggested are shown in **Figure 6**: One is recombination of a shallowly trapped electron with a hole in a deep trap and the other is recombination of an electron in singly occupied oxygen vacancies (i.e., deeply trapped) with a photo-generated hole in the valence band. (A) represents - Typical exciton emission, (B) represents recombination of a shallowly trapped electron with a deeply trapped hole, and (C) represents recombination of a shallowly trapped hole with a deeply trapped electron. In order to simplify the maps, the shallow traps near the valence band (VB) and the conductance band (CB) are not marked ^[8].

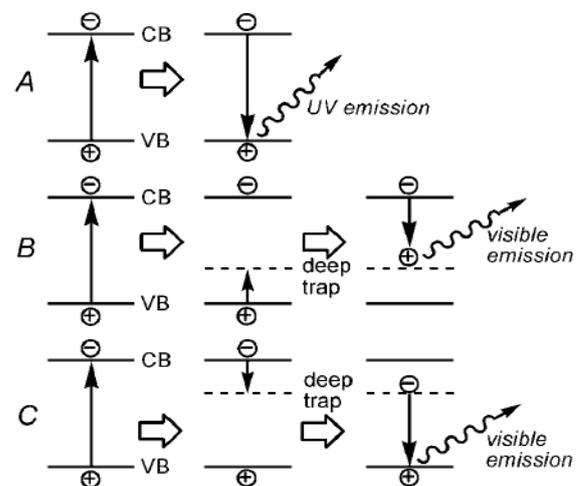


Figure 6^[8]: Mechanism for ZnO visible emission

4.2. Piezoelectric Property

The piezoelectric property of ZnO has been extensively exploited in various applications like force sensing, acoustic

wave resonator, acousto-optic modulator etc. The crystal structure of ZnO with oxygen atoms and zinc oxide atoms bonded tetrahedrally, form the basis of the piezoelectric nature. In such a non-centrosymmetric structure, the center of positive charge and negative charge can be displaced due to external pressure induced lattice distortion. This displacement results in local dipole moments, thus a macroscopic dipole moment appears over the whole crystal.

The piezoelectric coefficient of ZnO nanobelts is measured by AFM (atomic force microscopy) with conductive tips. ZnO nanobelts are deposited on a conductive substrate, then the whole substrate is coated with 5 nm thick Palladium [Pd] serving as top electrode on the nanobelt. After the nanobelt is located by AFM, piezoresponse force microscopy is used to measure the effective piezocoefficient of the surface of the nanobelt. As the result, the effective piezocoefficient of nanobelt is observed to be frequency dependent ^[10].

4.3. Magnetic Doping

Spin Polarized Dilute Magnetic Semicord (DMS) overcomes the conductance mismatch associated with semiconductor devices. With Co, Fe and Mn as dopants, ZnO is a promising host material for ferromagnetic doping. Because of its wide band gap, ferromagnetic ZnO is regarded as an excellent material for short wavelength magneto-optical devices. These studies enable the use of magnetic ZnO nanowires as nanoscale spin-based devices ^[10].

5. Applications

a. Sunscreen lotion

Nano-ZnO particles are transparent in the visible region of the spectrum. They act as **physical filters** against the UVB and especially UVA radiation of the sun. As these particles are very minute and crystalline in nature, they reflect the UV rays and hence act as sun-blocking agents for skin. Because of their small size, they don't get absorbed into the skin and are compatible with skin. **Table No. 1** compares the UV blocking effect of nano-ZnO with other blocking agents.

Sunscreen Ingredients	Amount of Ray Protection		Chemical (C) or Physical (P)
	UV A	UV B	
	Aminobenzoic acid [PABA]	○	●
Octyl salicylate	○	●	C
Phenylbenzimidazole	○	●	C
Titanium dioxide	◐	●	P
Zinc oxide	●	●	P

Protection Level: ○ Minimal;

◐ Considerable; ● Extensive

Table 1^[17]: UV blocking effect by various sunscreen ingredients

The high photoreactivity of nano-ZnO makes the safety of zinc oxide nanoparticles a controversial subject nowadays. However, a new method to cover the ZnO nanoparticles with special coating called as, Z-coat with dimethicone, improves the stability of them and helps to

reduce their photoreactivity. So, ZnO nanoparticles are the most effective to use as UV blocking agents in Body Lotions than the other ingredients^[17].

b. UV protection in textiles

Bioactive or antimicrobial and UV-protecting textiles are in great demand nowadays. The textiles coated with metal oxide nanoparticles is an approach to the production of highly active surfaces to have UV blocking, antimicrobial, water repellent and self-cleaning properties. Zinc oxide (ZnO) nanoparticles embedded in polymer matrices like soluble starch is a good functional nanostructure. When, clothing is treated with nano-ZnO its UV-protection ability as well as the antimicrobial properties get enhanced.

This principle is nowadays majorly used in synthesis of textiles used in the medical field. The UV-blocking property of a fabric is enhanced with an ultraviolet absorber finish that absorbs ultraviolet radiation and blocks its transmission through fabric to the skin. Nano-ZnO has increased surface area and also has intense absorption in UV-region. It is more stable than other organic UV-blocking agents.

5.3. Antimicrobial activity in textiles

Zinc oxide–soluble Starch nanocomposites were impregnated onto cotton fabrics. These ZnO nanoparticles were found to absorb strongly at 361 nm due to the quantum confinement effect, improving the UV-stabilization of the fabric. The cotton fabrics impregnated with these nanocomposites showed excellent antibacterial activity against two representative bacteria, *Staphylococcus aureus* (Gram positive) and *Klebsiella pneumoniae* (Gram negative), hence showing a very good antimicrobial activity [14].

5.4. Weatherability and Leach Resistance of Wood Impregnated with Nano-Zinc Oxide [13]

To test the effectiveness of ZnO based wood preservatives, the test specimens prepared from sapwood portion of southern pine tree, were vacuum impregnated with nano-ZnO treatments. These specimens were treated with aqueous solutions of 30 nm ZnO in water with concentrations of 1, 2.5, and 5% based on metal oxide. Untreated specimens were also tested. These treated specimens were dried for 3 days and then were used for further testing.

5.4.1. Weathering

Treated and untreated specimens were weathered outdoors for 12 months and visually evaluated for UV damage (i.e. splitting, chalking and graying). The specimen surface in direct light was considered the exposed surface, and the underside of each specimen was considered the unexposed surface for reporting results.

The following results were observed-

After 12 months of outdoor weathering, a specimen without any treatment was found to be damaged badly. Specimens treated with nano-ZnO were visibly brighter than untreated specimens particularly on the unexposed surface. Especially at higher treatment concentrations, the least chalking and least graying of surface was observed. Water repellency rated by visible water beading on wood surfaces only lasted for 8 weeks. Also, water repellency was found to be higher in case of highly loaded nano-ZnO specimens. This is useful characteristic to prevent bacterial and fungi growth on specimen.

5.4.2. Chemical Leaching

For this test, five specimens (19 × 19 × 19 mm) per treatment were

placed into 500-mL beakers, submerged in 100 mL of DI water and subjected to a vacuum to impregnate the specimens with the leaching solution. These samples were mildly agitated for 14 days. The leachates were collected after 6 hrs, and 1, 2, 4, 6, 8, 10, 12 and 14 days. Leachates were analyzed for zinc with ICP-AES and expressed as ppm zinc for the average leach rate of the 5 blocks per treatment concentration.

It was observed that, the surface with only zinc sulfate was readily leached where as no leaching of nano-ZnO occurred at any treatment concentration. Hence, this shows that the ZnO nanoparticles help to promote the antimicrobial properties to the specimen.

c. Finger –printing

Nanostructured ZnO particles are being used as a fluorescent powder for detection of finger prints on a non-porous surface in forensic department. The ZnO nanoparticles preferentially adhere to the fingerprint marks giving a contrast between the fingerprint features and the background surface. ZnO has been used as White Small Particle Reagent (SPRs). SPRs are particles which adhere to sebaceous or fatty substances in latent

finger prints. In the SPR method, ZnO powder was dispersed in distilled water containing a surfactant. The specimens are immersed in the suspension, washed with distilled water, and then dried at room temperature before imaging. On illumination with long wave UV light, a visible luminescence of ZnO provides a contrast between fingermarks and surface substrates. This method is strictly used in case of non porous substrates like polyethylene, glass and aluminium foil. Major advantage associated with this process is that there is minimal background staining on non-porous surfaces. The SPR is significantly more effective on polyethylene and on aged prints than the dry powder technique. As an improvement in the technique, ZnO nanoparticles doped with Lithium ions were used to enhance the visible luminescence^[11].

6. Conclusion

Over the past few years, ZnO nanoparticles of varied shapes like-nanorods, nanotubes, nanocombs, nanopropellers and nanoflowers- have been reported. Nano-ZnO of different shapes gives different properties. By merely changing the synthesis process and the capping agents, it is possible to manipulate the properties of ZnO

nanoparticles. Its wide applications ranging from opto-electronic devices to sunscreen lotions make them exciting for future research and applications. Thus, the versatility of ZnO nanoparticles make them a promising host for advancements in various applications like light emitting diodes, varistors, dye-sensitized solar cells, electro- and photo-luminescence devices, chemical sensors etc. in the near future.

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PLATINUM IN PUMPKIN SHAPED MOLECULES FOR ANTICANCER DRUG DELIVERY

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Abstract:

Despite the synthesis of hundreds of new platinum (II) and platinum (IV)-based complexes each year as potential anticancer drugs, only three have received world-wide approval: cisplatin, carboplatin and oxaliplatin. The next big advance in platinum-based chemotherapy is not likely to come from the development of new drugs, but from the controlled and targeted delivery of already approved drugs or those in late stage clinical trials. Encapsulation of platinum drugs inside macromolecules has already demonstrated promise, and encapsulation within cucurbit[n]urils has shown particular potential. Partial or full encapsulation within cucurbit[n]urils provides steric hindrance to drug degradation by peptides and proteins, and the use of different sized cucurbit[n]urils allows for the tuning of drug release rates, cytotoxicity and toxicity.

Keywords:

Cancer, Drug delivery, Cytotoxicity, Cucurbituril, Platinum, Cisplatin, Oxaliplatin

1. INTRODUCTION:

In the 40 years since the discovery of cisplatin¹, hundreds of new platinum (II) - and platinum (IV)-based complexes have been synthesised and tested as anticancer drugs. From these, only carboplatin and oxaliplatin have received world-wide approval. Several new drugs, including satraplatin, picoplatin and

multinuclear drugs like BBR3464 are in various stages of clinical trials. All of these drugs have similar structures that are one or more platinum atoms coordinated to amine or amine carrier ligands and chloro, carboxylate, oxalato or acetate leaving groups. Because they share similar structures, their mode of action is the same (i.e. the prevention of DNA transcription

and replication leading to cellular apoptosis), they are all susceptible to the development of drug resistance and all display severe dose-limiting toxicities. Therefore, the biggest advance in platinum-based chemotherapy in the next decade will probably come not from the development of further mono- and multinuclear derivatives, but from the creation of controlled and targeted drug delivery vehicles for already approved drugs, or for those drugs currently undergoing clinical trials. Better delivery can be achieved through drug encapsulation inside a variety of macromolecules and two such strategies for the delivery of oxaliplatin using liposomes and polymers are currently being investigated.

Encapsulation of drugs inside a macromolecule provides two benefits. First, it protects the drugs from degradation by using steric hindrance to prevent the close approach of nucleophiles, particularly glutathione and thiol or thiolate-containing proteins. Secondly, encapsulation can increase the specificity of the drugs for, and uptake into, cancerous cells, through the enhanced permeability and retention effect. Cancerous cells are porous, having cavities that are up to 1000 nm in diameter and which are able to trap and retain large

molecules more effectively than normal cells (which have only small cavities). Because the chemical structure of the encapsulated drugs remains unchanged, they can still bind DNA in their normal way and without changing the DNA binding sequence or type of adduct formed. This has been demonstrated by the encapsulation of oxaliplatin using a variety of host molecules. For example, aroplatin is a neodecanato-based liposomal formulation of oxaliplatin that has already been tested on 213 patients in nine clinical trials. The drug recently entered Phase II clinical trials where it demonstrated partial responses in two patients with advanced colorectal cancer. Prolindac is a pH sensitive hydroxypropylmethacrylamide polymer-based formulation of oxaliplatin. From a Phase I clinical trial it demonstrated two partial responses in patients with metastatic melanoma or ovarian cancer. As well as liposomes and polymers, platinum drugs can also be encapsulated by small macrocycles. Cyclodextrins are cyclic oligosaccharides composed of α -D-glucose subunits, and are already used extensively in formulations of organic drugs. Host-guest complexes of carboplatin, an inert dinuclearplatinum complex $[(\text{dien})\text{Pt}(\text{I-NH}_2-(\text{CH}_2)_n-\text{NH}_2)\text{Pt}(\text{dien})]^{4+}$ (where $n = 8, 9, 10$ or 12 and $\text{dien} = \text{diethylenetriamine}$) and various

platinum complexes coordinated to modified β -cyclodextrins have been reported. For the latter complex, in vitro experiments demonstrated that the cyclodextrin–platinum complexes were completely inactive; no other in vitro results have yet been reported.

Recently, a family of small macrocycles called cucurbit[n]urils (CB[n]) has shown utility as drug delivery vehicles. In this focused review, the use of CB[n]s as drug delivery vehicles for a variety of platinum (II)-based complexes and the future direction of this technology is discussed.

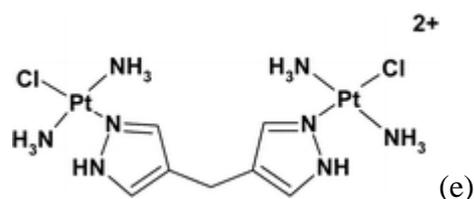
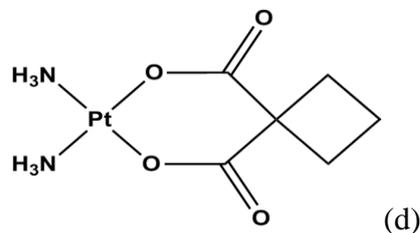
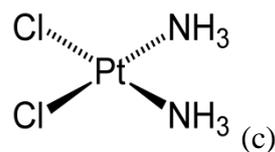
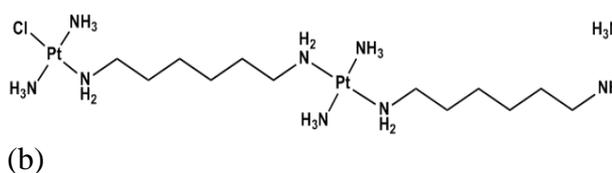
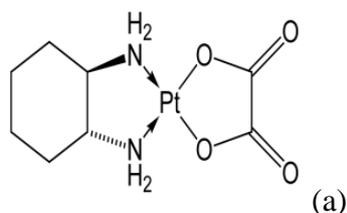


Figure 1: Chemical structures of the platinum (II)-based anticancer complexes that have been examined with cucurbit[n]urils³. (a) Oxaliplatin, (b) BBR3464, (c) Cisplatin, (d) Carboplatine, (e) di-Pt(trans-[PtCl(NH₃)₂]₂μ-dpzm)²⁺.

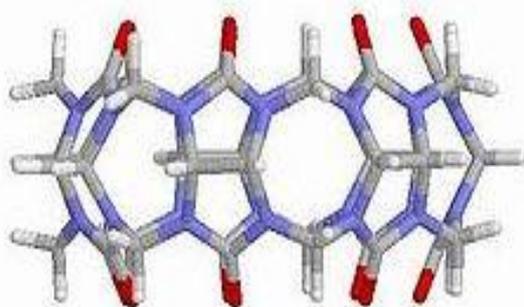
2. CUCURBIT[n]URILS:



Figure 2 a, b: Similarity between pumpkin and cucurbit[n]uril molecule

Cucurbituril (from *cucurbita* = pumpkin) is the fancy name given to the

pumpkin-shaped macrocycle. Cucurbituril is a family of homologues which are most favoured cavitands for host-guest complex formation. CB[6] was first discovered in 1905 by Behrend². Their discovery has led to a rapid increase in the interest in, and application of, CB[n] in a variety of fields including nano machines, chromatography, and drug delivery. Effective chemical and physical properties of these complexes with organic molecules and cations as molecular switches and catalysts have been well demonstrated. CB[n] is a pumpkin-shaped molecule, containing a hydrophobic cavity, formed by the acid catalysed condensation of glycoluril and formaldehyde. ^{Figure 3} Cucurbit[n]urils can be synthesised in a variety of sizes ($n = 5, 6, 7, 8$ and 10), and are capable of encapsulating smaller



molecules within their cavities. Cucurbit[n]urils contain two hydrophilic carbonyl lined portals, capping a central hydrophobic cavity. The different sizes of the portals and cavities means they are

able to bind a variety of organic and inorganic molecules. A variety of organic drugs and biologically relevant molecules have been encapsulated in CB[n] including: ranitidine, proflavine, curcumin, amino anthracene, anthraquinones, amino acids, DNA bases and anticancer titanocene and molybdocene compounds. Of most use in platinum drug delivery are CB[6], CB[7] and CB[8]. The portal of CB[5] is too small to allow the entry of coordinated platinum atoms and many organic ligands, and the cavity of CB[10] is generally too large to strongly hold a platinum complex when dissolved at biological concentrations ($k_b > 1M$). Cucurbit[n]urils are sparingly soluble in water, but become more soluble upon encapsulation of some platinum complexes, particularly cationic and/or multinuclear complexes. The solubility of CB[n]s in water also varies depending on the method used to synthesise and purify them; many CB[n]s precipitate from solution with co-crystallised acid molecules, which can be difficult to remove. Alkali earth metal salts also increase the solubility of CB[n]s, particularly saline^{3,4}. In the latter case, the cations are strongly bound at the portals and can help stabilise the binding of small guests inside the cavity. Chiral CB[n]s that are capable of recognising and binding

chiral guest shape been synthesised which have an application in the delivery of chiral drugs (e.g. the platinum drug oxaliplatin). CB[n] shape also has been found to form monolayers on gold surfaces, which has applications in cancer diagnostics.

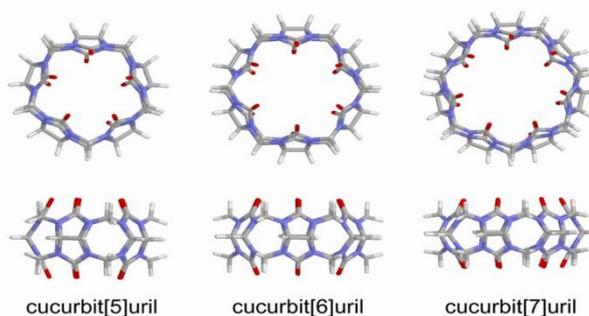


Figure 3: Different types of CB[n]

3. SYNTHESIS:

Cucurbiturils are [aminals](#) and synthesized from [urea](#) 1 and a [diketone](#) (e.g. [glyoxal](#) 2)

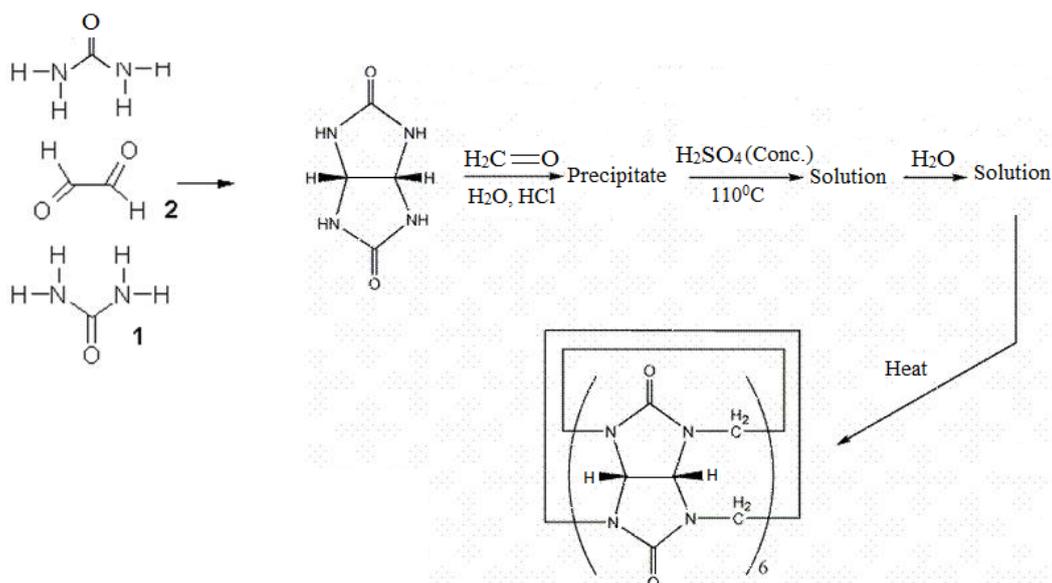


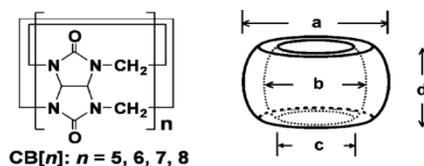
Figure 4: Synthesis of CB[n].

via a nucleophilic reaction to give the intermediate [glycoluril](#) 3. This intermediate is [condensed](#) with formaldehyde to give [hexamer](#) cucurbit [6]uril above 110 °C. ^{Figure 4} Ordinarily, multifunctional monomers such as 3 would undergo a [step-growth polymerization](#) that would give a distribution of products, but due to favourable [strain](#) and an abundance of [hydrogen bonding](#), the hexamer is the only reaction product isolated after precipitation. Decreasing the temperature of the reaction to between 75 and 90 °C can be used to access other sizes of cucurbiturils including CB [5], CB [7], CB [8], CB [9], and CB [10]. CB [6] is still the major product; the other ring sizes are formed in smaller yields. The isolation of sizes other than CB[6] requires fractional crystallization and dissolution^{5,9,10}.

3. PROPERTIES:

Cucurbit[n]urils contain two hydrophilic carbonyl lined portals, capping a central hydrophobic cavity. The different sizes of the portals and cavities ^{figure 5} means they are able to bind a variety of organic and inorganic molecules. Cucurbit[n]urils are sparingly soluble in water, but become more soluble upon encapsulation of some platinum complexes, particularly cationic and/or multinuclear complexes. The solubility of CB[n]s in water also varies depending on the method used to synthesise and purify them; many CB[n]s precipitate from solution with co-crystallised acid molecules, which can be difficult to remove. Alkali earth metal salts also increase the solubility of CB[n]s,

particularly saline. In the latter case, the cations are strongly bound at the portals and can help stabilise the binding of small guests inside the cavity.



		CB[5]	CB[6]	CB[7]
outer diameter (Å)	a	13.1	14.4	16.0
cavity (Å)	b	4.4	5.8	7.3
	c	2.4	3.9	5.4
height (Å)	d	9.1	9.1	9.1

Figure 5: Dimensions of CB²[n].

4. DRUG ENCAPSULATION BY CB[n]:

The encapsulated platinum complexes are obtained by either direct crystallisation or by titration of the metal complex into a cucurbituril solution. Equimolar, or in some cases a two- or three-fold excess of cucurbituril, amounts of the platinum complex and cucurbituril were dissolved in hot water containing 20 mM NaCl. Slow evaporation of the solution resulted in crystals of cucurbituril-encapsulated metal complexes. Aliquots of the platinum complex dissolved in D₂O (approx. 2 mM) were directly titrated into a 5 to 10 mL solution of the appropriate cucurbituril (2–4 mM) in D₂O to give the desired molar ratio. Aliquots of the solution were then taken for analysis by NMR spectroscopy^{4, 14, 15}.

Full or partial encapsulation of platinum complexes is stabilised through hydrophobic interactions within the CB[n] cavity and through ion–dipole and dipole–dipole interactions at the portals. The mode of binding can be examined through a range of spectroscopic techniques, most importantly using nuclear magnetic resonance (NMR)¹⁶.

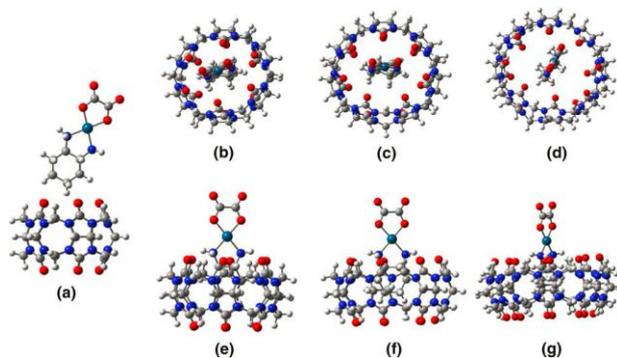


Figure 6¹³: Optimized structures of (a) CB[5]-oxaliplatin, (b) birds eye-view of CB[6]-oxaliplatin, (c) birds eye-view of CB[7]-oxaliplatin, (d) birds eye-view of CB[8]-oxaliplatin, (e) side view of CB[6]-oxaliplatin, (f) CB[7]-oxaliplatin, (g) CB[8]-oxaliplatin complexes.

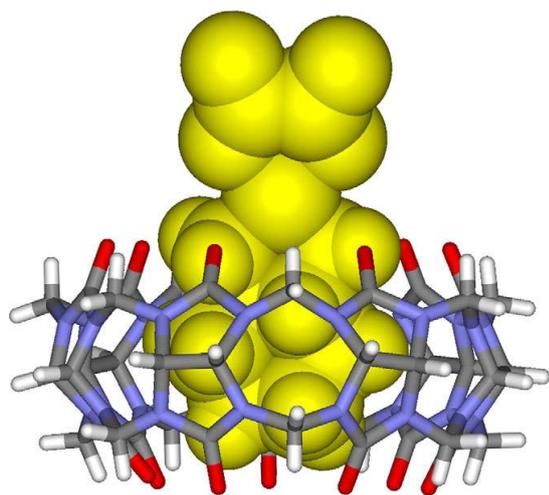


Figure 7: The encapsulation complex of oxaliplatin (yellow) within CB[7] based on the X-ray crystal structure data of Jeon et al⁸.

Complex of oxaliplatin with different CB[n] is of interest. The formation of inclusion complexes of CB[n]-oxaliplatin are facile in CB[n] $n = 6-8$, while for the cucurbit[5]uril, the oxaliplatin is expelled out of the cavity. In the complexes, the cyclohexyl group is found to be deep inside the cavity, with the formation of a hydrogen bonding between the portal oxygen atoms and the amine nitrogen of the oxaliplatin guest. The formation energy increases with the increase in the size of CB[n] and the energetically favoured complex was CB[7]-oxaliplatin. NBO analysis shows the transfer of charge from the metal centre to the CB[7] unit and the existence of hydrogen bonding between the oxygen portal and amine nitrogen. The strength of the interaction determined here reflects the ability of cucurbit[n]urils to act as a host for suitably oxaliplatin guests, even in aqueous solution^{6,7}.

5. DRUG PROTECTION:

Degradation of platinum-based complexes is a problem in their in vivo delivery¹⁷. Platinum atoms are readily bound by nucleophiles, particularly soft nucleophiles, and form bonds to guanosine and adenosine bases in DNA, cysteine and methionine residues in peptides and proteins, and various anions found in the human body, including: phosphates,

sulphates and carbamates^{18, 19}. The utility of CB[n] as a drug delivery vehicle primarily stems from its ability to protect platinum drugs from degradation, either through hydrolysis (as is the case for oxaliplatin) or through sulphur attack from thiol peptides and proteins. Oxaliplatin is also susceptible to light activated degradation, but upon encapsulation within CB[7], oxaliplatin is stable for over 1 year. Partial encapsulation of oxaliplatin by CB[7] also decreased significantly the drug's reactivity towards guanosine and L-methionine. The bound drug was 2–3-fold slower to react with guanosine at 37 °C and 15-fold slower to react with methionine, compared with the free drug. Partial encapsulation multinuclear complexes within CB[7] and CB[8] was shown to reduce their rates of reaction with guanine, L-cysteine and glutathione. Encapsulation of di-Pt within CB[7] reduces its rate of reaction with guanine 3-fold at 60 °C, whilst the dinuclear platinum complex $\text{trans-}[\{\text{PtCl}(\text{NH}_3)_2\}_2\text{1-H}_2\text{N}-(\text{CH}_2)_8-\text{NH}_2\}^{2+}$ (12), when encapsulated by either CB[7] and CB[8], was significantly less reactive towards L-cysteine and glutathione. It was found that CB[8] was better able to protect the metal complex compared with CB[7] due to the substantial folding of the diamino octane linker inside the cavity, which positioned the platinum atoms much closer to the CB[8] portals compared with

CB[7]. The degradation of platinum (II)-based DNA intercalator complexes by reduced L-glutathione has recently been reported. The complexes have degradation half-lives of between 20 and 68 h which are inversely proportional to their activity²⁰. When the platinum intercalators are partially encapsulated by CB[6], CB[7] or CB[8], however, no degradation is observed at time periods upto 7 days, under the same conditions.

6. EFFECT OF CB[n] BINDING ON DRUGS' IN VITRO AND IN VIVO EFFICACY:

Encapsulation of platinum complexes within CB[n] has an effect on both the metal complexes' cytotoxicity and toxicity. CB[n] molecules all of sizes appear to have no intrinsic cytotoxicity, with IC_{50} values of $>100 \mu\text{M}$ in many human cancer cell lines. Similarly, CB[n]s also appear to be relatively non-toxic, with in vivo studies in mice indicating that the maximum tolerated dose of CB[7] is around 200 mg/kg. The first metal complex to be studied with CB[n] was di-Pt. As the free complex, di-Pt has IC_{50} values in the murine leukaemia cell lines L1210 and L1210/DDP of 3.8 and 8.8 μM , respectively. When examined as a 1:1 host-guest complex with CB[7], the IC_{50} are 2.6 and 16.5 μM , respectively. In this case, CB[7] had no significant affect on the

cytotoxicity of the metal complex. Similarly, for BBR3571, a dinuclear platinum complex with potent in vitro cytotoxicity in a number of cisplatin sensitive and resistant cancer cell lines, the metal complex has identical IC_{50} values (0.0115 μ M) in the L1210 line with and without CB[7]. In the L1210/DDP resistant line only a slight decrease in cytotoxicity is observed, IC_{50} values of 0.0075 and 0.009 μ M for the free and encapsulated metal complex, respectively. The effect of CB[n] on the cytotoxicity of platinum metal complexes appears to be related, to some extent, to the strength of the binding. For BBR3464, a trinuclear platinum complex that was recently undergoing Phase II clinical trials as an anticancer drug, CB[7], CB[8] and CB[10] all decrease the cytotoxicity of the drug inversely proportionally to the size of the CB[n] molecule. That is, the larger the CB[n], the smaller the effect it has, presumably due to the easier movement of the drug in and out of the CB[n] cavity²¹. The effect of CB[7] on the cytotoxicity of oxaliplatin has been studied in five human cancer cell lines, including lung, ovarian, melanoma and colon cancers. Whilst free oxaliplatin is as active or more active than cisplatin in all the cell lines, encapsulation by CB[7] decreases the cytotoxicity of the drug 6- to 19-fold. For a family of platinum (II)-based DNA intercalators a clear correlation

between CB[n] size and cytotoxicity is harder to determine. CB[6] has a positive or only slightly negative effect on the cytotoxicity of $[Pt(5-Cl-phen)(R,R-dach)]^{2+}$ (5CLRR) and 5CLSS but causes the loss of all cytotoxicity for $[Pt(5-Cl-phen)(en)]^{2+}$ (5CLEN; where en = ethylenediamine). In contrast, CB[7] results in the complete loss of cytotoxicity for 5CLSS and 5CLRR ligands but has no effect on 5CLEN. CB[8] results in a slight decrease in cytotoxicity of all three platinum(II) DNA intercalator complexes tested²². The observed general decrease in cytotoxicity that many metal complexes experience upon encapsulation by CB[n]s could arise for two different reasons. First, it may be because encapsulation reduces the metal complexes' reactivity towards nucleophiles (similar to the decrease in cytotoxicity of less reactive carboplatin compared with cisplatin) and this result in a slower rate of DNA binding or a reduction in the number of DNA adducts formed. Alternatively, CB[n] may affect the cellular uptake of the metal complexes and thus prevent sufficient concentrations of drug from entering cells and inducing apoptosis.

Regardless of the mechanism causing the general decrease in metal complex cytotoxicity, this effect is manageable provided that the reduction in vitro activity also equates to a reduction in the metal complexes' toxicity and an improvement of

their therapeutic index. In vivo data are also available that demonstrates the utility of CB[n]s as drug delivery vehicles. The effect of CB[7] on the toxicity and efficacy of BBR3571 has been studied using an in vivo nude mouse model and the human ovarian cancer cell line 2008 xenograph. The addition of CB[7] almost doubles the maximum tolerated dose of BBR3571 when administered to tumour bearing nude mice. When free and encapsulated BBR3571 are administered in equivalent metal complexes doses, the encapsulated drug exhibits a similar ability to inhibit cancer tumour growth as the free drug.

Table 3: In vivo toxicity and efficacy data for the dinuclear platinum anticancer complex

BBR3571 (10) with and without CB[7] in female balb/c nude mice bearing the human ovarian cancer cell line 2008²².

Drug toxicity	BBR3571	BBR3571-CB[7]
MTD (mg/kg)	0.1	0.45
Drug equivalence	1	1.7
Administered dose (mg/kg)	0.1	0.27
Drug equivalence 1 1	1	1
TGIb (%)	48.5	44.9
GDIc	1.6	1.7

1. Tumour growth index (TGI) is defined as $100 - (\text{median relative tumour volume of treated group of mice} / \text{median relative tumour volume of the control group} \times 100)$.

2. Growth delay index (GDI) is defined as the median growth delay of the tumour in treated mice divided by the median growth delay of the tumours in untreated mice.

7. CONCLUSIONS:

Cucurbit[n]urils provide a unique method of protecting mono and multinuclear platinum drugs from degradation by thiol peptides and proteins. Whilst they can sometimes significantly decrease metal complexes cytotoxicity in vitro, they can also lower their toxicity.

The internal cavity is hydrophobic and capable of encapsulating the aliphatic or aromatic linking ligands of multinuclear platinum drugs. Secondly, the oxygen-rimmed portals could stabilise the encapsulation of the metal complexes through electrostatic interactions and hydrogen bonds with the platinum–amine groups, and could sterically hinder attack by biological nucleophiles. It is hoped that encapsulation of metal complexes within cucurbituril will allow it to be transported through the body, minimising deactivation or degradation by nucleophilic plasma proteins. The

development of water soluble CB[n]s will allow the further development of this technology and the creation of targeted drug delivery vehicles that can specifically recognise and delivery of platinum-based drugs to cancerous cells. They also show promising potentials for encapsulation of other drugs.

8. FUTURE DIRECTION:

The utility of CB[n]s as drug delivery vehicles for platinum anticancer drugs has been demonstrated but requires further research in two specific areas. First, further in vitro and in vivo trials are required to properly determine the structure–activity relationship between CB[n] size and binding and its effect on cytotoxicity. These need to be completed with different types of platinum complexes and with different CB[n]s to find the optimum combination. A systematic examination of the pharmacology of both free CB[n]s and CB[n]-encapsulated metal complexes is also needed, including their effect on metal complex uptake into cells, their mechanism of cell uptake, their metabolism and in vivo metabolomics. Secondly, whilst CB[n] encapsulation of platinum-based drugs addresses the problem of serum and intracellular drug degradation and deactivation by thiols, it is unlikely to increase the specificity of these

drugs for cancerous cells in preference to normal cells. Functionalization of CB[n]s with targeting groups would allow drug delivery vehicles to deliver platinum drugs specifically to cancerous cells. Unfortunately CB[n]s are highly stable compounds, resistant to both degradation and functionalization. They are stable against a range of oxidising agents and strong acids and do not decompose at temperatures up to 420°C. The design and development of targeted CB[n] drug delivery vehicles is therefore dependant on the development of a simple and reliable method to synthesise water soluble CB[n]s, preferably with carboxylic acid or amine groups which can be used to conjugate targeting compounds through peptide bonds.

9. ABBREVIATIONS:

BBR3464 - [trans-{PtCl(NH₃)₂}]₂trans-{Pt(NH₃)₂(μ-H₂N-(CH₂)₆-NH₂)₂}]⁴⁺

BBR3571 - trans-[[PtCl(NH₃)₂]₂μ-N⁴-spermidine-N¹,N⁸]³⁺

CB[n] - Cucurbit[n]uril

di-Pt - trans-[[PtCl(NH₃)₂]₂μ-dpzm]²⁺

dpzm - 4,4'-dipyrazolylmethane

phen - 1,10-phenanthroline

R, R-dach - 1R, 2R-diaminocyclohexane

S, S-dach - 1S, 2S-diaminocyclohexane

tri-Pt - [trans-{PtCl(NH₃)₂}]₂trans-{Pt(NH₃)₂(μ-dpzm)₂}]⁴⁺

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ALZHEIMER'S DISEASE: PATHOPHYSIOLOGY AND TOWARDS RATIONAL DRUG TREATMENT.

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Abstract

During the past two decades, one of the foremost challenges in health research was to understand better the cause(s) of AD for the development of safe and effective pharmacological treatments. However, irrespective of the form of therapy, the current approaches for the treatment of AD provide only temporary symptomatic relief, improve cognitive function, but do not slow the long-term progression of this disorder with several side effects. Moreover, these treatments have a modest effect on the progression of AD from Mild cognitive impairment, (*MCI*), to disabling dementia and death. Therefore, there is an urgent need to develop strategies to improve the efficacy, the transport across the blood brain barrier (BBB), the bioavailability, and subsequently to limit the adverse effects of pharmaceutical compounds for the treatment of AD. Nanotechnology represents an expanding strategy in this regard and promises advances to the diagnosis and may provide a possible solution to overcome challenges for the treatment of AD. An overview of the state of the art of development of AD pharmacotherapy and novel nanomaterials that have potential to improve diagnosis and therapy of AD and have been tested in different experimental models for delivery of drugs will be discussed.

Abbreviations:

MCI-Mild cognitive Impairment, AD-Alzheimer's Disease, AB-Amyloid beta,

NT-Neurofibrillary tangles.

1.1 Alzheimer's Disease Statistics

A global epidemic of Alzheimer's disease (AD) is occurring as the world's population ages¹. The prevalence of AD increases from ~3% at the age of 65 years to ~47% at the age of 85 years. In 2010, there are 3.7 million Indians with dementia². The worldwide prevalence of AD was 26.6 million, and by 2050 the prevalence will quadruple. It is the leading cause of persistent dementia in late life. Survival for a decade is common.

1.2 Stages of AD

i) Predementia: Subtle problems with the executive functions of attentiveness, planning, flexibility, and abstract thinking, or impairments in semantic memory (memory of meanings, and concept relationships) and Mild cognitive impairment.

ii) Early AD: There is increasing impairment of learning and memory. Language problems (shrinking vocabulary) are noticed. Difficulty in memorizing new facts or happening

iii) Moderate AD: Unable to perform most common activities of daily living. Behavioral and neuropsychiatric changes become more prevalent. Impaired short term as well as long term memory.

iv) Advanced AD: Patient is completely dependent upon caregivers. Complete loss of speech.

Diagnosis is usually confirmed by assessments of behavior and cognition. As the disease progresses, confusion, irritability, aggression, mood swings and withdrawal become commonplace. The disease excludes individuals from maintaining normal life events and in the latter stages of disease often requires long-term care and institutionalization³.

Histological examination is the only way to obtain a definite diagnosis for this pathology⁴.

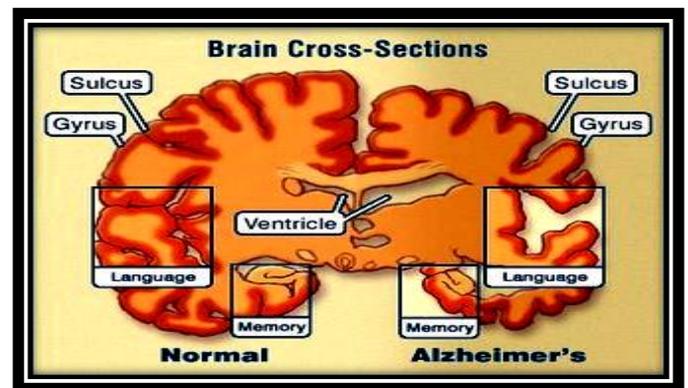


Figure 1

2. PATHOPHYSIOLOGY OF AD:

Pathologically, AD is characterized by loss of cortical, and to a lesser extent, sub cortical neurons and synapses (fig.2). This results in gross atrophy, including degeneration of the temporal and parietal

lobes and parts of the frontal cortex and cingulate gyrus.

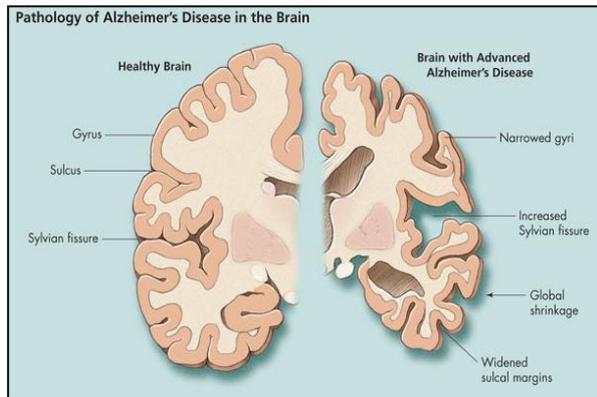


Figure 2: Pathology of Alzheimer's disease in the brain

The two types of characteristic lesions are Extracellular senile plaques (SP) and Intracellular neurofibrillary tangles (NT) (fig. 3)

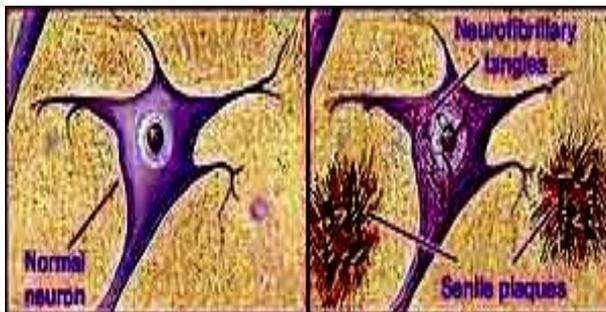


Figure 3: Characteristic Lesions in AD

2.1 Extracellular senile plaques (SP)

SP are composed of abnormal aggregations of amyloid- β (AB) ¹. Amyloid plaques are relatively insoluble dense cores of 5-10 nm thick amyloid fibrils with a surrounding

“halo” of dystrophic neurites, reactive astrocytes and activated microglia. The main proteinaceous component of amyloid plaques is the AB peptide. AB is not a single molecular entity, but rather is composed of a family of peptides produced by proteolytic cleavage of the type I transmembrane spanning glycoprotein AB precursor protein (APP). Once released by proteolytic cleavage, the AB peptide may exist in solution and can be detected in CSF and plasma. Extensive investigations using behavioral models, neuronal cultures and APP knockout mice suggest that APP may serve as a receptor for and appears to play a role during axonal regeneration and as a regulator of neural activity, connectivity, plasticity and memory³. In addition, it promotes the adhesion of cells to their substrate (Schubert et al., 1989) and protects neurons against excitotoxic and oxidative injury⁵.

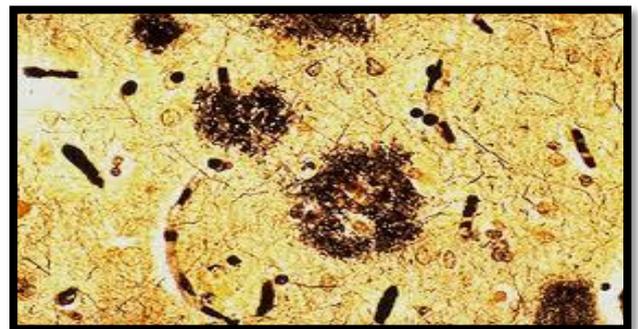


Figure 4

2.1.1 The Amyloid Beta Protein (AB)

The major protein component found in amyloid deposits is a 4 kDa AB protein. The AB peptide is a proteolytic product of the much larger ~100–130 kDa protein, called the amyloid precursor protein (APP). Complete sequencing of the AB peptide has shown that it consists of 39–43 amino acid residues. Before cleavage from the APP molecule, the N-terminal 28 residues of AB are extracellular and the

remaining residues are located within the transmembrane domain. C-terminal 12 amino acid residues of the AB peptide are hydrophobic (Fig. 5) and endow the peptide with the ability to self-aggregate and polymerize into amyloid fibrils. Beside AD, there are several other human diseases with amyloidosis, such as type II diabetes mellitus⁶.

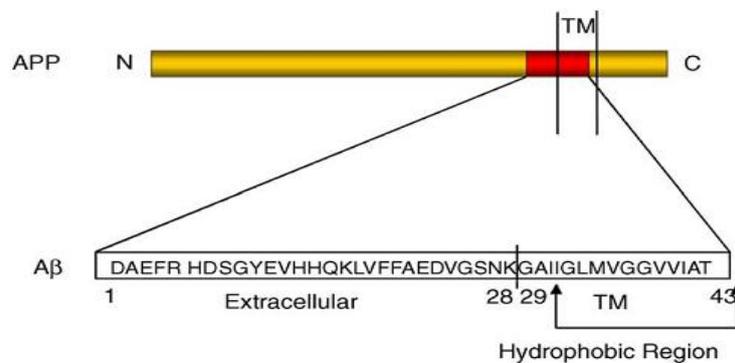


Figure 5: Structure of AB Protein

2.1.2 Trafficking and Proteolytic Processing of Amyloid Precursor Protein

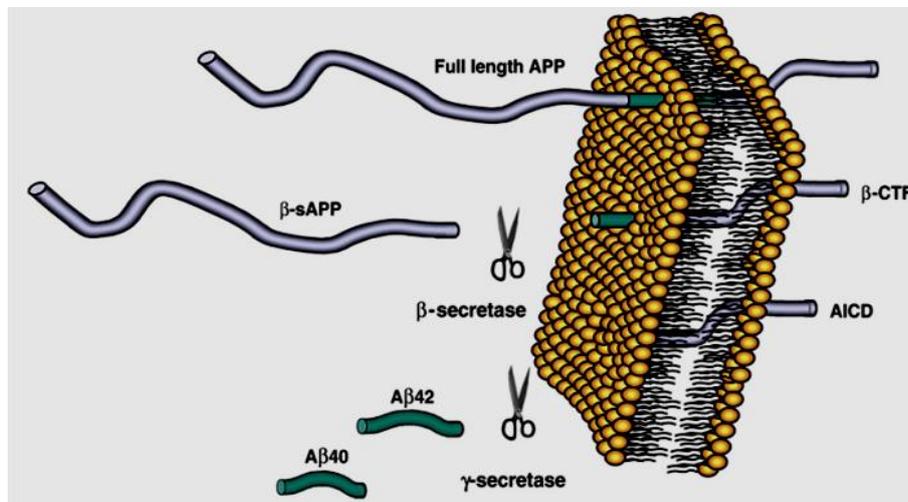


Figure 6: APP Proteolytic Processing

The majority of mature APP is proteolytically cleaved via one of two competing pathways, the non-amyloidogenic and amyloidogenic pathways. The APP is an integral membrane protein processed by the three proteases-alpha, beta, and gamma secretase, which have been implicated in the cause of AD. **Beta-Secretase** generates the -NH₂ terminus of AB, cleaving APP to produce a soluble version of APP (Beta-APPs) and a 99-residue -COOH terminal fragment (CT99) that remains membrane-bound⁶. In contrast, **Alpha-secretase**, which cleaves on the C-terminal side of residue 16 of the AB sequence to produce APP alpha-s, an 83-residue COOH-terminal fragment (CT83). Both CT99 and

CT83 are substrates for **Gamma-secretase**, which performs an unusual proteolysis in the middle of the transmembrane domain to produce the 4-kDa Beta-Amyloid (AB) and CT57-59 [amyloid intracellular domain (AICD)] from CT99, and a 3-kDa peptide called p3 and CT57-59 from CT83. The processing of the APP C-terminal fragment by gamma-secretase is mediated by the presenilins. Proteolysis by Gamma-secretase is heterogeneous, a 40-residue peptide (AB₄₀), whereas a small proportion is a 42-residue COOH-terminal variant (AB₄₂). The longer and more hydrophobic AB₄₂ is much more prone to fibril formation than is AB₄₀ and even though

AB₄₂ is a minor form of AB, it is the major AB species found in cerebral plaques⁷.

2.2 Neurofibrillary Tangles (NT)

A second defining pathological hallmark of AD is the formation of (NTs), which are insoluble filamentous accumulations found in degenerating neurons. They are composed of a cytoskeletal protein called 'tau', which normally binds to microtubules and regulates their state of polymerization. In AD, tau becomes hyperphosphorylated and self-aggregates, leading to microtubule depolymerisation and degeneration of dendrites and axons in neurons. NTs are frequently localised in the hippocampus, entorhinal cortex, amygdala and the perirhinal cortex⁶.

2.3 Genetic Risks of AD

Although most AD cases belong to the group of so-called late onset or sporadic forms of AD, there is also a genetic component of this disorder. Interestingly, a familial accumulation of AD has been reported as early as 1934. Today, it is well-known that 10% of AD patients have some family history. A total of four genes have, so far, been implicated in the pathogenesis of AD: the genes for the AB precursor protein (APP), for presenilin 1 and 2 (PS1,

PS2), and the gene for apolipoprotein E (ApoE). The ApoE4 allele is associated with both familial and sporadic late-onset AD.

2.4 Metals Imbalance and Biochemical Changes in AD

In **Normal Physiological Condition**, the vesicular zinc transporter ZnT3 transfers zinc into synaptic vesicles. Upon stimulated release zinc concentrations can achieve 300 mM within the synaptic cleft. Copper is released post-synaptically following N-methyl-D-aspartate (NMDA)-induced activation, which causes the translocation of ATP7a and its associated copper-laden vesicles to the synaptic cleft. Both copper and zinc are able to inhibit the NMDA receptor response, which may feedback to prevent further copper from being released into the cleft. AB would typically be cleared by movement into the periphery or degradation by extracellular proteases such as neprilysin and insulin degrading enzyme (IDE). Despite high peak concentrations upon neuronal stimulation, the average concentrations of free synaptic copper and zinc is kept low over time by a variety of other ways including putative energy-dependent reuptake mechanisms as well as buffering

by Metallothioneins (e.g. MT3) from neighboring astrocytes.

In **Alzheimer's disease** there is decreased mitochondrial energy which leads to reduced metal reuptake, which causes the average concentration of metals to rise over time. This allows copper and zinc to react with AB released into the synaptic cleft to form oxidized, cross-linked soluble oligomers and precipitated amyloid. AB can bind up to 2.5 moles of metal ions, but

becomes more densely aggregated as it becomes loaded with zinc. While the soluble AB monomers are constitutively degraded, zinc-loaded AB oligomers are resistant to degradation. MT3 is also decreased in AD, so promoting abnormal metal-AB interaction and sequestered metal ions by AB allows unopposed glutamate activation of the NMDA receptor, which could lead to the increased release of post-synaptic copper⁸.

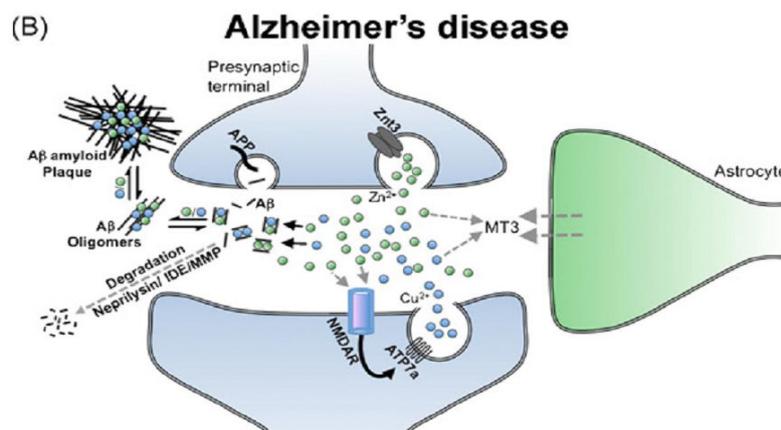


Figure 7: Metal Imbalance in AD

3. CHALLENGES IN DRUG DELIVERY FOR AD:

The targeted drug delivery to the central nervous system (CNS), for the diagnosis and treatment of neurodegenerative disorders such as AD, is restricted due to the limitations posed by the blood brain barrier (BBB) as well as due to opsonization by plasma proteins in the

systemic circulation and peripheral side-effects³.

3.1.1 Transport mechanisms of the BBB

a) Paracellular diffusion

The tight junctions between endothelial cells results in a very high transendothelial electrical resistance of 1500-2000 $\Omega \text{ cm}^2$ compared to 3-33 $\Omega \text{ cm}^2$ of other tissues

which reduces the aqueous based paracellular diffusion that is observed in other organs.

b) Transcellular diffusion in brain capillaries, intercellular cleft, pinocytosis, and fenestrae are virtually nonexistent;

exchange is mainly transcellularly. Therefore, only lipid-soluble solutes that can freely diffuse through the capillary endothelial membrane may passively cross the BBB.

c) Absorptive-Mediated Endocytosis

Absorptive-mediated transcytosis is triggered by electrostatic interactions between the positively charged moiety of the peptide and the negatively charged plasma membrane surface region.

d) Receptor-Mediated Endocytosis

To get molecules to cross the BBB they need to be manipulated in a manner such that penetration into the brain is achieved. Sometimes this is achieved by synthesis of chimeric peptides. They are formed by covalent binding of the non-permeable but pharmacologically effective portion of the peptide to an appropriate vector that can be transported across the BBB. The intact chimeric peptide is transferred into the brain's interstitial space by receptor-

mediated exocytosis. Subsequently, the binding between the vector and the pharmacologically active peptide is cleaved and, finally, the released peptide exerts its pharmacological effect in the brain. It occurs at the brain for macromolecular substances, such as transferrin, insulin, leptin, and IGF-I&IGF-II, and is a highly specific type of energy dependent transport⁹.

e) Carrier mediated transporter (CMT)

Carrier mediated transporter (CMT) system is expressed on both the luminal and abluminal membranes of the brain capillary endothelium and operates in both directions, i.e., from blood to brain and brain to blood directions. The CMT systems can be exploited for brain drug-delivery after reformulating the drug in such a way that the drug assumes a molecular structure mimicking that of the endogenous ligand (glucose, amino acids). For example, pseudonutrients are the polar small drug molecules which are made by mimicking the structure of nutrients⁹.

4. THERAPEUTIC APPROACHES:

Alzheimer's disease is highly prevalent and well characterized, with a number of potential therapeutic options but regrettably few currently in clinical

practice³. AD therapy would improve substantively if drugs could be delivered specifically to affected brain areas. Therapy could also improve diagnostics if plaques, tangles and/or neuropathological activities could be seen earlier in the disease course. These include, but are not limited to Nineteen compounds are currently in Phase II trials, out of which three compounds (AN1792,lecozotan SR, and SGS742) failed at this stage of development. There are many more candidate molecules that are at the pre-clinical stage of development and are likely to proceed into clinical trials based on the cholinomimetic therapy, the amyloid cascade, the metal and the oxidative stress mechanisms³.

4.1 Acetylcholinesterase Inhibitors

Profound losses in the cholinergic system of brain, including dramatic loss of choline uptake and ACh level in the neocortex and

hippocampus and reduced number of the cholinergic neurons in basal forebrain and nucleus basalis of Meynert, are closely associated with cognitive deficits observed in the disease. Blocking acetylcholine hydrolysis with AChEI is the most popular approach. After the FDA approved **Tacrine** in 1993, several kinds of AChEIs such as **donepezil, galantamine, and rivastigmine** have become available for the symptomatic treatment of patient with mild-to-moderate AD. However, weakness of such AChEIs caused by limitations related to short biological half-life, transient and weak effects, narrow therapeutic range, low BBB, and frequent adverse effects block their way to treating cognitive deficits in AD. Cholinergic-based therapy using AChEI is currently known to be the best clinical approach for improving cognitive deficits in AD⁷.

Table 1 gives details of various AChE inhibitors

Feature	Tacrine (Cognex)	Donepezil (Aricept)	Galantamine (Reminyl)	Rivastigmine (Exelon)
Dose	40mg/day	5mg/day	8mg/day	6-12 mg/day
Dosage Frequency	4 times daily	Once daily	Twice daily	Twice daily

Side Effects	Severe Hepatotoxicity, Nausea, Vomiting.	Anorexia, Nausea, Vomiting at Higher doses.	Nausea, diarrhoea, Abdominal Cramps at higher doses	GI upset, Weight loss, Vomiting, Dyspepsia
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Table 1

4.2 Glutamatergic-system Modifiers

Overstimulation of the N-methyl-D-aspartate (NMDA) receptor by glutamate leads to neuronal calcium over-load and is implicated in the neuronal death characteristic of AD. Conversely, physiologic activation of the NMDA receptor appears to be necessary for normal cognitive function. **Memantine**, a noncompetitive (channel-blocking) antagonist with moderate affinity for the NMDA receptor, appears to block pathologic neural toxicity associated with prolonged glutamate release without blocking physiologic activation of the

NMDA receptor. It is approved by FDA in Severe Alzheimers¹⁰.

4.3 Therapeutics and diagnostic targeting of metal ions in AD

One logical and increasingly popular theory for the use of neurotherapeutic small molecules in AD is to target the initiating event in the generation of free radicals⁸. As a preventive approach antioxidant molecules may be used for their ability to neutralize free or incorrectly

bound metals, thereby interfering with the ‘down-stream’ generation of reactive oxygen species and other radicals. Numerous molecules with antioxidant properties, such as estrogen, melatonin, vitamin C and E (L-ascorbate and -topopherol, respectively), ginkgo biloba extract, curcumin and flavonoids have neuroprotective effects against AB-induced toxicity in cell- based experiments and animal models^{3,4}.

4.4 AB Vaccine therapy

Immunotherapy targeting the AB peptide is a leading approach to disease-modifying treatment. AB antibodies might bind and remove small AB aggregates in the brain, thereby neutralizing the effects of toxic AB species on synapses. In an alternative mechanism, strategy is based on the binding of AB peptide in the blood that would “draw” the peptide from the brain through the BBB, possibly by a receptor-mediated process thus resulting in an increase in AB efflux from the brain to the periphery. The **heparin, gelsolin, and other molecules** are thought to “sink” or trap AB peptide in the blood and, at least

in animal model, reduce AB accumulation in the brain. As **amyloid vaccine AN-1792** led to the development of **Aseptic meningoencephalitis** in 6% of the patients, a second-generation vaccine, ACC-001, with an improved safety profile (with a short AB sequence as the immunogen, presumably preventing the induction of a toxic cellular immune response), was shown to be safe in a Phase I study and is currently in Phase II clinical trials with 360 patients with mild to moderate AD⁴.

4.4.1 Passive AB immunization

The furthest along in clinical testing is **Bapineuzumab (AAB-001)**, a humanized monoclonal antibody that recognizes the amino terminus of AB; with the Phase II a study yielding some encouraging results, particularly in the subgroup of patients not carrying the ApoE4 allele and the Phase III trial is under investigation.

4.5 Anti-inflammatory Therapy

Major support for the theory that inflammation contributes to neurodegeneration and that suppression of inflammation may therefore be beneficial comes from epidemiological studies. COX-1 is expressed in brain microglia and may be upregulated in some regions of AD

brain, it may be necessary for effective suppression of antiinflammatory activity in the AD brain. In experimental models, neurotoxic stress, including ischemia and excitotoxicity and apoptosis is associated with upregulation of neuronal COX-2¹¹.

4.5.1 Curcumin

Curcumin (diferuloylmethane) is a low-molecular-weight, natural polyphenolic compound that is isolated from the rhizome of turmeric (*Curcuma longa*). It has a low intrinsic toxicity but a wide range of pharmacological activities including antioxidant, anti-inflammatory, antimicrobial, anti-amyloid, and antitumor properties. The yellow curry spice is part and parcel of Indian vegetables⁴. The incidence of AD in India is remarkably low compared to the U.S; this intriguing finding could be related to widespread use of curcumin in India¹¹.

4.6 Nanotechnology Based Therapeutic Approaches

A paradigm in cerebral drug targeting is by using particulate carriers. Nanoparticles are advantageous as they possess the high drug-loading capacities, thereby increasing intracellular delivery of the drug; the solid matrix of particulate carriers protects the incorporated drugs against degradation,

thus increasing the chances of the drug reaching the brain and Carriers can target delivery of drugs, and this targeted delivery can be controlled. One additional benefit of nanocarriers is that their surface properties can be manipulated in such a way as to evade recognition by the macrophages of the reticuloendothelial system (RES), hence improving the likelihood of nanoparticles reaching the brain¹².

4.7 Cholinesterase inhibitors-loaded NPs Polymeric NPs

4.7.1 Tacrine-loaded Chitosan NPs

Chitosan is a natural polysaccharide comprising copolymers of glucosamine

and N-acetylglucosamine, used as a safe excipient in drug formulations for over two decades; biocompatibility and biodegradability, make it a very attractive substance for diverse applications in pharmaceutical field. Chitosan has a positive charge when compared with many other natural polymers and is mucoadhesive. Wilson et al. prepared Tacrine-loaded chitosan NPs by spontaneous emulsification process. The biodistribution studies of drug-loaded NPs (drug to polymer ratio 1:1) were then carried out in rats. Tacrine freely crosses the BBB; a delivery system that releases the drug in a sustained manner as well as prolongs the residence time in blood may be helpful to improve the bioavailability of drug in the brain⁴.

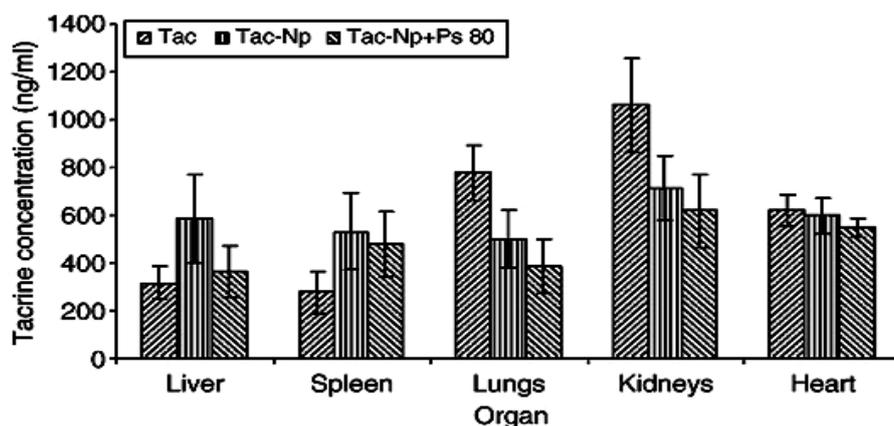


Figure 8: Tacrine concentration(ng/ml) in different organs after Tacrine-loaded chitosan NPs administration.

4.7.1.1 Tacrine loaded (PBCA) NPs

Targeting tacrine in the brain was also investigated using polymeric poly (n-butylcyanoacrylate) (PBCA) NPs prepared by emulsion polymerization. Tacrine (1 mg/kg) was administered by i.v. injection in the form of a simple solution in phosphate buffered saline; bound to PBCA

NPs, and bound to PBCA NPs coated with 1% polysorbate 80 (Tween-80) in Healthy adult Wistar rats weighing 180–220 g were obtained from and tacrine concentration was analyzed 1 h post-injection. The brain concentration of i.v. injected tacrine could be enhanced by 4.07-fold as compared to the free drug tacrine after binding to poly (n-butylcyanoacrylate) NPs coated with 1% polysorbate 80¹³.

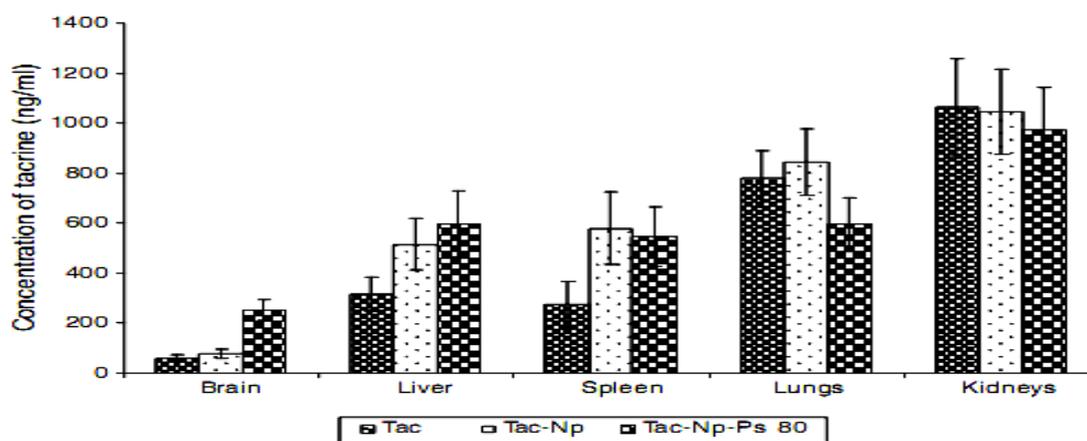


Figure 9: Tacrine concentration (ng/ml) in different organs after Tacrine-loaded PBCA NP's administration

Importance of Polysorbate 80 in Brain Targeting:

Poly(butylcyanoacrylate) nanoparticles coated with polysorbate 80 adsorb apolipoprotein Band/or E after injection into the blood stream. The polysorbate acts mainly as an anchor for the apolipoprotein-overcoated nanoparticles thus would mimic lipoprotein particles and could interact with and then be taken up by brain

capillary endothelial cells via receptor-mediated endocytosis. It is possible that uncoated tacrine, rivastigmine loaded nanoparticles indeed were captured by the reticuloendothelial system, and the particles continuously released the drug into the blood stream resulting in elevated plasma and brain levels of tacrine (because tacrine crosses the blood–brain barrier). The developed formulations may also

reduce the total dose required for the therapy with concurrent reduction in dose related toxicity¹⁴. However, a successful passage of the drug loaded NPs across the BBB is not fully predictive of its therapeutic effect, because after penetration of the drug across the BBB it is equally important to evaluate whether its biological activity is retained or not.

4.7.2 EGCG Solid Lipid Nanoparticles

SLN's (Nano epi gallo catechin 3-gallate) differ from traditional liposomes because they do not require micelle formation. Rather, they are drug: lipid complexes, enables the formation of smaller diameter particles that was hypothesized would be useful for increasing the oral bioavailability of EGCG. Nanolipidic particles (NanoEGCG) were prepared using a proprietary cosolubilization methodology involving use of monophasic liquid preparations.

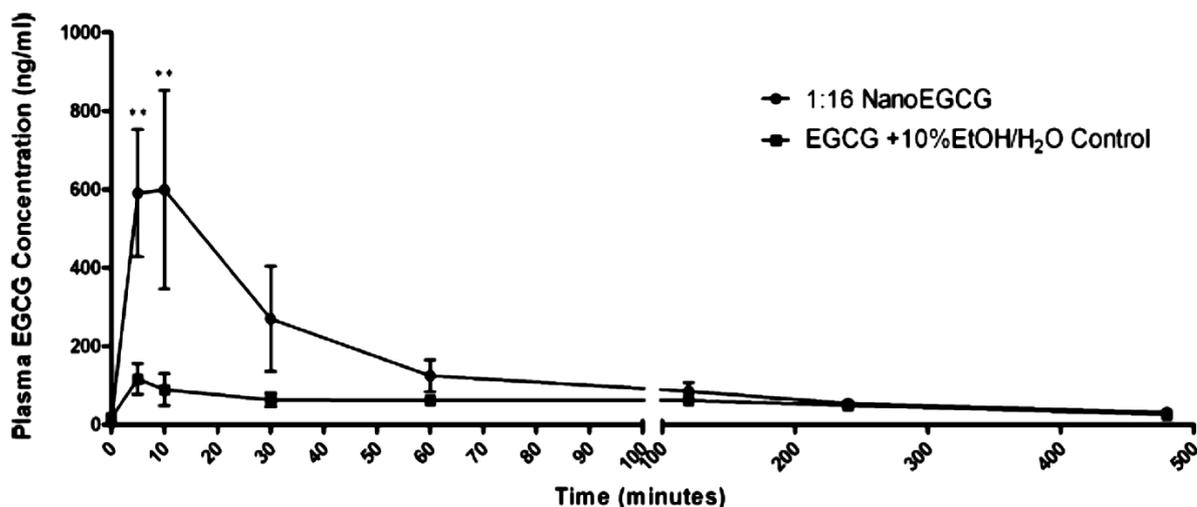


Figure 10: Plasma EGCG conc. After administration of NanoEGCG and EGCG+10% EtOH control

SLN's are highly effective at increasing the absorption of EGCG into systemic circulation. The control was very poorly absorbed in comparison to the

NanoEGCG. This study provides important preliminary evidence that nanolipidic particles might be useful for safely translating EGCG into human clinical trials. Not only did NanoEGCG more than

double the oral bioavailability of EGCG in rats but also was more effective at promoting alpha-secretase activity in vitro, even at reduced concentrations. Taken together, it is possible that NanoEGCG will be therapeutically effective at doses that would be considered acceptable in the clinical setting¹⁵.

4.7.3 PEGylated NP

Long-circulating PEGylated polycyanoacrylate nanoparticles act as an adequate vector to target spleen and brain simultaneously. These nanoparticles are formed by an amphiphilic copolymer where the hydrophobic block itself (poly hexadecyl cyanoacrylate, PHDCA) forms the particle core while the hydrophilic part (poly (ethylene glycol), PEG) remains as a surface-exposed 'protective cloud'. Such type of hydrophilic coating reduces the natural blood opsonization process of the particles and, hence, the recognition by macrophages, increasing particles half-life in blood.

4.7.4 Dendrimers

Dendrimers are a new class of polymers which are synthesized in a stepwise manner with branched monomer units. In the first step, branched monomers react with a polyfunctional core, leaving the reactive end groups on the surface. The more layers of monomers are attached, the

higher the generation of the dendrimer synthesized¹⁶.

Polyamidoamine (PAMAM) dendrimers of the third generation, G3, for example, possess 32 groups on the surface. New nanotherapies have been designed to inhibit the formation of AB aggregates during intermediate steps.

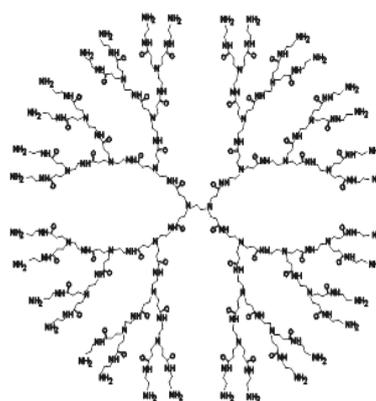


Fig. 11. Structure of a generation three (G3) PAMAM dendrimer.

Figure 11: Dendrimer Structure

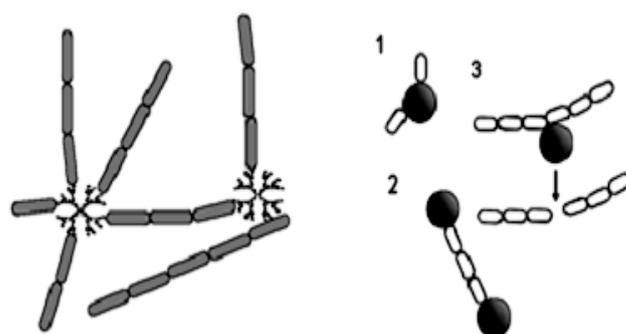


Figure 12 : Dendrimer Action on AB

Polyamidoamine dendrimers inhibit aggregation of AB peptides. Anti-assembly

strategy of dendrimers can be performed either via their binding with peptide monomers or through blocking the end of protofibrils and fibrils. These anti-assembly effects of dendrimers take place at their higher concentrations. Klajnert et al suggested that the higher concentrations of dendrimers will have toxic effect rather than therapeutic results, because in higher concentrations, antiassembly effect of dendrimers happens and prevents AB fibrillization and thereby results in the accumulation of toxic low molecular

weight AB oligomers. Low concentrations of dendrimers are supposed to have therapeutic effects, according to their effect on lowering the oligomeric species lifetime. This is because low concentrations of dendrimers induce AB oligomers to form less toxic fibrillar species¹⁷. The aggregation kinetics of the amyloid peptides were monitored using the dye Thioflavin T (ThT), whose fluorescence is dependent on the formation of amyloid aggregates.

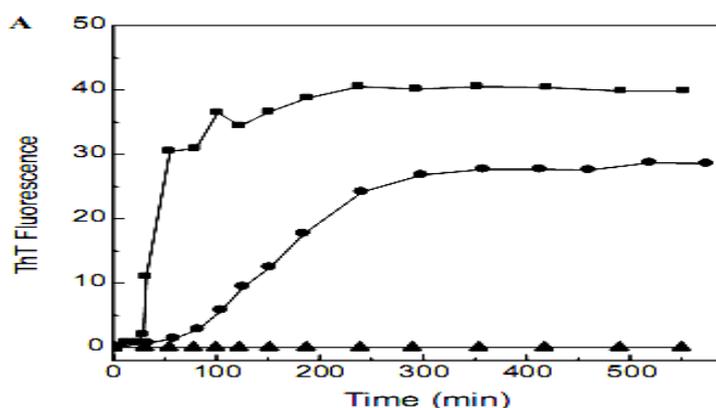


Figure 13: Time dependent Fluorescence variation of ThT

4.7.5 Fullerenes

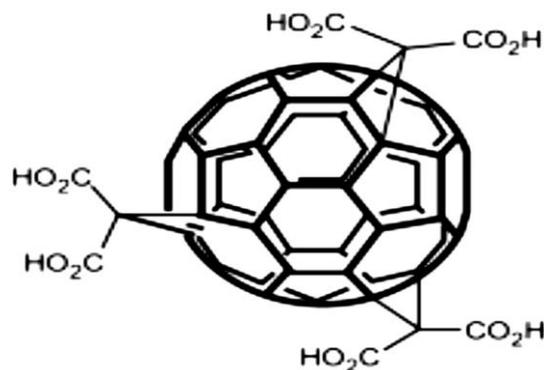


Figure 14: Fullerenes: Structure.

Fullerenes have also been shown to inhibit AB fibrillization. C60 fullerenes affected AB aggregate assembly. Upon intracerebroventricular injection, C60 fullerenes were able to prevent impaired cognitive performance on tasks normally induced by the presence of AB. Presumably, the neuroprotective effect of fullerenols is due to both antioxidant reactions and inhibition of AB42-induced Ca^{2+} neurotoxicity¹⁷. Huang et al. validated the latter finding in their investigation into the effect of fullereneol-1 upon AB-induced Ca^{2+} influx in the cultured neurons¹⁸. Dugan et al. have shown that fullerene poses complete neuroprotective properties against NMDA receptor mediated neurotoxicity. NMDA receptor function is important to neuronal mechanisms of learning and memory. Altogether, applications of functionalized fullerene derivatives including carboxyfullerene and hydroxyfullerene (fullerenols), are promising in discovery of new drugs for AD; however further research on their pharmacodynamic and pharmacokinetic properties is necessary¹⁷.

4.7.6 Theranostic Magnetic iron-oxide NPs

A recent example demonstrating this possibility has been the complete removal

of amyloidogenic fibrils from an aqueous phase by Binding amyloid fibrils to magnetic iron-oxide (maghemite) NPs and then removing these NP-protein complexes from the solution using a magnetic field³. Maghemite NPs nanoparticles have attracted extensive interest due to their super paramagnetic properties and their potential applications in many fields. They are biocompatible and potentially non-toxic to humans. Iron oxide is easily degradable and therefore useful for in vivo applications. The fluorescent maghemite NPs had a combination of the magnetic and fluorescence imaging into one nanostructured system; they had a great advantage as multimodal imaging agents. It was further stated that the hybrid system prepared might enable the early detection of plaques using both magnetic resonance imaging and fluorescence microscopy, and therefore may be applied for in vivo AD diagnosis studies. Besides this, the fluorescent-magnetic NPs can also find useful application as selective biomarkers to detect the location and the removal of amyloid plaques derived from different amyloidogenic proteins that lead to NDs⁴.

4.7.7 Theranostics Gold (Au) NP

Theranostics Gold (Au) NPs can target and remove AB deposits with the application of electromagnetic energy. Au NPs

conjugated with fragments of AB peptide or coated with a peptide known to interact with AB aggregates (e.g., CLPFFD-NH₂) can be incorporated into AB fibrils. Stable interaction between Au NP–protein complexes and their target, AB aggregates, is a key goal in the application of this technology. AB aggregates that incorporate Au NPs can be selectively ablated by laser exposure or with the application of microwave fields providing new avenues for both targeting and then removing AB deposits. Microwave radiation is perhaps less invasive while still allowing for selective ablation of AB deposits. These provide new avenues for both targeting and then removing AB deposits³. The thermal energy was produced from a low gigahertz electromagnetic energy source (microwave) by the gold nanoparticles, which are already attached to the specific target (i.e. AB). Gold nanoparticles are selected for this experiment because of their nanometric size, high surface-to-volume ratio, biocompatibility, high electron density and mobility. These properties make it feasible to provide a specific bond target with a selective supply of energy in a remotely controlled manner, and without any adverse effects on the molecular proximity¹⁷.

4.7.8 Diamondoids

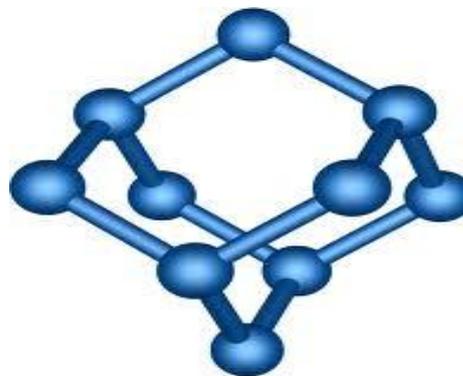


Image from: H. Ramezani et al., *J. Comput'l & Theor'l Nanoscience*, 4(1):96-106, 2007.

Figure 15: Diamondoid structure

In the context of classical chemistry, "diamondoid" refers to variants of the carbon cage molecule known as adamantane (C₁₀H₁₆), the smallest unit cage structure of the diamond crystal lattice. Interestingly, Memantine, a FDA approved neuroprotective drug against AD pathogenesis is a derivative of adamantane (1-amino-3, 5-dimethyladamantane), which is a diamondoid. Diamondoids are cage like saturated hydrocarbons, known as one of the nanotechnology molecular building¹⁷.

4.7.9 CHP Nanogels

Biocompatible nanogels composed of a polysaccharide pullulan backbone with hydrophobic cholesterol moieties (cholesterol-bearing pullulan, CHP) as

artificial chaperones to inhibit the formation of $A\beta_{1-42}$ fibrils with marked amyloidogenic activity and cytotoxicity. The CHP-nanogels incorporated up to 6–8 $AB_{(1-42)}$ molecules per particle and induced a change in the conformation of AB from a random coil to α -helix- or β -sheet-rich structure. This structure was stable even after 24-h incubation at 37 degree C and the aggregation of AB_{1-42} was suppressed. Nanogels composed of amino-group-modified CHP (CHPNH₂)

with positive charges under physiological conditions had a greater inhibitory effect than CHP-nanogels, suggesting the importance of electrostatic interactions between CHPNH₂ and AB for inhibiting the formation of fibrils. Cell viability was estimated by the 3-(4,5-dimethyl-2-thiazolyl)-2, 5-diphenyltetrazolium bromide (MTT) assay. The absorbance of the cells that had been treated only by the vehicle was set to 100% viability.

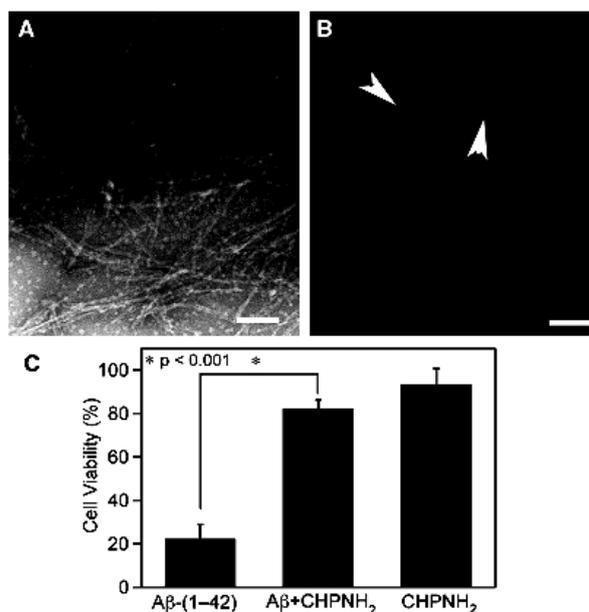


Fig. 5. TEM images of 24-h incubated $A\beta(1-42)$ ($15 \mu\text{M}$) without (A) or with (B) CHPNH₂ nanogels at a glucose-to- $A\beta$ ratio of 4000 (scale bar = 100 nm). Arrow heads show nanogel particles. (C) Cytotoxicity of 24-h incubated $A\beta(1-42)$ against PC12 cells as determined by the MTT assay ($n = 6$, \pm S.E.). The final concentrations of $A\beta$ and CHPNH₂ nanogels were $1 \mu\text{M}$ and 4mM (as glucose), respectively.

Figure 16: TEM images of AB_{1-42} without(A) or with(B) CPNH₂NP. C shows cell viability

The cell viability was decreased to 22%. The co-existence of CHPNH₂ nanogels significantly reduced the toxicity of AB and recovered the viability to 82% at a

glucose-to-protein ratio of 4000. Furthermore, it should be noted that nanogels themselves had no harmful effects. Therefore, smaller amounts of nanogels appear to sequester several AB

molecules in a particle, imposing a non-fibrillar β -sheet conformation and inhibiting the formation of fibrils. The spectrum of AB without a nanogel changed from that of a random coil to one of a β -sheet-rich structure accompanied by an increase in ThT fluorescence after a 24-h incubation at 37 degree C. In the presence of large amounts of nanogels, where each particle contains one protein molecule, AB₁₋₄₂ maintained an α -helical structure and exhibited less than 15% ThT fluorescence even after a 24-h incubation, suggesting that the nanogels effectively

suppressed the aggregation of AB₍₁₋₄₂₎. Moreover, with the addition of MbCD (methyl- β -cyclo dextrin), the trapped AB is released as a monomer without the formation of putative toxic oligomers. Furthermore, CHPNH₂ nanogels have greater cellular up-take efficiency than the cationic liposomes widely used in drug delivery systems. Another advantage of nanogels is that they can control the conformation of AB. Therefore, nanogel-AB complexes are applicable for conformation-specific vaccination¹⁹.

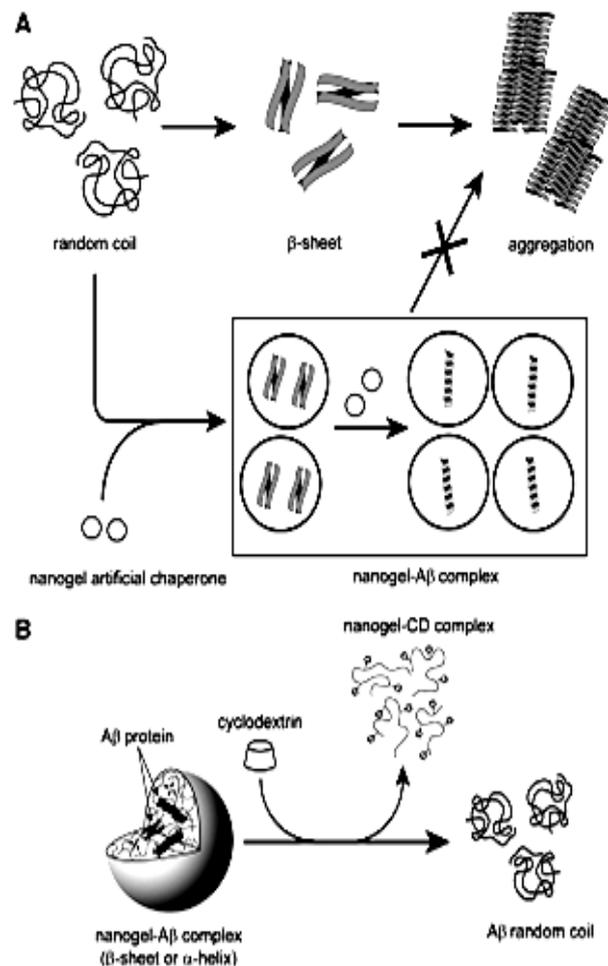


Figure 17: Mechanism of Action of Nanogels

Over the last decade diagnostic and therapeutic potential of NPs for the AD have been extensively investigated. Although experimental data have demonstrated effective transport of drugs across BBB using NPs for the treatment of AD, still there is a need to optimize this general strategy, in terms of efficiency, specificity and safety. One should be cautious because a successful passage of drug loaded nanoparticulate delivery system across a simulated BBB model is not fully predictive of its therapeutic effect, because after penetration of the drug across the BBB it is equally important to evaluate whether its biological activity is retained or not. Safety and toxicity aspects of the NPs are important considerations that need to be taken seriously, understood and resolved before the extensive clinical use of these formulations for the treatment of AD.

4.8 Intranasal Mucoadhesive Microemulsion of Tacrine

Mucoadhesive drug delivery systems are those that provide intimate contact of the drug are those that provide intimate contact of the drug with the mucosa for an extended period of time. Since the nasal mucosa offers numerous benefits as a target tissue for drug delivery, a wide

variety of therapeutic compounds may be administered intranasally for topical, systemic and central nervous system action. The use of mucoadhesive system as microspheres is to provide a drug protection from enzymatic degradation and thus increase the contact time with the nasal mucosa. These Intranasal (IN) microspheres can be efficiently utilized to avoid hepatic first-pass metabolism, improve therapeutic efficacy and enhance residence time on nasal mucosa. The gamma scintigraphy images clearly demonstrate the accumulation of formulations in brain at 15 minutes post dosing when administered via IN routes. However, after IV administration very little or no accumulation of radioactive formulation was observed. This suggested selective nose-to-brain direct transport of drug. The accumulation of higher radioactivity in the brain after intranasal administration of TMME compared with TS and TME demonstrates the role of mucoadhesive microemulsion in brain targeting. Thus after nasal administration of different tacrine formulations, rapid delivery of tacrine to the brain compared with IV administration may be because of preferential nose-to-brain transport after IN administration. This was further supported by the lower T_{max} values for brain

compared with blood for all the 3 nasally administered formulations. Under normal circumstances, nasally administered formulations get cleared quickly from the nasal cavity due to mucociliary clearance²⁰. Mucoadhesive agents are well reported to prolong the contact time of the formulation with the nasal mucosa and thereby enhance rate and extent of absorption of the drug²¹.

4.9 The Rivastigmine Transdermal Patch (Exelon)

A transdermal drug delivery system has the potential to change the treatment paradigm for many AD patients.

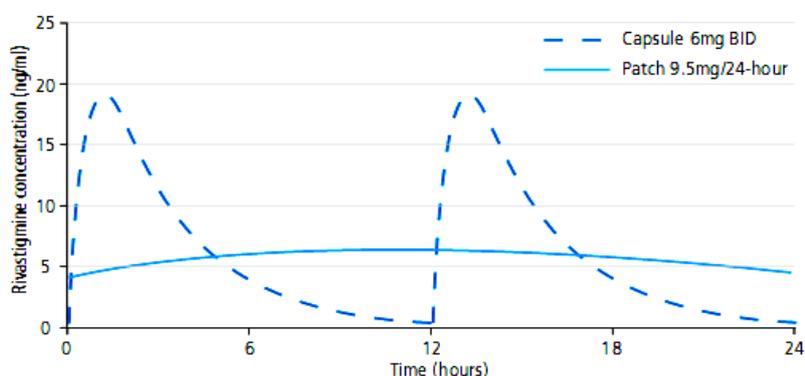


Figure 18: Rivastigmine TD Patches in comparison to Rivastigmine Capsules

Cholinesterase inhibitors have been shown to exhibit dose–response relationships with higher plasma levels of the drug corresponding to higher levels of enzyme inhibition. However, the incidence of adverse events (AEs) also increases with higher oral doses, particularly gastrointestinal occurrences such as nausea and vomiting. Consequently, not all patients in clinical practice are able to achieve and maintain the recommended therapeutic doses of conventional oral cholinesterase inhibitors. A transdermal

patch can provide smooth and continuous delivery of the drug, reducing C_{max} and prolonging t_{max} while maintaining drug exposure. This pharmacokinetic profile has the potential to reduce the incidence of cholinergic side effects, allowing patients easier access to optimum therapeutic doses, thus improving the effectiveness of treatment over oral administration. Additional benefits of transdermal administration, include a simplified treatment regimen, convenience and ease of use²².

Rivastigmine is chemically well-suited to transdermal delivery. The rivastigmine patch uses modern matrix technology, combining the drug, antioxidants, a polymer mixture (to control the drug delivery rate) and a silicon matrix adhesive into a single layer through which the drug diffuses. Unlike early transdermal patches, there is no 'reservoir' of the drug within the patch or adjunct (such as ethanol) to facilitate diffusion of rivastigmine through the skin.

5. FUTURE:

Three important avenues for disease-combating interventions will be developed through nanomedicine approaches. First, the improvement of site-directed drug delivery in brain regions most affected by disease will be achieved through '**smart formulations**' and the ability to bypass or engage the BBB, thus improving the outcomes of therapeutic approaches. Second, regenerative nanomedicine will provide new agents to specifically repair or modulate disease targets. However, such interventions must not only find their way into affected disease areas of the CNS but also show limited or no toxicities. Third, early disease diagnosis will lead to improved intervention outcomes since treatments are likely to be more effective.

Interdictive therapies that can halt or reverse the disease course have been tried but were met with varied degrees of success.

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MONOCLONAL ANTIBODY THERAPY IN
RHEUMATOID ARTHRITIS



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ABSTRACT:

Rheumatoid Arthritis (RA) is a systemic autoimmune syndrome in which chronic inflammation of the joints is believed to be initiated by autoantibodies and maintained by cellular inflammatory mechanisms. The inflammation and damage is being caused by various pro-inflammatory cytokines, primarily, TNF- α (Tumor Necrosis Factor – alpha). Other such cytokines include IL-1 (interleukin), IL-6, IL-8 and GM-CSF (granulocyte monocyte colony stimulating factor). Monoclonal Antibodies are biological response modifiers which aid in immunosuppression in RA. They block or bind to these cytokines, thereby reducing inflammation, joint damage, and pain. They are less toxic than conventional drugs used. This paper is a review of the studies on the mechanism of action of various monoclonal antibodies against certain cytokines i.e. TNF – alpha, IL-1, IL-6, and inflammatory cells such as B cells and T cells. We have focused on TNF antagonists, such as Infliximab, as TNF–alpha is a major pro-inflammatory cytokine in RA.

Keywords: Rheumatoid Arthritis, Monoclonal antibodies, Tumor Necrosis Factor-alpha.

1. INTRODUCTION:

Rheumatoid Arthritis is a systemic autoimmune syndrome, in which chronic inflammation of the joint is believed to be

also responsible for stimulating destructive mechanisms in the joint which lead to structural damage and subsequently to functional declines and disability.^[1]

The rheumatoid joint contains numerous cell types that are involved in these inflammatory and destructive processes. As seen in Figure 1, the inflamed synovial membrane contains synovial macrophages and fibroblasts (synoviocytes), whereas plasma cells, dendritic cells, T lymphocytes, and mast cells are found in the subsynovial layer. The composition of the synovial fluid varies, but is principally composed of neutrophils.

initiated by autoantibodies and maintained by cellular inflammatory mechanisms. In rheumatoid arthritis (RA), an unknown immunological trigger begins an inflammatory process that ultimately manifests clinically by typical signs and symptoms of disease, such as joint swelling and tenderness. Inflammation is

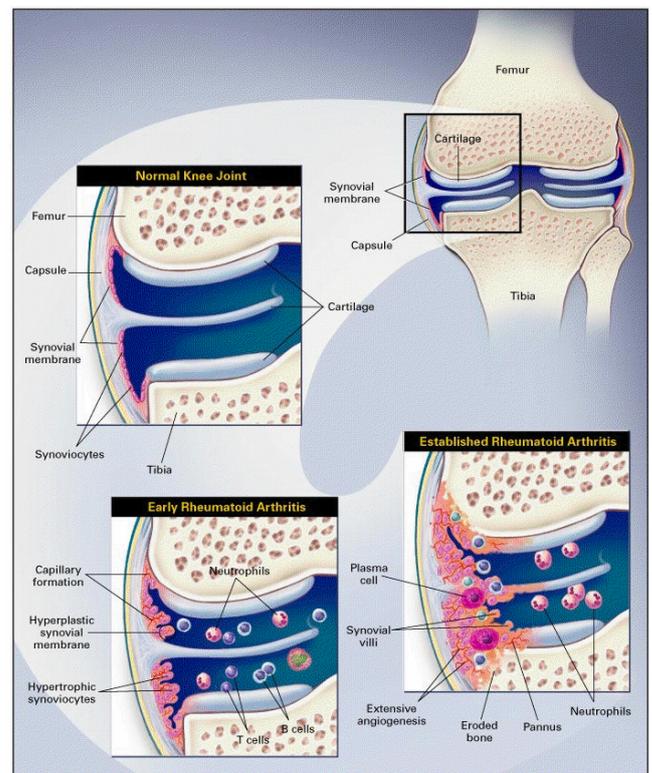


figure 1

This figure presents a schematic of normal and inflamed rheumatoid joints. A fibrous capsule encloses the joint within which the synovial membrane encloses synovial fluid in the synovial space. Cartilage covers the surface of each bone, acting to stop bones clashing and as a shock absorber. A rheumatoid joint has a very different appearance. Most obvious is the greatly

increased size of the joint. The synovial membrane, which normally is just a few cell layers thick, becomes vastly enlarged and is infiltrated with leukocytes, in particular T-cells (which direct the fate and extent of immune reactions) and macrophages (which engulf pathogens).

Source: Dr. Mesecar-Lecture 2, PHAR 408, Spring (2007)

The formation of immune complexes in the joint spaces leads to the activation of the complement system, which further leads to destructive inflammation. CD4+ T cells, B cells and monocytes-macrophages migrate into and remain in the synovial interstitium, presumably as a result of specific chemotactic stimuli and interaction of cellular adhesion molecules with counter ligands expressed on extracellular matrix molecules.^[26]

This acute inflammatory phase may be followed by delayed-type hypersensitivity (DTH) chronic inflammation, which is macrophages driven. A majority of the pro-inflammatory cytokines in the synovium are macrophage derived such as IL-1, TNF-alpha, IL-6, GM-CSF (granulocyte monocyte colony stimulating factor). According to the alternative theory (the "macrophage-fibroblast theory") of RA, the macrophages and fibroblasts seem to be responsible for creating a self-

The inflamed synovial membrane becomes a tissue described as a pannus. This structure invades the synovial space and begins to destroy the structure of the joint by degrading cartilage and inducing bone destruction.

perpetuating state of chronic inflammation in which T cell participation may no

longer be crucial. Thus the pathogenesis of RA involves interplay between immune complexes, cytokines and DTH reactions.^[14, 26]

1.1 Inflammatory mediators in RA

The rheumatoid joint contains a variety of proinflammatory cytokines besides IL-1 and TNF-alpha which include IL-6, IL-8, IL-15, IL-16, IL-17, IL-18, IFN-gamma, granulocyte macrophage-colony stimulating factor and chemokines such as IL-8, macrophage inflammatory protein-1alpha and monocyte chemoattractant protein-1. Under normal physiologic conditions, the actions of these proinflammatory cytokines are maintained in balance by anti-inflammatory cytokines, such as IL-4, IL-10, IL-11, and IL-13, and by natural cytokine antagonists, including IL-1 receptor antagonist (IL-1ra), soluble

type 2 IL-1 receptor, soluble TNF receptor (sTNF-RI), and IL-18 binding protein. In the rheumatoid joint, however, the balance swings in favor of the proinflammatory cytokines.^[8,10,26]

IL-1 and TNF-alpha have numerous functions throughout the body, many of which are important in RA. Both IL-1 and TNF activate a variety of cell types found in the rheumatoid joint, including macrophages, fibroblast-like synoviocytes, chondrocytes, and osteoclasts, resulting in the release of other proinflammatory mediators and enzymes.

TNF- α triggers production of other cytokines, induces endothelial adhesion molecules, stimulates collagenase and stromelysin and stimulates osteoclast differentiation. Hence, the blockade of TNF- α has a more global effect on inflammation than the blockade of other cytokines.^[8]

2. RHEUMATOID ARTHRITIS TREATMENT

Rheumatoid arthritis is a chronic disorder for which there is no known cure. The current goal of treatment aims toward achieving the lowest possible level of the disease activity and remission if possible, the minimization of joint damage, and

enhancing physical function and quality of life.

The management of RA was revolutionized with the advent of corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs) as the disease course could now be modified favorably. Conventional DMARDs, however, have several limitations like slow onset of action, induction of partial remission and modest 5-year retention rates.^[15]

Some drugs used include NSAIDs, Corticosteroids, DMARDs - Methotrexate, Hydroxychloroquine, Sulfasalazine, Leflunomide, Intramuscular Gold, Azathioprine, Cyclophosphamide, etc, Tumor Necrosis Factor Inhibitors – Etanercept, Adalimumab, Infliximab, T-cell Co-stimulatory Blocking agents – Abatacept, B-Cell Depleting Agents – Rituximab, Interleukin-1 Receptor Antagonist therapy – Anakinra.

A better understanding of the pathophysiology of RA has enabled scientists to develop designer drugs termed 'Biologicals' that tackle the key inflammatory cytokines like TNF- α .

'Biologicals' or 'biological response modifiers' are therapeutic agents that have the potential to inhibit the behaviour of cytokine, cellular activation, and inflammatory gene transcription by various means. These include monoclonal

antibodies, soluble cytokine receptors and natural antagonists. The first two biologicals developed for the treatment of RA were the TNF- α inhibiting agents, namely, Etanercept and Infliximab. Thereafter newer agents were developed, including Anakinra, a recombinant form of the naturally occurring IL-1 receptor antagonist, and Adalimumab, a fully human monoclonal antibody against TNF- α .

3. MONOCLONAL ANTIBODIES – “The Magic Bullets”

It has long been established that certain antibodies can be used to suppress the immune system. Recent advances in biotechnology have improved significantly on the conventional antiserums of the past. It is now possible to produce virtually unlimited quantities of specific homogeneous antibodies called "monoclonal antibodies". These antibodies have invariably added to our ability to identify and selectively bind distinct cells of the immune system, unlike the conventional antiserums which elicited non-specific responses.

As a result, monoclonal antibodies can be used to manipulate the immune system in ways that were not previously possible.

3.1 Production

The idea of using antibodies to focus therapy on cells with specific surface antigens is not new. Paul Ehrlich first conceived of the idea almost a century ago when he considered using antibodies as "magic bullets" that might be effective not only against bacterial cells but also against cancer cells. Until recently, it was impossible to achieve this goal because normal B lymphocytes, with the capacity to produce specific antibodies, would not survive long term in culture. Only malignant cells such as multiple myeloma cells could be maintained perpetually in vitro as cultured cells.

In 1975, however, George Kohler and Cesar Milstein developed techniques through which they could generate cells that possessed the specific antibody-producing characteristics of a normal lymphocyte and the "immortal" characteristics of a myeloma cell. Individual clones derived from these unique cells could survive in culture and produce large quantities of identical (monoclonal) antibodies.^[5]

First, a mouse is immunized with the antigen(s) against which a monoclonal antibody is desired. As a consequence, lymphocytes capable of producing antibodies to the antigen(s) proliferate in its spleen. The spleen cells are

subsequently removed and incubated with myeloma cells in the presence of an agent that facilitates fusion of cell membranes. Some of these cells fuse with each other, producing hybrid cells that may retain the antibody-producing capacity of the spleen cell and the immortal quality of the myeloma cell. Clones derived from such hybrid cells are referred to as "hybridomas." Selected hybridomas can then be grown in cell culture to produce monoclonal antibodies or frozen as a permanent source of specific antibody-producing cells.^[5, 6]

3.2 Advantages

Conventional antisera are heterogeneous in nature, composed of many structurally and functionally distinct antibody molecules that react with many different antigenic determinants. They are not reproducible but their composition varies depending on their source and the particular point in time when they are obtained.

In contrast, monoclonal antibodies are homogeneous, reproducible agents that can be characterized precisely and that have a highly restricted pattern of reactivity. The homogeneity and specificity of monoclonal antibodies that are produced from hybridomas makes them particularly suitable for *in vivo* administration for

therapeutic purposes. The most important advantage of monoclonal antibodies over the antiserum is the ability to produce pure antibody without a pure antigen. That is, it is possible to use a preparation containing many different antigens-such as a suspension of lymphocytes-to produce a panel of monoclonal antibodies, each of which will react with specifically one antigenic determinant.

As a result, it is possible to generate monoclonal antibodies that will identify subsets of cells that might otherwise be difficult to distinguish, such as helper or suppressor T cells, pathogenic or nonpathogenic organisms, benign or malignant cells, etc.^[5]

Clinical studies using mouse monoclonal antibodies have been disappointing because the human immune system recognizes them as 'foreign'. This results in their rapid clearance from circulation and in some cases, can lead to the induction of a severe allergic reaction to the mouse antibodies – an effect known as the human anti-mouse antibody (HAMA) response.

3.3 Chimaeric monoclonal antibodies (mAbs)

To reduce the potential for HAMA responses, the variable regions of the mouse antibody genes can be recombined

with constant regions from human antibody genes. The recombinant gene encodes a chimaeric mouse–human antibody that has antigenic specificity derived from the mouse, but is a human isotype. Hence, the resultant protein has human effector functions and fewer mouse antigenic determinants, and is therefore less likely to be immunogenic in humans. Mouse variable regions are also known to cause an immune response in humans, and chimaeric antibodies containing only mouse complementarity determining regions (CDRs) have subsequently been developed. CDRs are the region of the antibody molecule that are largely responsible for antibody–antigen binding and using only these elements rather than the full variable region of the antibody, further reduces the risk of immunogenicity. Replacing some mouse CDR sequences with human sequences aids in further humanizing antibodies; mouse residues are minimized but retained at the key binding regions, to maintain affinity.^[6,10]

One of the earliest successful applications of mAbs in therapy involved rheumatoid arthritis (RA), and this is currently the disease with the largest number of patients treated with mAbs. In RA, cytokines, which are important regulators of immune

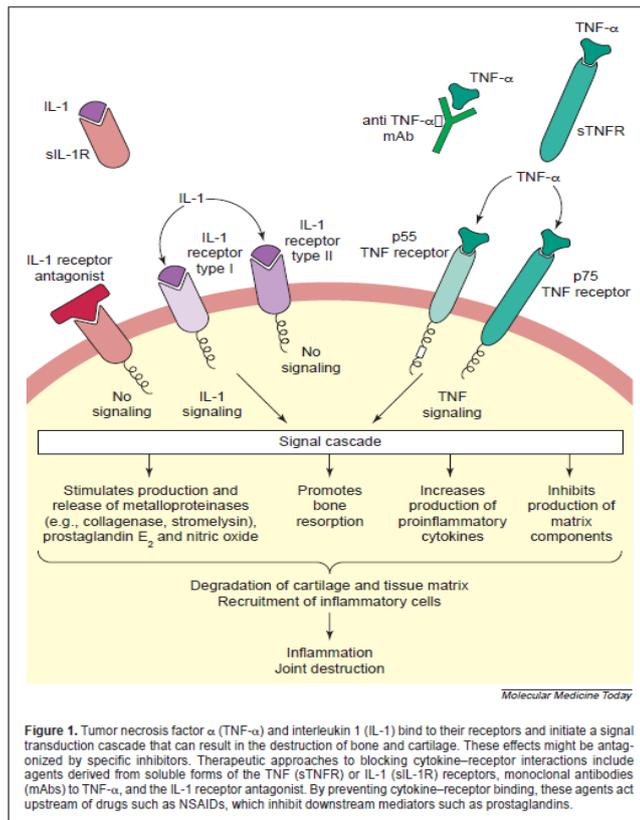
and inflammatory responses, are linked in a network or cascade with tumor necrosis factor α (TNF α) at its apex.

3.4 Mechanism of Action

Monoclonal Antibodies function as immunosuppressive agents in various autoimmune disorders. They block the pro-inflammatory cytokines released during RA. Studies in short-term cultures of rheumatoid synovial membranes demonstrated that inhibition of TNF α by anti-TNF α mAbs inhibited the production of interleukin (IL)-1, IL-6, IL-8 and GM-CSF (granulocyte macrophage colony stimulating factor) cytokines produced locally in all of the rheumatoid synovial membrane samples, regardless of the duration of disease or its treatment.

These biological-response modifiers include inhibitors of Tumor necrosis factor-alpha (TNF- α) (Adalimumab, Etanercept, and Infliximab), a recombinant inhibitor of interleukin (IL)-1 (Anakinra), a chimaeric anti-CD20 monoclonal antibody (Rituximab), and a co-stimulation blocker (Abatacept). Additional therapies for RA under current investigation include new TNF- α inhibitors, anti-IL-6-receptor monoclonal antibodies, and antibodies targeting proteins involved in B-cell function and survival.

Figure 2



Source: Carteron N. L., Cytokines In Rheumatoid Arthritis: Trials and Tribulations, *Molecular Medicine Today* (Aug 2000), Vol 6

3.4.1 Antibodies directed against TNF-alpha:

Two biological agents have been licensed for clinical use. The first is Infliximab (Remicade™), a chimaeric anti-TNF mAb comprising a human IgG1k antibody

with a mouse Fv of high affinity and neutralizing capacity. Fv is the variable fragment of an antibody molecule that specifically binds an antigen; IgG1k is an immunoglobulin of IgG1 class with a kappa light chain; and Fc is the constant fragment of the immunoglobulin molecule. The second agent is Etanercept (Enbrel™), an engineered p75 TNF receptor dimer linked to the Fc portion of human IgG1. Both agents act as competitive inhibitors of TNF binding to its receptors.

Other anti-TNF agents with proven clinical efficacy include CDP571, a humanized murine complementarity-determining region-3 engrafted mAb; D2E7 (Adalimumab), a 'human' antibody produced by phage display Celltech/Pharmacia's PEGylated (linked to polyethylene glycol) CDP870 anti-TNF antibody; and Amgen's PEGylated anti-TNF receptor antibody.

3.4.1.1 Infliximab:

Infliximab, a chimaeric (25% mouse Fv1, 75% human IgG1) monoclonal antibody, specifically binds to both membrane-bound and soluble TNF α with high affinity to form stable immune complexes. The binding of Infliximab to TNF α prevents the binding of TNF α to its receptors and blocks the initiation of the intracellular signaling that leads to gene transcription and subsequent inflammation.^[8]

3.4.1.2 Pharmacokinetics and clinical response

Therapeutic response to Infliximab correlates with the pharmacokinetics of Infliximab and basal expression of TNF α in synovial tissue. Measurements of Infliximab blood levels and TNF α expression in joints suggest that TNF α blockade at the site of production is the key to its mode of action. Infliximab given repeatedly at a high dose of 1 mg/kg was associated with a rapid loss of response and accelerated clearance from the blood. However, the synergy of Infliximab was observed when combined with MTX, which can be explained by a lowered incidence of anti-Infliximab antibodies observed with combination therapy.^[3]

3.4.1.3 Infliximab regulates the cytokine network

It was noted in one of the first trials that, following the administration of Infliximab, simultaneous reductions in CRP and IL-6 concentrations were observed in the blood. In a subsequent study, a rapid reduction in serum IL-6 concentrations in Infliximab-treated patients was observed, but not in patients receiving placebo. As CRP production by hepatocytes is regulated primarily by IL-6, this data is consistent with the conclusion that downregulation of IL-6 production in RA joints was as a result of TNF α blockade.

A reduction of IL-1 synthesis in synovial tissue by an anti-TNF α antibody *in vitro* was a crucial observation that led investigators to suspect the involvement of a cytokine cascade in RA; however, it has been difficult to verify these observations *in vivo*. Following Infliximab therapy, a reduction in serum concentration of IL-1ra (IL-1 receptor antagonist) and soluble TNF receptors has proved that two major anticytokines are regulated by TNF α . The simultaneous reduction in pro-inflammatory and anti-inflammatory molecules indicates the dominance of TNF α in the cytokine network and a probable explanation for why anti-TNF α therapy does not restore a long-lasting

remission but instead perpetuates the cytokine imbalance, and hence there is relapse of disease upon withdrawal of therapy.^[3, 21]

3.4.1.4 Infliximab regulates cell recruitment

The marked reduction in the swelling and tenderness of joints following Infliximab treatment was associated with a reduction in the cellularity of the synovium of RA patients. In a detailed analysis of serial biopsies before and after Infliximab, it was observed that a reduction in CD3+ and CD68+ cells was accompanied by a reduction in IL-8, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and E-selectin.^[3]

3.4.1.5 Infliximab regulates a major angiogenic factor (VEGF) and angiogenesis

From the early stages of disease, rheumatoid synovial inflammation is observed to be accompanied by angiogenesis. The increase in blood vessel density provides a conduit for the increased trafficking of inflammatory cells into joints. This further leads to the formation of vascular pannus tissue that invades and destroys cartilage and bone in the minimum area of the attachment of synovium to subchondral bone. The cytokine vascular endothelial growth

factor (VEGF) induces new blood vessel formation and is in higher amounts in the joints and blood of RA patients. Infliximab therapy reduces circulating VEGF levels and the density of neovasculature in the synovium.^[3]

3.4.1.6 Infliximab prevents cartilage catabolism and bone erosion

Infliximab was seen to preserve of chondrocytes and cartilage matrix. The lack of pannus invasion of the bone was a notable feature in response to treatment with Infliximab. In RA patients, protection of cartilage and bone was observed — possibly with healing — as judged by comparison of baseline and 54-week radiographs of hands and feet in patients treated with Infliximab. This finding supports the conclusion that mechanisms of tissue destruction in RA are TNF α -dependent. A reduction in matrix metalloproteinases following Infliximab treatment has been documented and this implies that this therapy induces a downregulation of matrix-degrading enzymes.^[3]

3.4.1.7 Adverse Effects (of anti-TNF therapy):

TNF antagonists are generally safe; however, there have been concerns over increased risks of acute infusion-related reactions, lymphoma, delayed

hypersensitivity reactions, atypical and opportunistic infections. From a public health standpoint, the development of active Tuberculosis in some patients who received TNF-alpha inhibitor therapy is a matter of serious concern. Clinicians should be vigilant for tuberculosis (or its latent form) in patients being treated with TNF antagonists because tuberculosis often presents itself as an extrapulmonary or disseminated disease.^[4, 11, 24]

Therefore, before beginning therapy, the patient must be assessed for the presence of tuberculosis in its latent form. The patient is asked to start anti-TB drugs while undergoing Infliximab treatment.

The frequency of non-lymphoid malignancies in patients who have participated in anti-TNF α studies is similar to the expected frequency in the age-matched population, as assessed by using Cancer databases. Similarly, although cases of lymphoma have been reported in long term follow-up studies of Infliximab-treated RA patients, the observed incidence appears to be within the expected range. However, longer-term follow-up of a larger number of patients is required before it is possible to definitively exclude (or confirm) any association.^[12, 16]

3.4.2 Antibodies directed against other cytokines:

IL-1 is another pro-inflammatory cytokine abundantly expressed in RA synovium. It stimulates resorption of cartilage and bone through activation of osteoclasts and inhibits synthesis of proteoglycan and articular collagen. IL-1 blockade has been established with daily, subcutaneous administration of IL-1 receptor antagonist (Anakinra, KineretTM), a naturally occurring inhibitor of IL-1.

Anakinra (Kinaret) is a recombinant form of IL-1Ra that competes with IL-1 for binding to cell surface-bound IL-1 receptor, but does not induce intracellular signaling. A significant drawback is its short half-life (6 hours) in plasma, which necessitates daily treatment with high doses required to maintain a significant therapeutic effect. The combination of Anakinra and Methotrexate is well-tolerated and provides significantly greater clinical benefit than Methotrexate alone.

[10, 11]

IL-6, stimulated by TNF-alpha and IL-1, present in fair amounts in the synovial fluid, regulates the production of acute phase proteins by hepatocytes, and activates bone absorption by osteoclasts. The therapeutic potential of a humanized anti-IL-6 receptor mAb is currently being assessed in randomized trials in Europe and Japan. The response onset time seems

to be longer than that for TNF blockade, with diarrhoea being one of the most commonly reported side effects.^[11]

Its receptor, the IL-6Ra chain, employs an accessory molecule, gp130, for signal transduction and cell activation. Gp130 can be activated by both the transmembrane IL-6Ra and its soluble form via trans-signaling. Employment of a humanized antibody to the IL-6Ra chain targets both the membrane-bound and the soluble IL-6Ra. Moreover, monotherapy with Tocilizumab had good inhibitory effects on progression of joint destruction. Interestingly, IL-6 inhibition with Tocilizumab is also highly efficacious in the treatment of systemic-onset juvenile arthritis. Tocilizumab might become approved in Europe in the near future.^[14]

Other potential cytokine targets for antibody-based biological therapies in RA include IL-8, IL-15, IL-17 and IL-18, and the results of clinical trials are awaited.

3.4.3 Antibodies directed against inflammatory cells:

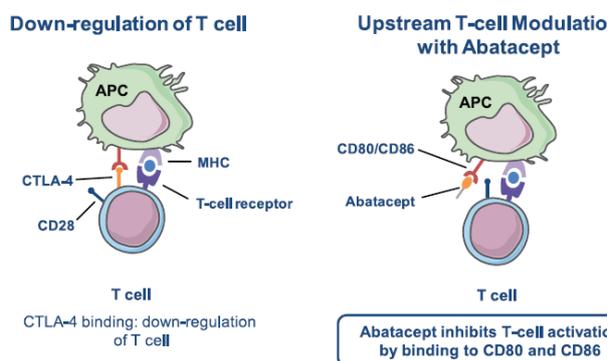
3.4.3.1 Targeting T cells

Inhibition of T cell activation with a co-stimulation inhibitor, Abatacept, consisting of cytotoxic T lymphocyte antigen-4 (CTLA-4) fused to an Fc portion of an immunoglobulin G molecule (CTLA-4-Ig) is also an effective and approved

treatment option for RA. This molecule binds to the co-stimulatory molecules CD80 and CD86 on Antigen Presenting Cells and thus prevents their interaction with their receptor on T cells, CD28, thereby interfering with T cell activation.^[7,13]

Based on their patterns of expression during the immune response, it appears that CD86 is the primary co-stimulatory ligand involved in early T-cell activation, whereas CD80 is the functionally predominant co-stimulatory ligand in established responses. In chronic RA, CD80-specific inhibitors would be the preferred agents, leaving primary T-cell responses to recently encountered foreign pathogens relatively unaffected. This suggests that there might be advantages in CD80 monotherapy or selective blockade of CD80 for the treatment of established RA.^[14]

Figure 3



Source: Solomon G. E., T-Cell Agents in the Treatment of Rheumatoid Arthritis, *Bulletin of NYU Hospital for Joint Diseases* (2010), Vol 68, Issue 3, 162-5

Safety: The safety profile of Abatacept is reassuring with low rates of both serious adverse events and major infections. In the 2-year extension data from conducted trials, the rates of significant adverse events was similar to the rates seen in the placebo group and fell well within the ranges reported for patients receiving anti-TNF therapies.^[7]

3.4.3.2 Targeting B cells

The potential of **B lymphocyte depletion** as an approach to therapy is under investigation using an anti-CD20 mAb, Rituximab. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids with a molecular weight of 145 kD. An improved clinical response was observed in the combination therapy groups.

Mechanism of action of Rituximab: It may be acting by eliminating circulating B cells. B cells are very efficient antigen-presenting cells, particularly after they have been activated. Thus loss of B-cells would result in less stimulation of T-cells and also lesser production of autoantibodies.^[9]

4. Conclusion

Where do we stand today?

Currently, we can achieve stringent remissions of symptoms, i.e., no evidence of active disease. However, cure is not yet in sight. Although cure will ultimately require knowing the cause of this disorder, interference with the vicious cycle of the inflammatory occurrences in the very early stages of the disease process may reverse the events usually destined to become chronic in predisposed individuals. Such a window of opportunity is addressed by currently ongoing clinical trials, and it is yet to be seen if this supposition can be realized.

The future of Biological Response Modifiers (BRMs)

BRMs hold the promise of providing both important clinical benefits and key insights into the pathophysiology of RA. Because BRMs target one specific molecule, they might be less likely to cause the adverse effects associated with older DMARDs, which typically interact with multiple receptors. Many of the most effective DMARDs, including Methotrexate, Leflunomide, gold, and Penicillamine, can cause severe, sometimes irreversible, toxic effects. Most non-steroidal anti-inflammatory drugs (NSAIDs) can result in significant gastrointestinal toxicity, abdominal pain, nausea, indigestion and ulcers. Corticosteroids, such as prednisone, are highly effective at relieving pain but

can cause weight gain, and, in some patients, can contribute to the development of osteoporosis. The favorable safety profiles of some BRMs might make them well-suited for early RA therapy.

The high cost of these antibodies may be a prohibitive factor. The cost varies from around Rs 50,000 to around a lakh rupees, depending on which mAb is under consideration. So, in spite of its effectiveness in immunosuppression and remission of the symptoms of RA, with relatively less toxicity than most DMARDs, it is definitely not within the reach of the common man.

It is therefore suggested that the government take steps to subsidize the cost of these mAbs so that the drug will be a more accessible to the public at affordable rates. With advances in technology, newer methods can be developed, which can bring down the cost of production of mAbs, while possibly enhancing its effectiveness and duration of action.

A complete understanding of the pathophysiology of RA could fuel the search for more and better treatments or even, perhaps, a vaccine or other 'cure.'

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Pharmacochemical Nano-switches



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Final Year B.Pharmacy

Abstract

Hydrazones undergo a configurational and/or conformational changes on sequential addition of acid and base. This gives an on/off switching function to the molecule. Also dual-controlled nanoparticles exhibiting AND logic can act as a switch. Spectroscopy like ^1H NMR is used to study the working and action of these molecules. Such chemical molecular switches help in attaining even more sophisticated levels of controlled release and site targeted drug delivery.

Keywords : Nano-switches, hydrazones, pH, nanoimpellers, nanovalves.

1. Introduction

The name “Pharmacochemical Nano-switches” suggests;

Pharmaco - Related to drugs, Chemical
- Chemically operated, Nano - Of nano size

Switches – serves an on/off function.

(Here, it gives output when turned on i.e. release of drug when required and no release on turning off, when the drug is not required.)

Pharmacochemical nano-switches are nanoparticles in which the drug is incorporated or to which the drug is

attached and they are chemically operated through a stimulus, for example pH, to release the drug whenever and wherever required and kept intact with no release when not required. Hydrazone based switches are one such example which are controlled by acid/base modulations¹. And with the help of this prototype, a new switch QPH-E (hydrazone-based rotary switch with quinolinyl stator and pyridine ring as a part of rotar)² is discussed with the aim of chemically controlling both the configuration and conformation of a single molecule. Also dual-controlled

nanoparticles which show AND logic can be employed to serve this function³.

2.The Need

a) To by-pass first pass metabolism in the liver.

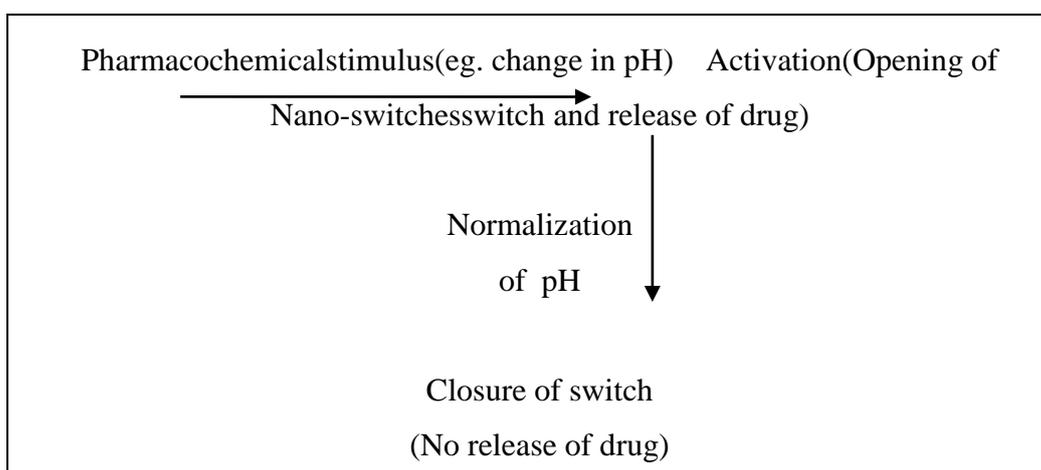
b) To provide site targeted delivery of drugs without affecting healthy cells/tissues of the body.

c) To prevent systemic toxicities and side-effects with local and systemic tolerance.

d) As a substitute for surgery in certain cases.

3.Working

The working of Pharmacochemical Nano-switches can be explained as follows;



To understand the working of ‘Pharmacochemical Nano-switches’, the following examples are considered.

3.1 A pH Activated Configurational Rotary Switch: Controlling the E/Z Isomerization in Hydrazones

Hydrazones are very easy to synthesize, starting from corresponding ketone and azeridine.

1,2,3-Tricarbonyl-2-arylhydrazones⁴ exist in solution as a pair of intramolecularly

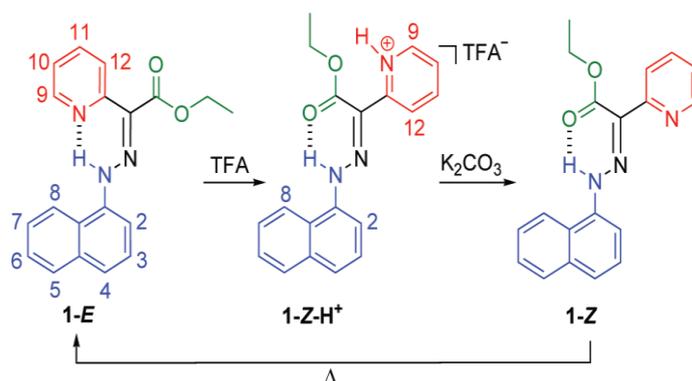
H-bonded hydrazone isomers^{5,6a} that can equilibrate in the presence of catalytic amounts of acid or base^{6b}.

This process results in the exchange of the relative positions of the substituents around the C=N bond i.e., E/Z isomerization. This original bistable system is based on a hydrazone

building block, and pH^7 is used to control the configuration around the $\text{C}=\text{N}$ bond. It was observed that replacing one of the carbonyl groups in 1,2,3-tricarbonyl-2-arylhydrazones with a “proton acceptor” group such as pyridine will lead to a system that can be converted fully, effectively and controllably from one isomer to the other by the consecutive addition of acid and base. In order to add another element of nonsymmetry into the system

it was decided to use a naphthylhydrazone derivative for the studies. This line of thought led to compound **1-E** that upon protonation affords **1-Z-H⁺**, which when treated with base yields the “metastable” **1-Z** configuration that thermally equilibrates back to **1-E**.⁸ (See Figure 1).

Figure 1 : Acid/ Base controlled E/Z isomerization of 1-E.



3.1.1 Characterization for suitability study

The ^1H NMR spectrum of **1-E** in CD_3CN shows a characteristic H-bonded N-H resonance at 15.8 ppm, in addition to the expected aromatic and aliphatic signals. Initially the E:Z ratio in the solution is 97:3⁹. The addition of 1.4 equiv of $\text{CF}_3\text{CO}_2\text{H}$ (TFA) to a CD_3CN solution of **1-E** results in the

protonation of the pyridine subunit¹⁰, which is accompanied by a color change of the solution from light yellow to orange and drastic changes in the ^1H NMR spectrum. First of all, the N-H proton signal at 15.8 ppm disappears and a new signal appears at 13.9 ppm. This shift indicates that a rotation around the $\text{C}=\text{N}$ bond has occurred (E/Z isomerization) and that the N-H proton is now H-bonded to the

carbonyl group of the ester subunit, yielding **1-Z-H⁺**. The ¹H NMR spectrum of **1-Z-H⁺** shows the presence of a large and broad signal at 4.1 ppm, presumably resulting from excess TFA. Upon passing the CD₃CN solution of **1-Z-H⁺** over a plug of K₂CO₃ or the addition of 1.4 equiv of triethylamine

(Et₃N), the color of the solution changes back to light yellow. The ¹H NMR spectrum, immediately after passing the solution over K₂CO₃, shows the complete disappearance of **1-Z-H⁺** and the presence of both **1-E** and **1-Z** in solution respectively. Interestingly, the signals of **1-Z** gradually decrease with time and those of the **1-E** configuration grow in return¹¹. This process is the thermal equilibration between the “metastable” configuration and the stable one, **1-Z** and **1-E**, respectively. This process comes to completion within 2 h at RT, and the system regains its original equilibrium ratio of 97:3. Thus we have a conceptually new type of chemically induced rotary switch using a hydrazone building block.

3.2 Switching Around Two Axes : Controlling the Configuration and

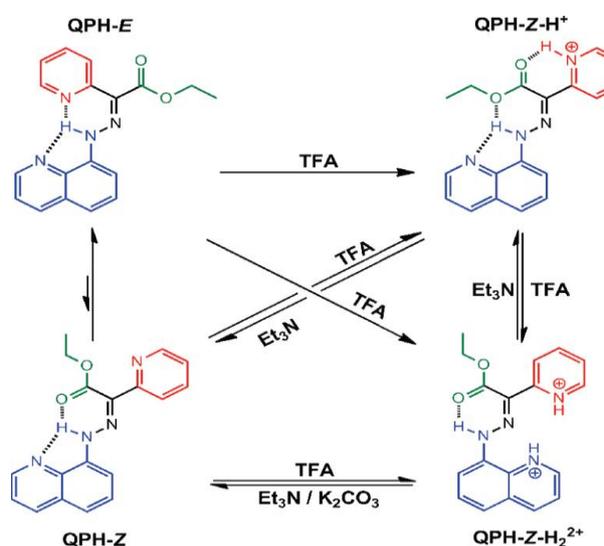
Conformation of a Hydrazone-Based Switch

Previously it is observed how the configuration of a hydrazone-based switch¹² can be controlled by acid/base modulations. Inspired by this prototype, a new switch **QPH-E** (hydrazone-based rotary switch with quinolinyl stator and pyridine ring as a part of rotar) is designed with the aim of chemically controlling both the configuration and conformation of a single molecule. The protonation of **QPH-E** by trifluoroacetic acid (TFA) leads to **QPH-Z-H⁺**, accompanied by a configurational change originating from the rotation about the C=N double bond¹³. Further protonation leads to rotation about the C-N single bond, generating a new conformational isomer, **QPH-Z-H₂²⁺**, that retains the Z configuration. After deprotonation with triethylamine (Et₃N), both **QPH-Z-H⁺** and **QPH-Z-H₂²⁺** convert into a neutral metastable species **QPH-Z**, which eventually equilibrates to give back the thermodynamically more stable **QPH-E** isomer. The configuration and conformation of the system can be modulated based on the sequence at which the acid and base are added, leading to a switch that can be prompted to rotate around two

different axes (See Figure 2). This has been validated using ^1H NMR and UV-visible spectroscopy.

Hydrazone QPH was also synthesized easily by the coupling of the diazonium salt derived from 8-aminoquinoline with ethyl-2-pyridylacetate.

Figure 2: Schematic Illustration of the Switching Process.



3.3 Dual-Controlled Nanoparticles Exhibiting AND Logic

Here, dual-controlled nanoparticles (DCNPs) are discussed in which two different types of machines, namely, nanoimpellers¹⁴ and nanovalves¹⁵, are brought together in and around mesoporous silica nanoparticles supports¹⁶. The molecular machines are designed to operate in tandem with one

another in such a way that the DCNP systems function as AND logic gates and provide sophisticated control of the contents of the pores. In the DCNP systems discussed here, light-responsive nanoimpellers¹⁷ and pH-responsive^{18a,b} nanovalves are operated in tandem with one another in such a way that the release of encapsulated guest molecules (the output) requires activation of both the nanoimpellers using 448 nm light (input 1) and the nanovalves using pH changes (input 2). Two different pH responsive nanovalve systems have been employed in this work, resulting in the formation of two different DCNPs: DCNP-1, which employs base-responsive nanovalves, and DCNP-2, which features acid-responsive nanovalves. Nanoimpellers are based on photoresponsive azobenzene derivatives that are tethered to the inner pore walls of the mesoporous silica nanoparticles supports. Azobenzene exists in two configurations (trans and cis) and can be interconverted between the two upon absorption of light. When azobenzene derivatives attached to the nanopore interiors are exposed to a wavelength of light that is absorbed by both the trans and cis isomers, a dynamic wagging motion¹⁹, which can be used to impel unbound guest

molecules out of the nanopores, is generated within these derivatives. On the other hand, the nanovalves employed here^{20,21} are based on pH-switchable [2]pseudorotaxanes in which cucurbit[6]uril(CB[6]) rings encircle bisammonium stalks that are tethered to the outer surfaces of the nanoparticles supports. The base-responsive nanovalves used in DCNP-1 consist of CB [6] /bisalkylammonium [2]pseudorotaxanes. At neutral pH, the bulky CB [6] rings interact tightly with the tethered stalks through ion-dipole interactions, blocking the nanopore orifices and trapping the guest molecules. When the pH is increased and the stalks become deprotonated, the binding interactions are disrupted, and the CB [6] rings dissociate from the stalks, thereby opening the nanovalves and allowing the contents to be released. The acid-responsive nanovalves used in DCNP-2 consist of bi-stable CB[6]/trisammonium pseudorotaxanes. At neutral pH, the anilinium nitrogen atom remains unprotonated and the CB[6] ring resides on the tetramethylenediammonium recognition unit close to the nanopore orifices. When the pH is decreased and the anilinium nitrogen atom becomes protonated, the CB [6] ring shuttles to the more distal

hexamethylenediammonium recognition unit, and the nanovalves are opened.

Mesoporous silica is an ideal support for synthetic molecular machines because it is optically transparent (allowing for activation by light and spectroscopic monitoring) and relatively easy to functionalize on both the insides of the pores and the outer surface²².

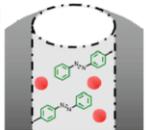
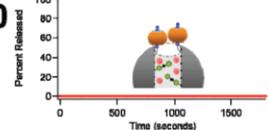
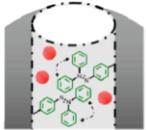
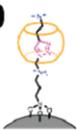
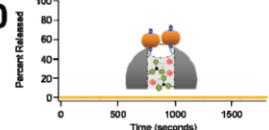
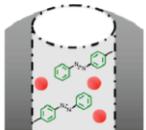
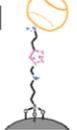
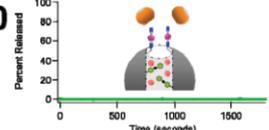
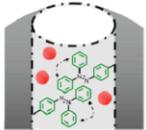
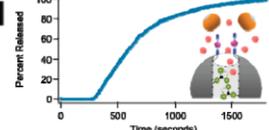
3.3.1 Testing the operation of dual-controlled systems

In order to test the operation of the dual-controlled systems, the DCNPs were loaded with the fluorescent probe ClRe-(CO)₃-2,2'-bipyridine as the guest molecules and luminescence spectroscopy was used to follow their fate. For the nanoimpellers, a 36 mW, 448 nm excitation beam was directed at the nanoparticles and used to activate the dynamic wagging of the azobenzenes. The nanovalves were opened by adjusting the pH appropriately. For DCNP-1, the solution was adjusted to pH 10 by the addition of 2 M NaOH (See Table 1), and for DCNP-2, the solution was adjusted to pH 4 by the addition of 0.01 M HCl. The release of ClRe(CO)₃-2,2'-bipyridine required activation of both the nanoimpellers

and the nanovalves. When light or pH activation alone was used, activating just one machine, the unactivated machine was able to keep guest molecules constrained, and no release of guest molecules occurred.

Only when both controlled release mechanisms were activated simultaneously, the release was observed.

Table 1: Truth table for an AND gate based on DCNP-1.

Input 1 (448 nm Light)	Input 2 (Base)	Output (Release of Guest)
0 	0 	0 
1 	0 	0 
0 	1 	0 
1 	1 	1 

4. Formulation

The Pharmacochemical nano-switches can be formulated as tablets or capsules on using suitable excipients or can also be administered parenterally by formulating suitable injectable solutions or suspensions.

5. Disease conditions and pH

The Pharmacochemical nano-switches can be implemented to provide site targeted drug delivery in disease conditions which are characterized by a distinct pH value. Few of its applications are discussed as follows.

5.1The chemotherapy used in treatment of cancer has serious side-effects. The drugs like Melphalan are mutagenic and can cause leukemia. Its oral absorption

is erratic and intravenous formulation has higher risk of side-effects. Such drugs can be given through the pharmacochemical nano-switches. The pH is on an average lower in the tumor mass than normal tissue. Most of the solid tumors have lower extracellular pH (6.5) than the surrounding tissues (pH 7.5). The pH is compartmentalized in tumor tissue into an intracellular component (pHi), which is similar in tumor and normal tissue and an extracellular component (pHe), which is relatively acidic in tumors²³. This acidic nature of the tumors would cause the release of the drug from the Pharmacochemical nano-switches and this switch would be turned off giving no release of drug at the site of normal healthy cells.

5.2 Aneurysm occurs in the arteries as a result of deposition of lipids, cholesterol etc which form a plaque thus narrowing the lumen of the artery. Mainly it occurs in the abdominal artery. Presently aneurysm is treated through surgery where a by-pass is done or the area where the plaque is formed is cut and removed and the artery is again stitched. The Pharmacochemical nano-switches can be used here as a substitute for surgery. Drugs that would dissolve the

plaque can be incorporated within these switches and they would release the drug at plaqued area. If the plaqued region of the artery has a different pH than the surrounding area it would help to activate the switch. The switch would turn off on dissolution of the plaque. Also they can be used to treat atherosclerotic plaque in similar manner.

5.3 Also anti-ulcer drugs can be administered through these switches to reduce their adverse effect on gastric acid secretion²⁴.

5.4 The most simple application of Pharmacochemical nano-switches is in treatment of acidity. The pH of the stomach decreases in hyperacidity. The very simple use of the Pharmacochemical nano-switches can be observed over here. Antacid agents can be given through these switches which would be turned on in the acidic pH of the stomach to release the antacid and as soon as the acidity is lowered the switch would turn off.

5.5 Also if a pH change is detected in the beta cells of islets of langerhans²⁵ during entry of glucose the Pharmacochemical nano-switches can be implemented here to give release of insulin to treat diabetes.

6. Advantages

- 1)The Pharmacochemical nano-switches provide a new mode of drug delivery.
- 2)The side-effects and the foreign body reactions may be prevented with local and systemic tolerance.
- 3)Being nanoparticles the Pharmacochemical nano-switches do not give anaphylactic reactions.
- 4)Provide a new way of efficient targeted drug delivery and controlled release.
- 5)Their synthesis is also not very complicated.

7. Conclusion

There are various modes of targeted drug delivery systems. Also certain new modes are under research. The Pharmacochemical nano-switches is one of the new ways to achieve targeted drug delivery. They rely on the pH of the surrounding environment to give their action. These Pharmacochemical nano-switches can help in attaining even more sophisticated levels of controlled release. They can be synthesized as per the requirement without much efforts and the drug can be incorporated with it. They provide efficient drug action at the desired site with minimized side effects.

Acknowledgement

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8) No change was observed in ^1H NMR spectrum of 1-E upon the addition of 1.0 equiv of Et_3N or K_2CO_3 to the solution. Upon the addition of 0.1 equiv of acid (TFA) only the appropriate amount of isomerization occurred. This rules out the catalytic equilibration process observed in other 1,2,3-tricarbonyl-2-arylhydrazone systems.

9) This isomer ratio remained constant even after heating the solution at 55°C for 1 h.

10) The addition of 1.4 equiv of TFA yields 98% pyridine protonation. For full protonation 2.0 equiv were required. Only 1.0 equiv of TFA was needed to fully protonate the starting material, ethyl-2-pyridylacetate. The H-bonding with the N-H proton and the conjugation with the aromatic system apparently decrease the basicity of pyridine nitrogen in 1-E. Subsequently when $\text{CH}_3\text{SO}_3\text{H}$ was used as the acid, only 1.0 equiv was needed to fully protonate the pyridine subunit.

11) When Et_3N was added to the solution, the fully equilibrated spectrum was generated instantaneously and this process was not observed. The reason for this might be the larger contact time the solution has with Et_3N .

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SINGLE MOLECULE STUDIES OF DNA BINDING PROTEINS AND FOLDING OF RNase H PROTEINS USING OPTICAL TWEEZERS



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A Sneak Preview :

Optical tweezers were invented in the mid-1980s by Arthur Ashkin and co-workers at the Bell Telephone Laboratories¹⁸. Since then there has been a steady stream of developments and applications, particularly in the biological field. In the last five years, work using optical tweezers has increased significantly and they are becoming a mainstream tool within biological and nanotechnological fields. It is twenty years since Ashkin et al.¹ published their seminal paper ‘Observation of a single-beam gradient force optical trap for dielectric particles’. The technique is now referred to as ‘optical tweezers’ or ‘optical trapping’ and their original paper has received 400 citations—half of these during the last five years. In essence, optical tweezers rely upon the extremely high gradient in the electric field produced near the waist of a tightly focused laser

beam, creating a force sufficient to trap micron-sized dielectric particles in three dimensions. Commercial tweezers systems are now available, and although originally devised by physicists, it is mainly biologists who put optical tweezers to use. Optical tweezers can trap objects in the nanometer to micrometer size range, and manipulate trapped objects with sub-nanometer accuracy³ although nanometer resolution is more typical. More importantly, optical tweezers are compatible with various types of light microscopy, such as bright field, differential interference contrast, phase contrast and fluorescence⁴. These features have allowed optical tweezers to become one of the most successful single-molecule techniques used in biological science.

Initially, optical tweezers were applied to the single-molecule investigation of cytoskeletal motor proteins^{5, 6}. Recent

advances have made it possible to study DNA binding proteins at the single-protein level. This important group of proteins includes those which affect conformational changes in nucleic acids, as well as energy-fueled molecular motors. In this review, the principle of the optical trap is explained briefly. Then, the application of optical tweezers to the study of DNA binding proteins is presented.

However, technology does not stand still and tweezing techniques are presently undergoing a further spate of development leading to new possible applications. Recently, the study of proteins acting on DNA was aggressively undertaken at the single-molecule level. This paper gives a review of a most recent application of optical tweezers which has revealed the dynamic behavior of folding process of *Escherichia coli* ribonuclease H RNaseH protein [Cecconi et al. *Science* 309, 2057 (2005)] and also the single molecule studies of DNA binding proteins.

The Principle Behind Optical Tweezers:

The Basics

What is it? Optical Tweezers use light to manipulate microscopic objects as small as a single atom². The radiation pressure from a focused laser beam is able to trap small particles. In the biological sciences, these

instruments have been used to apply forces in the pN-range and to measure displacements in the nm range of objects ranging in size from 10 nm to over 100 nm.

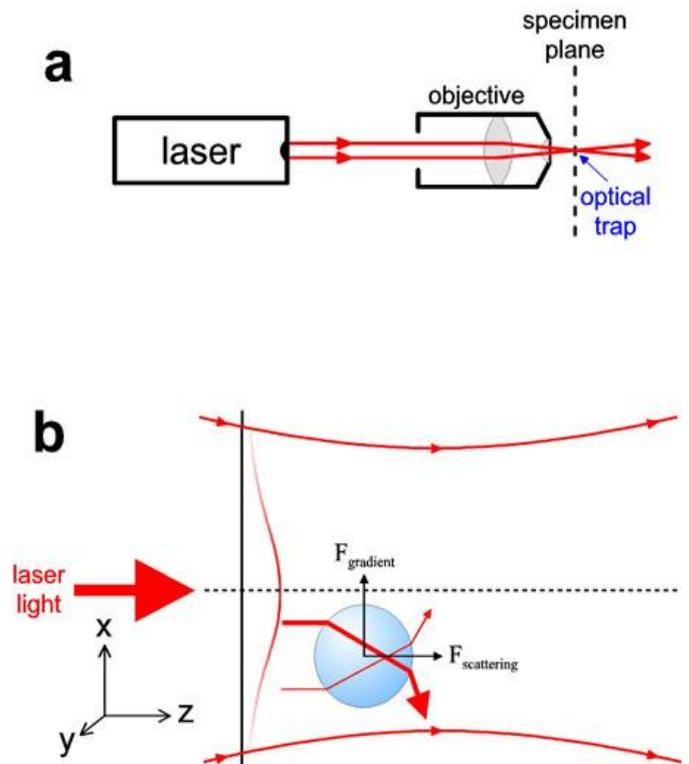


Figure 1. Optical Tweezers principles.

How does it work? The most basic form of an optical trap is diagramed in Fig 1a. A laser beam is focused by a high-quality microscope objective to a spot in the specimen plane². This spot creates an "optical trap" which is able to hold a small particle at its center. The forces felt by this particle consist of the light scattering and gradient forces due to the interaction of the particle with the light (Fig 1b, see Details).

Most frequently, optical tweezers are built by modifying a standard optical microscope. These instruments have evolved from simple tools to manipulate micron-sized objects to sophisticated devices under computer-control that can measure displacements and forces with high precision and accuracy.

Applications

Optical Tweezers have been used to trap dielectric spheres, viruses, bacteria, living cells, organelles, small metal particles, and even strands of DNA. Applications include confinement and organization (e.g. for cell sorting), tracking of movement (e.g. of bacteria), application and measurement of small forces, and altering of larger structures (such as cell membranes). Two of the main uses for optical traps have been the study of molecular motors and the physical properties of DNA. In both areas, a biological specimen is biochemically attached to a micron-sized glass or polystyrene bead that is then trapped.

The ability to trap and manipulate small objects, such as polystyrene beads, results from light possessing momentum which is in the direction of propagation of the beam (Fig. 2). When the direction of light is altered by a particle *via* reflection or refraction, a corresponding change in

momentum occurs. The law of conservation of momentum requires that the bead must undergo an equal and opposite momentum change, giving rise to forces acting on the particle.

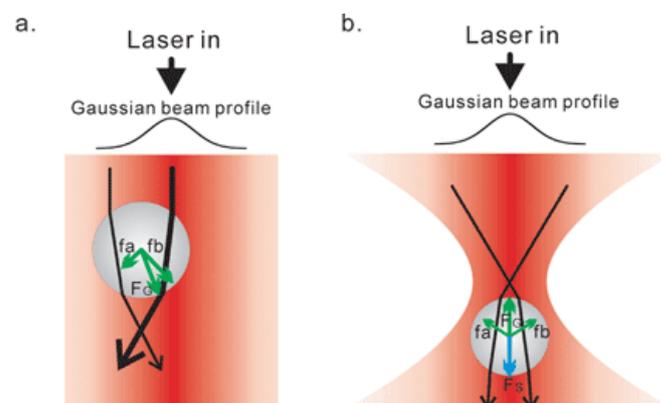


Fig. 2 Schematics showing the principle of optical tweezers based on ray optics. The representative laser paths are shown as black lines with arrows indicating the direction of beam propagation. The thickness of the black lines indicates the intensity of laser beam. The forces are shown as green and blue lines with arrows indicating the direction of forces. For detailed description refer to ref.4

Small particles (ranging in size from 10 nm to 10 μ m in diameter) experience two types of forces near the focus which results in their stable three-dimensional trapping. Scattering forces arise from reflection of light at the surface of the particle, pushing the particles along the path of the laser beam in the direction of propagation of the light. In opposition to these, gradient forces tend to draw particles towards the center of the trap, thereby preventing their escape. Once the gradient forces dominate,

a stable three-dimensional trap results. Schematics showing these forces are presented in Fig. 2 and the reader is referred to ref. 4 for a more detailed description.

Science behind the Invention:

Over thirty years ago, Ashkin started experimenting with optical beams to manipulate objects¹⁸. He realized that an unfocused laser beam draws objects of high refractive index towards the centre of the beam and propels them in the direction of propagation. An arrangement of two counter-propagating beams allowed objects to be trapped in three dimensions. These experiments allowed him to observe the effects of radiation pressure and overcome the usually much larger radiometric (heating) effects of light by using relatively transparent objects in a transparent medium. He later discovered that a single, tightly focused, laser beam could be used to capture small dielectric particles in three dimensions. This technique enables small particles to be picked up and moved at will using a beam of visible light; hence the effect was christened optical tweezers. Forces acting within optical tweezers are understood either in terms of light momentum and ray optics or the force associated with the gradient in the optical electric field. For

particles larger than the wavelength of the trapping light, ray optics analysis of the deviated light path gives the change in momentum flow and hence the reaction force acting on the object. For particles smaller than the wavelength, the ray optical approach is less satisfactory and it is better to consider the forces in terms of the electric field near the trapped particle. Forces can then be divided into those arising either from scattering of light or those arising from an intensity gradient. For particles of higher refractive index than the bathing medium (e.g. glass or polystyrene microspheres or bacteria in water), the gradient forces dominate and particles are drawn to the focal spot of a laser beam. For particles of low refractive index or strongly scattering material (air bubbles in water or metal particles), the gradient force is reversed and more complex beam arrangements are required if trapping is to be maintained (e.g. an annular beam).

1. Single molecule studies of DNA binding proteins using Optical Tweezers

1.1 Application to biological motors

The first biological motors studied at the single-molecule level with optical tweezers were cytoskeletal motor proteins²⁰. These motor proteins (i.e.,

myosin, kinesin and dynein) generate mechanical force to move along protein tracks (for example, actin filaments and microtubules), using energy liberated from the hydrolysis of ATP. Force generation allows these motor proteins to engage in work inside cells, including that required to perform chromosome segregation, vesicle transport and muscle contraction. Using optical tweezers, precise measurement of the fundamental step size and maximum force generated by single molecules of these motor protein molecules has been achieved (for example, the step size and maximum force are 8 nm and 6 pN for kinesin, respectively).

For these studies, the optical tweezers were used to manipulate individual motor protein molecules via direct attachment to micrometre-sized polystyrene beads. The purpose of the beads is two-fold. First, they are used to deliver the motor to its tracks. Second, they are used to monitor the position of the bead attached motor proteins most recently with an accuracy of 0.1 nm, far beyond the diffraction limit of light. To track bead movement, the bright-field image of the bead is projected onto a photodetector, such as a quadrant photodiode or position sensitive detector, and the change in position of the image is measured

(i.e., nanometry). Alternatively, the interference pattern of the bead can be projected onto a photodetector, where the change in the pattern is converted to a position signal to monitor bead movement (i.e., interferometry). Furthermore, and simultaneously, the measured displacement in each case can be converted to force exerted by the motor protein. As an application, a sensitive feedback system is being used to measure the position of a molecular motor under a constant load. When the bead attached to the molecular motor pulls with a force greater than a preset level, the position of the optical trap is moved to decrease the force. The error signal generated gives the position of the molecular motor²¹.

1.1.1 Nucleic-acid polymerases

This family of DNA motor proteins plays essential roles in the life of an organism. While translocating along a DNA template (that is, a DNA track), DNA polymerases faithfully replicate DNA while RNA polymerases faithfully transcribe DNA into RNA. RNA polymerase (RNAP) is a highly processive motor, translocating thousands of base pairs without detaching from the DNA template. The energy used to drive RNAP translocation comes from

the nucleoside triphosphate addition to the 3'-end of the nascent RNA molecule. During translocation, RNAP must accurately read the sequence of the template strand and transcribe mRNA that is subsequently translated into protein. Transcription occurs with high fidelity, and by comparison to DNA polymerase, must include a proofreading mechanism, as suggested by bulk-phase studies²². During proofreading, the enzyme would be expected to transiently pause and possibly even backtrack to allow removal of misincorporated bases.

To provide detailed insight into transcription fidelity, a series of studies were done using initially, the single-trap coverslip configuration and subsequently, the dual trap configuration to minimize noise (Fig. 2). The results revealed that the translocation velocity varied significantly between individual RNAP molecules. Second, for individual polymerase molecules, translocation was non-uniform, as traces of individual enzymes exhibited periods of constant velocity interspersed with several pauses of various duration. The pauses were classified based on their duration. Longer pauses had lifetimes greater than 20 seconds.¹¹ They were distributed uniformly, occurring on average once every 1000 bp transcribed. Importantly, individual RNAP molecules

were demonstrated to be capable of backtracking a distance of approximately 5 bp consistent with anticipated proofreading. In order to test whether backtracking was coupled to proofreading, GreA and GreB were added to the reaction. These proteins are transcription elongation factors which induce cleavage of nascent RNA. After backtracking, by cleaving the nascent RNA still bound to RNAP, the end of the RNA where transcription should be reinitiated is repositioned closer to the active site. This would be expected to enhance the rate of reinitiation and be observed as an overall decrease in pause duration. Consequently, in the presence of GreA and GreB, both the frequency and the duration of pauses were found to decrease. Therefore, the observed backtracking is consistent with a proofreading mechanism, which consists of rearward movement followed by nucleolysis of RNA. The second class of pauses was shortlived, with a duration of 25 seconds or less, occurring with a frequency of γ 10 events every 1000 bp. These constituted > 95% of the pauses observed, with duration and frequency unaffected by load applied to the enzyme by the optical tweezers, from 237 to +27 pN (negative and positive values indicates hindering and assisting force for

translocation, respectively). This is in contrast to the long-lived pauses described above, where frequency decreased from 1 event to 0.03 events every 1000 bp under load of +8 pN. The independence of the duration from load showed that motion accompanying the short pauses was as small as 0.06 bp, hence the short-lived pauses do not correspond to backtracking motion. Instead, the short-lived pause is a transient state, which could potentially precede long-lived pauses.

Most recently, the individual steps taken by RNAP during transcription were

observed. The study demonstrated that RNAP advances predominantly in 3.7 Å (0.37 nm) increments along DNA. The distance of 3.7 Å is similar to that of one base pair in B-form DNA (i.e. 3.4 Å), suggesting that RNAP advances one base pair each time a nucleotide is incorporated. Thus, during transcription, RNA polymerase translocates in increments of predominantly 1 base pair. When incorrect bases are incorporated, it pauses and backtracks to facilitate base removal, thereby ensuring transcription occur with high fidelity

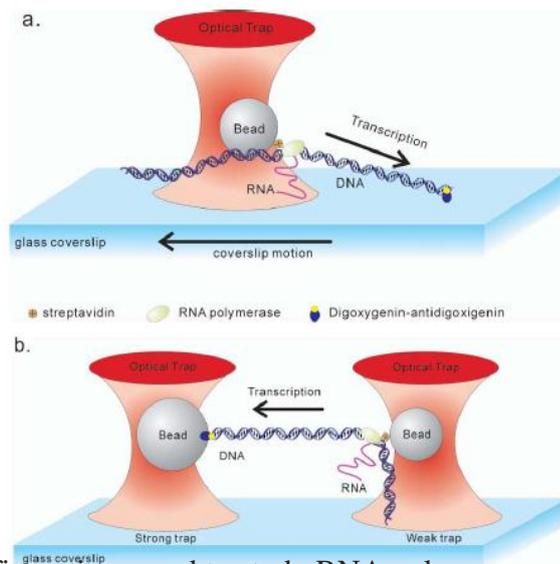


Fig. 3 Optical tweezers configurations used to study RNA polymerase. (a) A single trap configuration is shown. One end of the DNA is attached to a glass coverslip via a digoxigenin– antidigoxigenin linkage, while RNA polymerase is attached to an optically trapped bead via an avidin–biotin bond.⁷ The bead position is maintained by stage motion to provide constant tension (typically from right to left). (b) A schematic of a dual-trap configuration is shown. An RNA polymerase–DNA complex is trapped by two optical traps simultaneously. The left DNA end is manipulated via a digoxigenin–antidigoxigenin linkage, while RNA polymerase is attached via an avidin–biotin interaction. In this figure, the upstream end of DNA is linked to the left bead so that RNAP transcribes from right to left. The tension of the DNA–RNAP complex was kept constant during transcription by moving left stronger trap.

2.Folding of RNase H Protein:

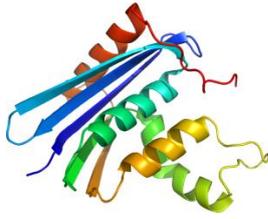


Fig. 4 RNase H Protein

Ribonuclease H or RNase H is a ribonuclease that cleaves the RNA in a DNA/RNA duplex to produce ssDNA. RNase H is a non-specific endonuclease and catalyzes the cleavage of RNA via a hydrolytic mechanism, aided by an enzyme-bound divalent metal ion. Importance of Ribonuclease H, or RNase H, is that it is essential for HIV's function. Once HIV RNA has entered a cell and been copied into DNA by reverse transcriptase, it is no longer needed, since the DNA copy is what will be incorporated into the cell's genome. In fact HIV needs to get rid of the RNA so that the freshly-made DNA can get on and do its job. RNase H helps by degrading the DNA-bound RNA. Hence it is an important target for antiretroviral drugs. Recently, Cecconi et al. studied the folding of RNaseH using single-beam optical tweezers. Force-induced unfolding of the molecule using optical tweezer was performed in order to probe the intermediate state. Two 500 base pairs DNA handles were attached to distinct

positions on opposite sides of RNase H. Each handle was also independently attached to one of the two polystyrene beads. One of the beads was immobilized by a micropipette, and the other was trapped with a laser. Two different transitions were observed in the force extension curves when the protein was pulled apart two consecutive times. The high-force transition (19 pN) upon the first pull yielded the increase in extension of 50 nm; this matched the contour length of the unfolded protein and therefore was interpreted as complete unfolding of RNase H (N \leftrightarrow U). After the protein is relaxed to a low force and is stretched again, reversible transitions of 40 nm in extension were observed at 5.5 pN (I \leftrightarrow >U); this implied that upon refolding, the protein does not completely return to the native state and that transitions between the folded state and a folding intermediate were occurring. This interpretation was supported by the fact that a longer wait in a low force, or a longer refolding time, restored the high-force transition. Such three-state behavior is also observed at a constant force for which the protein undergoes multiple transitions between the unfolded state and the intermediate state before finally settling on the native state.

RNase H Folding Transitions: Optical Trap

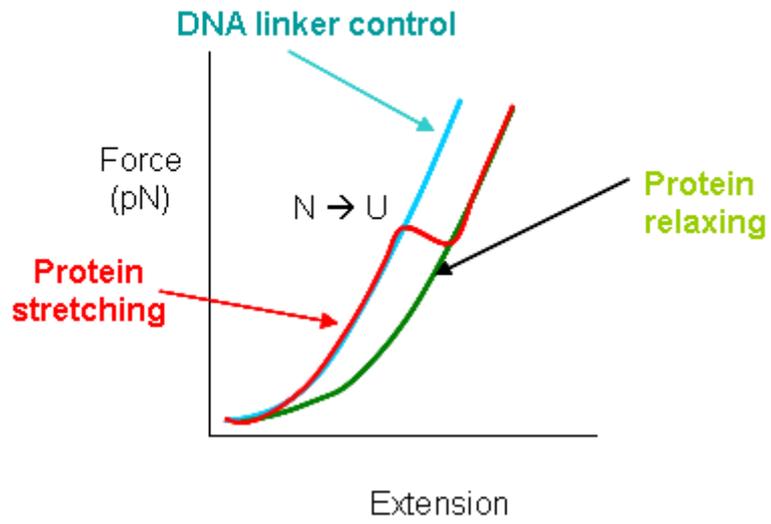


Fig. 5 RNase H folding transitions: Optical Trap

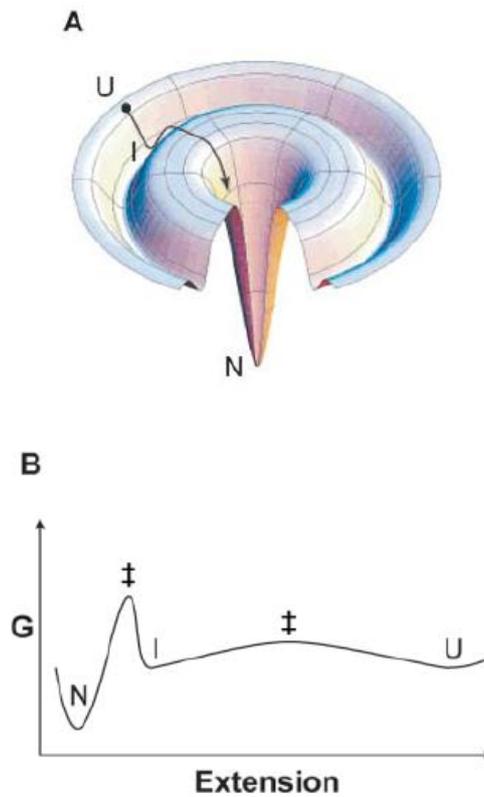


Fig. 6 Folding Landscape of RNase H protein

Conclusion:

Biological applications of optical tweezers are moving to a new level. Biologists thirst for more detailed mechanical and biochemical information on how single molecules work¹⁹. Recent advances in which optical tweezers have been combined with single molecule fluorescence imaging are a very exciting development. However, biologists also need advances in the tweezers design itself. They now want to grapple with single biological molecules and to sense the vibrations of individual domains and side chains with high time and high spatial resolution. The desire for higher-resolution data throws down the gauntlet to physicists to devise new breeds of optical tweezers that are sharper and more dextrous than those in use today.

As a model system, RNase H provides further incentive to investigate the folding pathway of more complex systems and potentially protein domains with strategically placed DNA handles. Further, a more accurate description of the folding landscape of proteins and transition states could be made, because single molecule methods can probe rare and potentially off pathway transient states.

In the coming years, further modifications to optical tweezer methods, capable of controlling the torque in the DNA or applying constant force using optical methods instead of a mechanical

feed-back system, will also be applied to single-molecule studies of DNA binding proteins. Due to their broad adaptability, optical tweezers will undoubtedly continue to contribute

significant insight to the understanding of protein–nucleic acid interactions, including those of ribosomes, DNA mismatch repair and recombination reactions.

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TECHNOLOGY GENERATION AND UTILISATION**Many phases, Changing Paradigms.****PATHWAYS FOR AN INNOVATIVE INDIA****Y.S.Rajan****(A Talk to be delivered at the Institute of Chemical Technology (ICT), Mumbai as Prof.B.D.Tilak Visiting Fellowship Lecture)****INTRODUCTION:**

It is much more common and fashionable now to use the word 'knowledge' so much so that many persons hyping on innovation totally leave out the word 'technology'. But truth of the matter is that modern economy, military, security, innovation, healthcare, entertainment, many social functions including culture, etc heavily rely on use of modern technologies. Even while some persons may accuse technologies of spoiling the environment, many real solutions to ecological sustainability, protection of biodiversity, natural disaster management and mitigation, addressing issues of arresting climate changes etc need more and more smarter use of right technologies. Some of these technologies may result from a revisit of the traditional technological heritage of human beings and adapting them in the modern forms.

Hence generation and utilization of technologies will continue to be a major

critical activity of human beings of all societies and nations.

However the processes governing uses of and generation of technologies and introducing new innovative products, processes and services, have gone through many major changes. The simplified assumptions of linear processes like idea – invent – experiment – limited production – commercial launch – standardization – imitation of the leaders by others – new processes of technology cycles etc are no longer valid.

The 1960's and the following decades have introduced many new complex paradigms and totally different legal and commercial practices for technologies. Therefore institutions specialization in generation of new technologies need to understand the new forces that are prevalent now in order so as to be relevant to the modern economy, society, military, etc. as well as to serve the people.

This talk (paper) is an attempt to provide a holistic picture of the historical perspectives and the current forces at play. Also it will attempt to provide pointers to the options and directions that can be attempted by technology professionals and institutions.

This talk (paper) is based on the actual field (executive and programme management) experiences of the speaker (author) as well as the knowledge derived through study of books which are the result of scholarly studies of various country / company performances by many experts around the world. Some of the references will be given here.

LAND – LABOUR – CAPITAL – TECHNOLOGY

Persons familiar with economics and technology management would be aware of such a description of the paradigm shift over a few millennia. A few millennia ago possession of land determined the political, economic and military strengths. Hence we had great emperors attempting to win over vast stretches of land areas and their nobles possessing lands in many villages. With the growth of agriculture diversifying to many different crops, animal husbandry, fisheries and with the spread of early industries with artisanal products, labour

(possession of or command of labour) became important. Labour created more wealth out of the land. Then the societies grow from the mere self – sufficient low subsistence levels of existence to larger trading. Till about the early 19th century China and India dominated the world trade and created most of the wealth (capital). Later with the industrial revolution science and technology (engineering) with automotive machines became a stronger force. During the later half twentieth century technology became the major force for economic, military and business strengths. The process is still continuing.

While the shift as described above is broadly correct, popular myth (even in elite circles in India) is that these factors were displacing each other. As such many persons thought (and think) that mastering of technology alone is adequate to grow the economy.

As a sub – set, those who were the protagonists of newer technologies like Information Technology (IT), Biotechnology (BT) etc started claiming that IT & BT alone can revolutionize the societies and economies.

Just as life is a continuum and is a complex adaptive system, the other factors like LAND - LABOUR – CAPITAL – TECHNOLOGY are also a continuum.

While the (historically) later entrants have their importance, the needs for the earlier factors do not disappear.

The current 'fights' in India over land acquisition and scramble for land by industrialists and business persons would show us how important land is even during the 21st century. Modern technologies help to achieve much more useable area from a small piece of land through multistoried building, under ground constructions etc. Also modern agricultural technologies help get much more yield per unit of land. Also newer concerns about environment and ecological balance add new dimensions to taking care of available land and its resources.

Similarly undue chasing of capital (through financial markets) created a 'fluff' of an artificial wealth. It led to an economic crisis in several parts of the world. Land price speculation and financial fluff in combination were one of the main reasons.

When it comes to the issue of labour, the attention given to continually educate and skill bulk of the people in pace with emerging technologies and new factors of globalization (new forms of trade and return on capital etc) determines how well countries continue to develop. In India there is a perpetual shortage of

skilled labour, as our attention was more around higher education, attracting investment etc. The general belief was that the 'market forces' will automatically take care of skilling. But actual life is more complex and we have on one side huge huge human resource in number and also simultaneously shortage of skilled workforce on the other hand. USA is also facing problems of unemployment because their assumptions and focus on growth was more around capital and technology and less on continual re - skilling their work force. 'Markets will decide' was the slogan. Hence they have a crisis on the employment front.

In the overall as new knowledge (new technology and new scientific knowledge) continues to grow, there is a need to continually fine tune the balance of Land – Labour – Capital – Technology. In India bulk of the govt. policies now is around capital – to attract investment, to facilitate businesses, to raise government capital through taxes etc (which are important but are not sufficient). On the technology front as well as in terms of skilling the workforce, we are severely behind our potentials.

We will address in this paper about where we are on technological front and in what way we as a country, and as

institutions, industry etc need to orient ourselves.

SCIENCE AND TECHNOLOGY POLICIES IN INDIA

India, amongst the newly liberating countries around the middle of the 20th century, had already some good base in science and technology institutions and higher educational institutions. Pre independent India had produced excellent world renown scientists based on India itself. It had also produced a few good technologists and technology entrepreneurs.

Post independent India laid a lot of emphasis on the establishment science and technology (S & T) institutions and higher education in S & T. Scientific policy Resolution (SPR) Govt. of India, was enunciated during 1958. (Ref 1) However the word science used therein led to multiple interpretations as it was convenient to various stakeholders. The word 'scientific' was originally meant (by Jawaharlal Nehru) to address all activities (and therefore all departments, ministries) of government. The idea was to emphasize scientific approach to decision making as well as to be aware of the scientific and technological developments while

promoting industries and a developmental services.

The word 'science' was used in its broadest meaning including technological applications and view point of life ('scientific temper').

Unfortunately SPR did not become the guiding force for industrial and other socio economic policies of India.

Public sector and private sector industries which grew under the planned economy being administered by the license – permit – quota – inspector raj were dependent heavily on imported equipment and technologies and turn key foreign consultancies. Though the words self reliance and phased manufacturing programme, know how and know why etc were often used in all government statements, repeated imports were accepted as a principle and practice. Even purchase procedures of government departments discouraged indigenously developed products.

For further study of the above, one may refer to the Article section of the website www.ysrajan.com for a three part exhaustive article titled Technology Policies in India. (Ref 2)

Such a 'safe' and 'risk averse' path suited the govt. administrators and the

public and private sector industrialists. They can travel the well beaten path under the guidance of those who made successful world standard products in their countries. Why take a tortuous route of indigenous development? A few exceptional cases were for Indian Space Programme and Atomic Energy. However it is to be noted that these sectors were those in which technologies and even products were denied to developing countries at that time. They were the exclusive preserves of a few countries which were engaged in the Cold War and Arms Race. No doubt the Indian scientists, technologists and engineers made excellent achievements in these select areas. But these are very small in terms of overall contributions to the economy measured in terms of the Gross Domestic Product (GDP) or in terms of employment. But they did give India a stature in the comity of nations.

But in the overall status of technology development and applications, that is, technology generation and utilization for various socio economic sectors be it agriculture, manufacturing or services, India was lagging behind many of the mid 20th century newly liberated countries like Israel, S.Korea, Taiwan, Singapore etc. Japan was making rapid strides in the technology conquest of the world trade to become a second largest

economy built on technological strengths (even with extremely poor natural resources available in that country).

Powerful and influential scientists, technologists and academicians in India did not do much to realize the true spirit of SPR, except by giving lip service slogans to the self reliance band wagon and slogans of know why. Some import substitution efforts at the periphery of the core sectors of Indian economy, society and military were touted as successes of self reliance. They were busy in getting more and more money from govt. and building up S & T and academic institutions. Of course the academic institutions fulfilled an important social and economic function of creating excellent human resources in S & T for research and development (R & D) as well as for running the industries and operational services.

Since there was little scope for industrial R & D, many young persons had to join the newly and fast expanding S & T institutions in India DAE, ISRO, DRDO, CSIR, ICAR etc. Many went abroad. Though these institutions had excellent infrastructure and special administrative systems to help flexible operations, opportunities to produce tangible end products and services did not exist for most of the S & T institutions. (except for

the 'mission' agencies like ISRO, DAE and to some extent DRDO). This is due to the lack of policy and procedural systems (currently used fashion word is ecosystem) to tie up the laboratories to the needs of operational sectors and industries.

Apparently this situation suited the S & T policy makers (mostly scientists) and S & T administrators (again mostly scientists). They were spared from the rigours of delivery schedules and therefore questioning by the end users. They had their 'freedom' to do what they wanted and what they consider as the best! The situation still continues.

Thus the hiatus between S & T institutions and the end users in the socio economic sectors (agriculture, manufacturing, services, military, security, etc) grew more and more. There were, of course, a very few exceptions; they were often due to struggles of some extraordinary individuals rather than through enabling systems (as there were in Japan, S.Korea, Taiwan, Hongkong, Singapore, Israel etc not to mention the developed nations like USA, UK, France, Germany, Sweden, Norway, Finland, Netherlands etc.)

One of the main reason for such a (sad) situation is because of the confusion caused by the usage of the word 'science'.

As mentioned earlier the use of the word 'science' by Jawaharlal Nehru in SPR and in his other speeches was meant to cover a wide area of human endeavor and not just scientific research or basic research. However the power elites of Indian S & T chose to ignore it and conveniently used the word 'science' as the basic research or some form of research not connected with the need to engineer products or services that will feed into the economy or later to the needs of the country. Fortunately ISRO, DAE and part of DRDO had a mandate to focus and deliver actual products and services. But it was not so for other S & T institutions. In some sense, it could not be so. A chemical S & T institution cannot be made to establish big chemical factories to produce fertilizers, pesticides' etc. But they can produce technologies and engineering processes to feed into such factories. There has to be a close link and not a stand off relationship. This process is unlike ISRO designing, developing, making and launching launch vehicles or satellites or DAE building and operating a nuclear reactor or nuclear bomb. When DRDO has to deliver a few missiles for the developmental phase it is in small numbers. But building and supplying tanks or fighter aircrafts or other operational equipment, numbers involved is large and therefore large scale production is involved. This is where

manufacturing engineering or manufacturing technology (this word applies to large scale delivery of services as well) comes in. It is an area totally neglected by our S & T institutions as well as academic institutions.

At this stage a reference is made to an article by Y.S.Rajan "What is Science? Who is Scientist?" in the website www.ysrajan.com under the Article section. (Ref 3) and also Role of Engineering in Development of Economy, Society and People, the first Prof.Satish Dhawan commemoration lecture organized by the Institution of Engineers, Karnataka. Delivered on 22nd September, 2010 by Prof.Y.S.Rajan. Also available in the website www.ysrajan.com . (Ref.4)

SCIENCE, TECHNOLOGY AND ENGINEERING

It will be good therefore to recall the definitions of the above terms and how they relate to economy society and people? Also how they are interlinked. It is better to see a few quotes from the address of Sir David Davies ("Engineering as an Innovator of change in Society and the Role of Engineering Academies", address by Sir David Davies, CBE, F Eng. FRS, Chief Adviser to the Ministry of Defence, UK and President, the Royal Academy of Engineering, at the annual function of the

Indian National Academy of Engineering (INAE). New Delhi, December 3, 1998). (Ref 5)

Quotes:

About Science: "Science is unquestionably a search for a better understanding of the laws of nature described in the broadest possible sense from astronomy to medicine and from engineering to genetics. Despite massive steps forward in each field, the understanding always remains incomplete...."

About Engineering: "Engineering on the other hand is about innovation, design and the construction of new products and new capabilities. We must take care not to define this solely in terms of physical products since engineering can also often offer new services often without the need for additional hardware..... However, whatever the form of the new innovation its design is inevitably a compromise between many different parameters. The success of the products is therefore bound up with the efficiency of the design process which has the role of matching the design to the requirements in as efficient a way as possible..." .

What is innovation?: “In terms of an engineering product or service an innovation enables it to offer some new advantage in capability or performance (including cost) that there is a strong coupling between engineering and science but this does not necessarily mean that this engineering innovation derives directly from the latest improvements or understanding in scientific theories.....”.

An example: “Perhaps the most obvious example here is the steam engine. That innovation arose from experimental observation but it was not based upon any current understanding a theory of heat at the time. Indeed the whole subject of thermodynamics was developed afterwards. It provided better understanding of the performance of heat engines and was further evolved in order to aid the design of improved equipment”.

Unquote:

For Sir David Davies the word technology and engineering are synonymous. In the later part of his talk he has discussed the role of Engineering Academies. He points out that for the implementation of most of the government policies for various social and economic sectors the strong link required is engineering. Policies have to link to the engineering aspects in the implementation.

He has implied that without such strong links most policy statements may not achieve the stated goals.

You may judge for yourselves what has happened in India over the past six decades and why the Indian performance lags seriously behind the policy and programme statements.

Another quote about the definition of technology and technology policy by Lewis M. Branscomb, *Empowering technology: implementing a US strategy* edited by L.M.Branscomb, 1993, MIT Press (Ref 6) emphasizes this point again: “A technology is the aggregation of capabilities, facilities, skills, knowledge, and organization required to successfully create a useful service or product. Technology policy concerns the public means for nurturing those capabilities and optimizing their applications in the service of national goals and the public interest”.

The word technology here encompasses engineering and the processes of engineering which includes implementation in the field.

The boundaries which distinguish technology (engineering) policy from economic and industrial policy are fuzzy at best. It is therefore necessary for Engineers and Engineering Academies or Institutions not to be quiet spectators or

mere implementers of policies done elsewhere but to be proactive shapers of various socio economic, trade and industrial policies. The current author has elaborated in detail the interplay of these policies in his book “Empowering Indians with economic, business, and technology strengths for the 21st century” (2001, revised print 2002). (Ref 7)

There is a wonderful definition of what is expected of technology by Rajiv Gandhi (for easy download see www.ysrajan.com Website - Article Section - “Definition of Technology”) (Ref 8)

As it is done in this paper it is good to use the word ‘technology’ and ‘engineering’ as more or less synonymous terms.

There are many uninformed or misinformed hypes about Indian capabilities in science and technology. “India as an IT super power”, “knowledge power” etc. and as a global science power.

It will be good to study in detail an exhaustive report by National Institute of Science, Technology And Development Studies (NISTADS) : “India Science and Technology 2008”. (Ref 9) Full report is available in www.nistads.res.in

Partly based on that report and information from other sources, there is an article by Y.S.Rajan based on the key note address delivered at the Project Management Practioners’ Conference 2010 on September 9, 2010 under the title **“GLOBAL POSITION OF INDIAN INDUSTRY AND ROLE OF TECHNOLOGY PROJECT MANAGEMENT”** (see www.ysrajan.com website). (Ref 10) The article will give in some detail on the challenging tasks in India for the technology project management professionals. This paper and the first Professor Satish Dhawan Commemoration lecture organized by The Institution of Engineers (India) (IE) referred to earlier, (Ref 4) together provide a good sample of tasks for technology generation, utilization including through technology transfer (TT).

But these tasks or missions or mega tasks and the subtasks cannot be taken up using the old linear paradigm of idea – invent ... etc. as pointed out in the introduction part of this paper. One needs to understand the new paradigms which have emerged and also as to how they apply to developing countries like India. These are addressed in the next section.

**TECHNOLOGY TRANSFER AND
ECONOMIC DEVELOPMENT –
SHIFT OF PARADIGMS during
1960's, 1970's, 1980's to now**

This word technology transfer' (TT) was hotly debated in India with several jargons of 'know how' ; know why' etc during the 1960's, 1970's, 1980's and even during the 1990's when the economy was liberalized and globalised. It referred to the whole range of contexts: from the principal supplier of embodied technologies (equipment supplier or turnkey project implementer usual by a foreign company), technical consultancy contracts as well as attempts towards commercialization of laboratory developed technologies to an industry.

As noted earlier, India continues to be a major importer of technologies even now. Currently one more context is being discussed: the acquisition of a foreign company (abroad or in India) by an Indian company with a view to benefit from its technology strengths.

It is good to begin with a detailed look at the evolution of several phases of TT with a quote from a recent article in Current Science Vol 98, No.11, 10 June, 2010 "Fuelling the Indian economic engine by retooling Indian technical education" by Vikramaditya G. Yadav and

Ganapati D. Yadav. Pp. 1142 – 1457. (Ref 11)

"As was the case with several formerly developing but now developed countries, imitation was absolute with little deviation from the borrowed policies. Not to be left behind, several of India's development policies too have conformed to those of the bandwagon."

"So why have not most Indians reaped the benefits of development despite several decades of reforms and execution of policies that were seemingly successful in other nations? Tersely stated, the global economic equation today is vastly different from what it was when the United States had just embraced industrialization and a nation now has to look inward as well as outward while charting its economic agendas. This could unforeseeably scramble national development priorities, especially for nations such as India, and wanton imitation by present day India of the executive policies of industrialized nations when they were at a similar stage of development will yield only minor benefit."

In order to understand the new context and how it has evolved during the 20th century, it is recommended that a scholarly book by S.Radosevic (Edward Elgar publishers) "International

Technology Transfer and Catch up in Economic Development” (1999), published by Edward Elgar, is carefully read.

Some important quotes from the book are appropriate here:

“The generation of new knowledge embodied in new products and processes and its diffusion throughout the economy is the main source of economic growth. This knowledge is only partly the result of endogenous technical effort. The more a country is lagging behind the technological frontier the more it has to rely on foreign knowledge and the import of technology through equipment, machinery, licenses or through copying (‘reverse engineering’).”

“Successful latecomers have combined heavy imports of technology with strong expansion of indigenous efforts devoted to technical change. The main locus of these activities were large domestic enterprises. These were complemented by domestic infrastructure and investment in education and training activities. So, the import of foreign technology is a necessary but not a sufficient condition for growth. Imports of technology and autonomous innovative efforts are not alternatives but complements. The historical experience of countries of central and eastern Europe shows what happens in the absence of this

complimentarity. The import of technology was not integrated into domestic technological efforts and the link with demanding foreign markets was absent. So, despite intensive endogenous technological efforts and a large pool of scientists and engineers technical change which would lead to long term growth was not generated”.

India also with its emphasis on the central planning of everything including science, technology and higher education followed the models of the eastern Europe. Therefore even while there was a major step up in the 1960’s such as establishment of IIT’s as well as massive expansion of national S & T laboratories, the insulation between the technology importing industries and the indigenous S & T development grew more and more during the subsequent decades. Some examples will be given later.

As Radosevic points out later in his book with several illustrations, most of the technology importing countries (industries) concentrated mainly on the costs of technology transfer. The terms of technology transfer again emphasized more on the financial and administrative aspects, and “virtually ignored the problems associated with the accumulation of technological capability”. India was no exception!

Public sector enterprises (PSE) under the control of state or central govts. did very little to create their internal technological capabilities. The S & T policy leaders and those who directed national laboratories or the chiefs of academic technical institutions were mostly from the basic research background in limited narrow fields. Though they may have academic excellence in such fields, technology management or technology policy analysis being complex subject of its own was not recognized by them. It was assumed that it can be “learnt” by doing when they become top administrators at (almost near) the end of their normal careers. Also the centralized planning system never attempted the integration of the industrial / business needs and societal needs with the S & T systems, though volumes of reports and minutes of meetings were written about such a coordination. Most of these “coordinations” were at a macro level, having little connections with ground realities (where real engineering and technology come in!).

Real tangible projects to build up accumulation of technological capabilities in the firms (industrial units) and corresponding further innovations in the S & T / University systems never took a front seat. Individual scientific projects

were taken up as decided by the scientific community (read it as the fancies of the scientific power elites). Back up analyses of the economic and social needs before undertaking S & T projects were never seriously considered except for some agencies like ISRO. Most of the S & T leaders / policy makers satisfied themselves by talking about “know why” as a substitute of technological capability and its continued accumulation.

During the 1980’s globalization processes around the world started speeding up. Many developing nations who had after their independence, adopted socialist and centralized planning, had started the process of liberalization of their economies. It is to be noted that the People’s Republic of China had started such a liberalization during 1978. The combination of liberalization of national economies with the globalization of trade, finance and production especially led by the transnational companies (TNC’s) qualitatively changed the modes of technology transfer. To quote Radosevic again:

“The most important change for technology transfer brought by the new stage of globalization is the changing relationship between finance, trade and production. The interaction between financial and trade liberalization (‘shallow

integration') and production and technology integration at the level of networks ('deep integration') is generating dynamics distinctively different from the situation in the 1960 s/70s. Trade patterns are increasingly determining the distribution of production tasks across national borders."....

"'Deep integration' has been facilitated by the liberalization of the international framework governing the flow of technology (mergers and acquisitions legislatures: joint venture rules; local content regulations; technology transfer controls). Compared to the 1960s and 1970s, developing countries are now much less in a position to control the interaction between finance, trade and production in old ways.".....

"However, the importance of local or national systems of innovation has not been reduced. This generates problems for national technology transfer policy which now has reduced control over its economic space."

There is an extensive discussion in Radosevic's book about the processes of "shallow" and "deep" integration and the modes and terms of technology transfer (TT). Post 1980's contract bargaining in TT strongly depend upon how Foreign Direct Investment (FDI) is used as the

sourcing link for domestic technology upgrading. Noting that most developing countries had little of the technological strengths of TNC's this bargain is more difficult and complex. (When Japan built up its technological and business strengths during 1960's and S.Korea during the 1970's and caught up with the developed world there was a much greater control of the TNC's and trade, by the national governments. Also they parallelly built up their innovative strengths over the TT given by TNC's)

During the initial period, FDI bringing TNC's, who also assure trade in export markets, may use the host country only in low value added activities. In this context, Radosevic elaborates the crucial issues facing the developing countries:

"There is also a danger that countries will become 'locked in' to low value added activities by foreign partners. Inward FDI may not only drive out local competitors, but may also restrict the creation of new technology by local suppliers, even if more technology disseminates to them from the TNC's. In short, TNCs may enforce both 'virtuous' and 'vicious' circles of increasing dependency on external sources of technology supply".

“‘Catching up’ in such a context requires several technological upgradings within international and technology networks. An issue of concern here is how technology transfer is used in the process of improving one’s technological position within the international production chains. It seems that in a liberalized trade and investment environment governments in developing countries have fewer opportunities to structure interaction between domestic and foreign enterprises, which has significant effects on technology transfer”.

“From being a controller of technology transfer governments will have to develop a role of network supporter or organizer. As in the past the formal mechanisms of control in technology transfer or today only access to production networks will not distinguish success from failures. The final results will depend much less on specific policies than on the policy implementation capability of governments and the kind of social organization and governance mechanisms that they build for an economy increasingly dependent on foreign markets, finance, production and technology networks”.

Further developments post 1995, due to the formation of World Trade Organisation (WTO) and the successful

attempts to uniformise IPR (intellectual Property Rights) laws amongst all its members, have created several barriers and challenges for building up of internal technological strengths the of developing countries at least to a level of respectable interdependency from the current levels of near total dependency described above.

That is the challenge facing India as well. Policy making bodies have very little awareness of these realities.

Before discussing India specific issues, it may be good to have a look at different mechanisms of TT (as would apply in the currently existing paradigm). A Table sourced from the book by Radosevic referred to earlier, is very useful.

Types and Dimensions of Technology Transfer

Transfer mechanism	Type of embodiment			Mode of Transfer			Role of seller /partner		
	Capital Embod	Embod	Disembod	Market (explicit)	Network (intermd)	Hierarchies (implicit)	Active	Enabling	Passive
Direct foreign investments	X	X	X			X	X		
Joint ventures	X	X	X			X	X		
Licensing			X	X					X
Imports of goods	X			X					X
Co-operative alliances*		X			X		X		X
Subcontracting		X			X		X	X	X
Export		X		X					X
Transfer by People		X			X			X	
Development assistance	X	X		X	X		X		

***Production sharing agreements, management and marketing contracts, service agreements, R & D consortia and other co-operative alliances, franchising, technical services contracts.**
(Source : Ref 12)

We will refer to many of these elements when we discuss India specific examples in the later sections.

Bulk of the Indian economic growth as of now is propelled by direct foreign investment, licensing, import of goods, subcontracting and to a limited extent by joint ventures. Other elements are limited. Since this table is about TT, internal R & D and its utilization by the firms is not indicated, though they are implicit in other elements if “deeper” globalization takes place; one explicit form

of this will be through cooperative alliances.

Let us now have a quick survey as to what happened in India in different sectors and where we are now.

WHAT DID INDIA DO, DURING 1960's, 1970's, 1980's 1990's and WHAT DOES IT DO NOW?

AGRICULTURE

When India became independent, its GDP was dominated by agriculture. A few years before independence the country suffered a major disastrous famine. During the fifties agriculture contributed more than half of GDP. Even during the 1960's and early 1970's its share was more than

40 per cent. Naturally the first five year plan which began during 1951 laid emphasis on agriculture.

Agriculture has received the attention of govt. of India even during the pre independent period. Some of the presently excellent agricultural research and education institutions were set up during the colonial period.

National commission on Agriculture 1976 in its report published by Ministry of Agriculture, Govt. of India, during 1977 (Ref 13) traces many of these developments and elaborately deals with research, development and education aspects. It has gone into the details of adaptive research, agro intelligence as well as the requirements of allied industries.

An interesting extract from the report is appropriate even in the current context:

“A major development of this period was the first ever elaboration in January, 1946, of an all-India policy on agriculture known as ‘Statement of Agriculture and Food Policy in India.’” According to the Statement, “The All India policy is to promote the welfare of the people and to secure a progressive improvement in their standard of living. This includes the responsibility of providing enough food for all, sufficient in

quantity and of requisite quality. For the achievement of these objectives high priority will be given to measures for increasing food resources of the country to the fullest extent and in particular to measures designed to increase the output per acre and to diminish dependence on the vagaries of nature. Their aim will be not only to remove the threat of famine but also to increase the prosperity of the cultivator, raise levels of consumption and create a healthy and vigorous population.” The ten objectives of the policy included: “increase in production of food grains and protective foods; improvement in methods of agricultural production and marketing; stimulating production of raw materials for industry and exports; securing remunerative prices for the producer and fair wages to the agricultural labour; ensuring fair distribution of the food produced and promoting nutritional research and education.”

Post independent India had special problems due to the partition: distribution of irrigation and other resources between India and Pakistan. Various traditionally established supply chains especially for cotton and jute were severely disturbed.

It is not intended to cover fully the history of agricultural development in India. During the later part of 1960's stress was laid on greater adoption of S & T for

raising productivity, in terms of irrigation facilities, spread of high yielding varieties, use of fertilizers and adoption of plant protection measures. Agricultural extension services were also done through various state level institutions and local agricultural universities.

When the report of 1977 is revisited, one would find that number of measures to build technological strengths in the farming sector have not been fully achieved, though there has been remarkable progress since 1950's. Also new methods brought in newer problems – partly technical and partly due to the raising expectations and other socio economic factors.

A recent report entitled “State of the Indian Farmer, A millennium study”, 27 volumes + CD ROM has been published by Academic Foundation, New Delhi in association with Ministry of Agriculture Govt of India (2004) (Ref 14). It is an extensive recent update about differentiation in markets, the experience with earlier S & T inputs, the lessons learnt therefrom and also the newer technological requirements and challenges. Issues of commercialization of agriculture, IPR issues etc are discussed at length.

There are a whole gamut of science, technology and engineering

challenges for the Indian S & T system from the critical and important problems of present day agriculture. These are not for the Indian Council of Agriculture research (ICAR) alone. Every discipline of science and engineering need to be deployed including advanced technologies from chemistry and biology. Select import of foreign technologies through various forms indicated in the table in the last section especially cooperative alliances can accelerate technological capabilities of Indian agriculture to truly fulfill many objectives given in the January 1946 Statement of Agriculture policy of India quoted earlier in this section.

It is sad that Indian S & T system and its apex bodies do not work on specific projects and missions resulting from such reports. This is because of the hangover of the past which grew the S & T institutions through Five Years Plan **of their own and annual budgetting**. The apex policy makers think that ICAR will take care of agricultural research and extensions. Since Govt. does not involve Industry for S & T generation and utilization activities, they do not bother about these issues either. Also various govt. policies and procedures inhibit industry and businesses in venturing into agriculture. So on one side the economy and society especially farmer and

agricultural labourers are awaiting for solutions to their problems; Farmers are ready to experiment to get better incomes. There is a good and comprehensive set of reports giving a clear picture of issues (including policy support systems). On the other side many capable S & T personnel plod along with routine research suiting their narrow tunnels of approved projects. Potential of India which is blessed with a large percentage of arable land and other biodiverse resources is yet awaiting to be realized.

The author is personally aware of a situation during 1990, when a Secretary in the central department of science and technology was ready to get approval of a total proposal from the then Prime Minister under his self – reliance programme, a project of Indian design, system engineering and establishing an advanced fertilizer factory which can become a forerunner of Indian Industry in fertilizer to be followed by other agro – chemicals. This would have led to a huge step up technological capability of Indian industry and S & T institutions. India could have been a global leader. He approached many top scientists / technologists to take up the challenge. None was ready!

Many Indian scientists are willing to take up piecemeal research projects. But

are not ready to bring them up to a production level working with an industry (firm) or creating a new firm. This is one severe lacuna of Indian S & T institutions whose bits and pieces of technologies generated, howsoever good they are, do not find their destination in the market place. Such a situation in turn leads to a vicious circle which leads the hiatus into a total isolation.

While the current mode of having agro related firms in India continuing repeated acquisition technologies (embodied and disembodied) as well as import of needed chemicals, mechanical equipment, electronic / electrical equipment for agricultural operations could also be continued, the author is of the firm belief that India should also require a few home grown firms as well, which can meet domestic demands and also meet global demands (exports, establishment of firms abroad with Indian home grown technologies etc). The reason for this need can be understood especially when one studies in detail the 27 volume State of the Indian Farmer reports. Agriculture (which word includes in wide and comprehensive sense crop production together with land and water management, animal husbandry, fishery and forestry) deals with life in the biosphere. As we learn to increase productivity and destroy

insects, pests etc, the other organisms also learn. For example it has been found that pests become resistant to newer pesticides over a period of 7 to 10 years. Similarly soils offer new challenges, when we increase productivity. Also people's demands change..... Therefore a continuing innovation is required in all these aspects. For a country as big as India (geography and population) there needs to be continuing R & D, application, production, extension services with home grown technologies. This will help in maximizing the benefits and profits from agriculture – which will continue to be an engine of growth of India though its share in overall GDP may remain around 20 to 25%. Status of agriculture will continue to affect other sectors of economy.

Also in the coming years there will be increasing demand for cleaner technologies, better phytosanitary conditions (which are partly due to agricultural residues), and better management of agricultural wastes (solid, liquid and emissions). Also challenges from the need to preserve biodiversity will require scientific, technological and engineering solutions. In the coming years agricultural IPR's would be very strict by applied. One cannot expect a Norman Borlaug willing giving away his

technologies as was the case for Green Revolution.

Without a robust and technologically strong home grown system in place meeting at least 25% of the total domestic demand and also with a noticeable global presence (more to challenge oneself to raise quality and also to make profits as well as to have a geopolitical influence) – from S & T to final deliveries and services of agriculture and agricultural industries – India may lag behind economically. While interdependence can be an accepted solution, a total dependence on foreign technologies also far agriculture and agro related industries will lead to serious current account deficits in Indian economy.

Reading again now the National Commission Report on Agriculture (1977), one can find how much of the past S & T / industrial opportunities in agriculture and related industries have been missed.

The 2004, 27 volume State of Indian Farmer Report (2004) is still current.

It is a challenge for Indian S & T, industrial, business and policy making community to rise up to meet the challenges of Indian technology generation

and its utilization on a massive scale as suggested above.

The current Indian policy discussions about Agriculture is more around the financial aspects, subsidies, delivery of free food, free electric supply etc. **There is no attempt for systematic understanding as to how to make it all economically_ecologically and socially sustainable.** The key is with the orchestrated use of science, technology, engineering by firms, businesses and delivery systems (public and private). And also there need to be a massive training of skilled workers, all through the supply chain (including experts) and other professionals including researchers. There is a need to increase the Indian IPR's on various aspects of agriculture to enable global competitiveness. Under the regime of WTO, no country can afford to relax IPR constraints on the premise that the efforts are only to meet the domestic demands. Since Indian demand is very high, it will surely attract global suppliers who would demand market access and a level playing field. So the challenges before industry, institutions and farmers are really very daunting.

Let us now have a brief look at the industrial sector.

INDUSTRIAL SECTOR:

This sector is vast covering many areas of manufacturing. These include chemicals, pharmaceuticals, agro food processing etc.

At the time of independence India was importing almost all the manufactured products. Geo-economic strategy of the colonial power was to use India's raw materials exported to UK and have the manufactured products exported to the world (including India). That is how wealth was created by the colonial power. In economic terms value addition was done in U K. The technology or engineering enabled such a value addition. In India (and in China as well then) around 1950's such industries were nearly non-existent but for a few chemical and metallurgical industries in India.

Bulk of the manufacturing that existed in India was artisanal in nature.

Post independent India thanks to the emphasis of central planning, built up many industries in the public sector. Invariably they were established through total import of technologies from different countries. This was a good option as endogenous capabilities and knowledge did not exist then. During the 1960's and 1970's, India had many elements of the manufacturing sector as it existed

elsewhere nearly in the same level of sophistication; the gap was low. Most of these industries, set up with foreign technology, know how and equipment, catered to the domestic demands (again fixed up by the central planning machinery). Imports for consumption were either curbed or attracted very high levels of customs duty. Thus it was the world of manufacturers who managed to get a license if it was in private sector. The public sector enjoyed a near total monopoly in that product line, as a part of the policy of the “commanding heights of public sector.” Many capital goods were produced by PSU’s.

A classic example of such a monopoly situation by the licensed private sector, was the Ambassador car, which became almost a national symbol. President, Prime Minister, Chief Ministers, Ministers and every govt. official had to travel by it. Fiat was a poor second. Both were in private sector. A poor third Standard disappeared. Even private sector persons followed the pattern!

In the field of chemicals it was better because many private sector units in small and medium sectors manufacturing a wide range of chemicals came up in the post independent India. This was partly so because the consumers were highly dispersed. Fertilizer companies were

highly protected and were subsidized to meet the lower sale price to the farmers; in the later decades this practice caused technological lethargy in the sector, lagging behind the world standards of material or energy efficiency.

1960’s and 1970’s were also periods of severe foreign currency shortage. Foreign exchange earnings were mostly through the primary sector and through export of raw materials such as ores. Industrial sector needed huge foreign exchange to meet the demands of equipment, technology know how and license fee to the principals abroad. The only place they could attempt savings (in the short term) in foreign exchange was through use of some local materials in the manufacture. Thus came the practice of “import substitution” which became the main focus of industrial R & D; it was touted however as self reliance. Since the tax structures for imported goods were very high (ironically much more for imported raw materials as against much lesser tax for purchase of a total system!) such import substitution R & D efforts did not have the pressure of cost effectiveness: somehow do it with indigenous materials was the aim.

Such efforts though useful in a short term then, it took away the main focus of mastering technologies of the

total system as was done by Japan, S.Korea, Israel, Taiwan etc. When the total systems became outmoded (maintenance costs became very high), new systems were imported; some private sector companies purchased reconditioned equipment from abroad to cut costs.

So was the Indian industrial growth. But there were bright spots. Rourkela steel plant at the time of its establishment was one of the best technological and cost effective plant by world standards. But slipped in position later due to complete neglect of continual industrial R & D to upgrade it. The plant's profits became a part of all earnings of PSE's and got lost! National laboratories hardly did any system level R & D and were not even aware of it. Some research at the periphery sufficed to produce papers by the laboratories. Publishing in an international journal was the peak they aspired for! No wonder India at 2010 has to import or have joint venture with foreign companies to establish steel plants in India or abroad. Such a situation is due to the decades of missed opportunities to upgrade the Indian Industry, over these decades the gap of sophistication between Indian industrial technology and those of other developed ones in the world, has increased manifold.

As regards the electronics industry which was emerging as a major industry world wide, during 1970's, India had a unique opportunity then. India had an electronics manufacturing base better than S.Korea during the late 1960's and early 1970's. India had made a valve based electronic computer called TIFRAC during later 1950's. There was a huge article on it in the series of books entitled Advances in Electronics during 1970's.

But overcentralised scientobureaucracy virtually killed the growth of Indian electronics industry under the false (perhaps well intended!) slogans of self reliance by the Govt. of India's Department of Electronics. It is ironical that the Department came out of the HomiBhabha report as a vision for Indian Electronics and which was passionately advocated by Dr.Vikram Sarabhai (he passed away in December 1971)

Hongkong etc were gearing up for the manufacture of microchips (not to mention the emerging Japan in 1970's and other countries). India was then struggling under a severe licensing regime. India lost a unique opportunity to have become a technological giant in electronics in terms of industry, R & D and innovation. Such a centralized control regime by the Department of Electronics did not even

result in giant R & D centres nor original software creators and producers. As a result, the telecommunication industry totally stagnated. The India's symbol in electronics was the huge and heavy black telephone set produced by the only telephone maker in the public sector.

Even during the 1980's the fledgling software companies like TCS, Infosys, WIPRO etc struggled for a decade till economic liberalization of 1991 gave them some oxygen to survive and later to grow well using the world wide IT wave and outsourcing.

In the chemical sector oil exploration with govt. efforts and resultant petrochemical plants gave a fillip to chemical engineering. Enactment of 1970 Indian Patent Act gave the opportunity for many Indian Pharmaceutical companies to grow using the provisions for the process patent.

Relative to other sectors of Indian chemical industry had a closer relations with industry (not to the optimum level though!). This was partly due to the nature of the chemical technology R & D and also due to fairly spread out nature of the industry. Still there were no breakthroughs that came in R & D or in industry as the relationship was mainly focused on import substitution, pollution mitigation, process

changes etc. Agricultural related chemical industry (input side like fertilizer, pesticides, micronutrients etc and at the output side alcoholic beverages, industrial alcohol, textiles etc) was another growth sector during the 1960's and 1970's.

Electric power sector started with hydro electricity and then grew with thermal plants. But coal mining industry which was a public sector monopoly, never attempted gradual value addition like beneficiation etc; nor addressed the special problems of Indian coal. A national laboratory concerned with coal during late 1960's took a bold step to import a pilot plant for coal gasification. But those scientists had to struggle to go forward as the central administration of the laboratory did not fund them adequately, as perhaps they did not understand the significance. The user industry, ministry of coal and the central headquarters of that national laboratory had little interest. Had that been pursued India would have been a world leader in clean coal technologies. See for more details "Technology and Power Perspectives" – Seminar 414, February 1994, special issue on Managing Energy. (Ref 15)

During mid 1980's partial liberalization of Indian industry began with a few areas. As foreign exchange problems were acute as foreign direct

investment (FDI) was severely curtailed, it led to a major foreign exchange crisis for India during 1990's. Fortunately that crisis also led to globalization and liberalization in the Indian economy, mainly to tide over the crisis in foreign exchange reserves. It helped FDI flows and along with it some embedded technology flows. Also it helped the (low end) outsourcing IT tasks to be taken up by Indian Industry. There was a massive growth. Foreign exchange reserves crisis became a thing of the past.

However 1990's liberalization by the Govt of India, never had the technological capability upgradation as a part of the national objective. Entire dialogue was terms of macroeconomics, financial markets, structural reforms for easing the access, tax reforms etc. No doubt they were all essential. Equally essential was the need to build technological capabilities of linking science, technology, engineering and businesses to use the global markets. Indian industry which emerged out of an oppressive licensing regime needed special support mechanisms to quickly complete the evolutionary processes needed to become technological leaders; these processes were absent or stymied in most of them.

Govt. of India nor industry groups attempted to build up these processes. The

only attempt by the post independent Govt. of India (GOI) earlier was through the National Commission on S & T (NCST) which had profiled several important tasks in this direction (1971). They were forgotten and the only action taken by the Govt. was the establishment of Department of Science and Technology (DST). Not fully appreciating (or being aware of) the processes of technological growth processes in industry as explained in the quotes by Radosevic earlier, or the important differences between science and engineering (& technology) or the definition of technology Branscomb etc, the entire funding was left at the hands of scientists. Soon DST and its offshoots primarily turned out to be funding of scientific research "of the scientists, by the scientists and for the scientists". No doubt a few attempts were made to develop relevant technologies.

By the time of economic liberalization 1991, DST and its off shoot "scientific departments" turned out to be funding mechanisms for building more and more infrastructure for science laboratories. Of course some of these efforts were useful in providing human resources to the new industries; for example Dept of Biotechnology's (DBT) massive investments in many universities for establishing post graduate courses.

The establishment of Technology Information Forecasting and Assessment Council (TIFAC –approved 1986 and established 1988) was a feeble attempt. A number of its forecasting and assessment reports, technomarket survey reports were useful to identify technological needs of Indian industry – in the short, medium and long term in the global context. The Home grown Technology (HGT) programmes (started 1991) helped to build the gap between industries and labs; it became a forerunner in terms of various procedures for the Technology Development Board (TDB) established during 1996. Notable amongst TIFAC’s outputs were the three major Technology Mission programme in Sugar industry, Advanced Composites and FlyAsh Utilization (1993). To a reasonable extent they helped Industry to taste the benefits of technology adoption and also helped many academic technologists and national laboratory scientists / technologists a unique opportunity to work with actual industry and business related projects.

TIFAC’s experience of Mission REACH was the result of unique experiments for inducing industry to invest in colleges / universities (non – IIT, non IISc) for establishment of Centres of Relevance and Excellence (TIFAC CORE). A recent paper quoted below (Ref

16) may be referred to. It was Government mediated programme to intensify industry academia linkages for human resource development, relevant R & D and commercialization and working closely with the fund contributing industry and others. See “Experiences of an innovative model from TIFAC” by Jancy Ayyaswamy, Neeraj Saxena & Antaryami Parida Technology Information, Forecasting & Assessment Council (TIFAC), New Delhi. Presented at the International Conference on: Science, Technology and Economy: Human Capital and Development. (Annual Conference of IASSI and Knowledge Forum Hosted by IIT Bombay)(venue: Institute Auditorium, IIT Bombay, Mumbai, November 11 – 12, 2010) (Ref 16) Can be viewed at the social sciences website. http://esocialsciences.com/KF_conference/index.html and also www.fgks.in

Another important output of TIFAC was through major national exercise of Technology Vision for India 2020. It was a joint exercise of scientists, technologists, industrialists, administrators, NGO’s and other public persons. The exercise involved use of various technology forecasting, assessment and foresight models. It used the questionnaire methods as well to capture

the ideas and insights of several practicing professionals.

A glimpse of the outcome was bought out as 25 volumes dedicated to the nation on 2nd August, 1996. A popular book “India Vision 2020 A Vision for a new Millennium” A.P.J. Abdul Kalam and Y.S.Rajan (Ref 17) gives a good summary of all these documents and also additionally describes linkages between various sectors, economy, society and national security.

TDB became a good source of funds to industry projects but was not large enough. It also spurred other such funding mechanisms in specific sectors like pharmaceuticals, biotechnology etc. While a number of them grew, they continued to be small in size. Neither did they cater to fresh new technology entrepreneurs as venture capital agencies did in other developed countries. (Due to many govt. procedural inhibitions which are totally risk averse and also because there was a constant lurking fear of danger of attracting criminal investigations against a bold but honest funding official. Indian public accountability systems are yet to graduate to support industrial and S & T innovations!). Most of these funds therefore focused on funding an industry which took up technologies from a national laboratory as TT rather than

working on the tasks needed to position the industries in the global value chains as described in Radosevic’s quotes given earlier. Also most of them were unaware of the new emerging phases of TT, technology generation and utilization and new IPR regimes. They believed in the old linear models of technology development.

India 2020 documents had many details giving excellent indicators for actions in the short – medium – and long term, in the global value chain. The report covered all vital sectors: Agriculture, Agro food processing, Materials, Engineering, Chemicals, Services, Advanced sensor etc. These documents which had broad acceptance of industry as well covered a whole range of items to cover all aspects of technology acquisition by Industries (Refer to the Table quoted before from Ref 12). That would have meant special GOI’s orchestrated efforts ranging from provision of conditionalities for FDI (negotiated with foreign investors with mutual agreement) to supporting special joint ventures to promoting cooperative ventures to forming industry – lab – university consortia for developing newer technologies (medium and long term) to support the global competitiveness of Indian Industry. Even some of DST’s and DBT’s funding of basic research could be oriented towards these overall goals.

Development, orchestration and execution of such a systematic market driven plan (with some govt. oversight) over a period of two decades require a special type of leadership of S & T agencies, academic institutions and govt. (state and central) departments and their agencies. An attempt to create such a mechanism through the Office of Principal Scientific Adviser to Govt of India (2000) with a cabinet rank did not yield any tangible action. Office of PSA as well as Scientific Advisory Council to the Prime Minister still exist. It is perhaps too much to expect from the Indian system which has over five decades grown up in cosy and narrow silos with individualistic orientations!

It is also to be noted that TIFAC had built up since 1995 an excellent Patent Facilitating Centre (PFC) noting the importance of IPR's in the globally interconnected world. It has a global recognition from the developed world and has helped many Indian Universities, Labs and industries. If an Indian industry becomes big (be it in domestic sector or outside) it is bound to attract various forms of IPR and other technology based litigations. In this context the problems which our major pharmaceutical industries go through now in USA or Europe, are not all surprising. If Indian exports grow in the

coming years to a reasonable size (as of now it is still small as can be seen from the information given in the article referred to earlier (Ref 9)), they will face problems ranging from challenges to IPR to adherence to global good laboratory practices to phytosanitary conditions (for agriculture and food related products) etc. These issues and challenges require good internal technological strengths to face and tackle.

Coming now to Micro Small and Medium Enterprises, let us look at a table derived by the author from the NISTADS report referred to earlier (Ref 8) and explained in Ref 9.

Table: MSME Salient Features

- ❖ 10.5 million enterprises (2001)
(new definition 13 million)
of which 5.8 million in rural areas and rest in town mostly non-metropolitan / peri-urban areas.
- ❖ 40% of total MSME in manufacturing sectors
16% in repairing and maintenance.
- ❖ Gross output of all MSME's (2001-2002)
Rs.2,822 billion and export Rs.141.79 billion
Share of GDP 8 to 9%;
40% total export; 30 million employed

- ❖ About 98% of MSME units in India have almost no relation to big industries or channel partners. (Thus ancillarisation is very small).
- ❖ About 85% of MSME's use traditional knowledge in production units; domestic R&D have a meager share in provisioning knowledge – only about 5 – 7% of the technical knowledge transactions are with public R&D.

(Source: NISTADS Report Ref.8)

As can be seen from the above there is a great need to mount a large nation wide effort (not just New Delhi driven!) to infuse technological strengths in to the MSME's. It will require a whole set of actions ranging from FDI policies to govt. procurement policies. A book specially addressing these aspects may be referred to "Global Business Technology and Knowledge Sharing : lessons for Developing Country Enterprises" by N S Siddharthan and Y S Rajan (Ref.18). There is a chapter on Technology Intermediation in the book. This is particularly required for MSME's. Scientists, technologists, engineers and management professionals have a great role to play for technology intermediation for Indian MSME's to graduate to contemporary levels to meet global competition. This idea was further developed by Y.S.Rajan as "Knowledge Intermediation" to include the fact that in addition to 'technology' other factors would also need to be included. This idea was already imbedded in Ref 18. However

an explicit use of 'knowledge' may bring it to the attention of more persons See for details Article Section of www.ysrajan.com website under the title "Knowledge Intermediation" (Ref 19)

We will close this section with further two references. One gives the micro level details of the processes involved. "New Product Development " Challenges of Globalization". (Y.S.Rajan and Kalpana J. Chaturvedi). Appeared in the international Journal of Technology Management (IJTM), Vol.X, No. Y, pp.000-000. (2000) (Ref 20).

Another article is the chapter – 5 of the book Empowering Indians. (Ref 6 pp.91 – 112). It is worth referring to it here as a specific item. It is titled "Policies for Science and Technology in the Era of Liberalization" (Ref 21). It covers all crucial elements needed for Indian Industry to position itself globally and the role of S & T by policies and contributions for the same. The ideas and the specific recommendations covered therein are valid even now during 2010 and beyond. The officially stated govt. policies on technology and science are too general and do not cover the whole eco system of science, technology, engineering, innovation, and business, society and national security. Ref 21 has described the **five basic elements** of S & T policy as: Need for Employment;

Improving the Quality of Life of People, Vitality of the Economy: Wealth creation, Trade and Technology; National security; and the Human Resources for S & T. In addition the chapter briefly described the complex interconnections between the five elements. All these five elements are on the top of the agenda even for the most developed country USA, as can be seen by explicit statements by the US President Barrack Obama.

WHAT NEXT FOR INDIA?

We have so far covered a wide terrain: the crucial differences between science, technology (engineering), innovation etc; changing paradigms in TT during 1960's, 1970's, 1980's and beyond. We have also touched upon briefly what happened to India during that period in Agriculture and Manufacturing, with a few examples.

While India has achieved well in a number of ways in terms of agricultural output, diversity of industries, presence of its goods and services in the international markets, human resources in diverse fields some excelling in global standards, an large S & T infrastructure, strong armed forces, etc they are yet small when one looks at the true potentials of India. A lot more needs to be done especially in terms of building up technological strengths and

global standing in terms of share, position etc. But it cannot be done using the assumptions of earlier paradigms. We need to look at the future based on current day realities.

The reason for covering the recent history of India's performance especially in terms of missed opportunities is to ensure that actions for the future are not clouded by the same ideas of the past being regurgitated again. Experiences of the author during the past decades have shown that S & T and other administrative systems in India, tend to do so (that is to regurgitated old failed ideas, very often only changing the jargons over a period suiting the then current fashions).

There needs to be a clear departure in the outlook, attitude and methods of selecting and executing S & T based or related projects in order to build up technological capability within Indian enterprises and to make Indian products and services globally innovative and competitive.

It is yet possible to do so. This section will address the approach to such actions.

First and foremost, the economic growth machine has to be kept going. That will mean attracting investment (foreign and domestic investors) and enabling them

to be profitable Investors in addition to various forms of legal, administrative, and financial support systems (not necessarily subsidies) will also require right types of human resources. It is only in rare cases they try to invest on training human resources; at best they may do the final touches, the “finishing” touches. The State has to enable creation of right skills; often times in India the parents invest on their children till they get good jobs. They even take loans. That is why there is a huge distortion in India in the higher education and the school education that feeds it: most of these are “self financing”. Bulk Govt. resources go to a few select elite S & T and academic institutions. There will be a need to drive the elite institutions to earn more from the end users. It is to be done not by mere speeches or policy statements. There has to be an economic pressure (incentives and disincentives) to make them work on problems needed for the Indian firms to graduate from the follower mode of technological acquisition to leadership mode.

These tasks may not be the usual mode of academic research as it takes place in India nor the current forms industry academia linkages. The real tasks may range from those elements which will add strengths to the firms or enterprises from their current levels of technological

capabilities be it in their own production lines for domestic or export markets or from their current levels of capability with which they execute jobs outsourced by foreign firms from abroad or operating in India. This is not in an import substitution mode of the past. **It is a process of upgradation of these firms in the global value chain through various forms of technological strengths:** embodied technologies (adding some equipment or software); upgrading the tacit knowledge (special on the job training or some incremental development projects which will develop insights for workers, middle managers, top managers etc); etc. Such upgradation processes should encompass all firms: big ones to MSME’s. For MSME’s especially the vast network of engineering, pharma, science etc colleges can be deployed, not just the elite institutions like IIT’s, IISc or other govt. supported ones like NIT. Involve all colleges including the self financing ones: it has a double effect; one to spread to all firms in India; another to upgrade India human resources base.

Outsourcing which is really the core of globalization process helps the Developed Country Firm (DCF) and also the Outsourced Country Firms (OCF). Though it has become a “dirty” word in some developed countries which were the

advocates of free trade and free global access, it has helped global economic and technological growth. The DCF firm gets not only a good cost competitive option to do some of the subsystems / elements of the total product (be it a car or consumer product or a software enabled service) thus making it globally competitive and thus helping it to earn more profits **but it also provides time – space and managerial space for DCF to concentrate on further higher value R & D** activities which will help them to create more innovative products. Regular **standardized work packages** are being taken care of by OCF firms; so DCF firms have some free space. This aspect is missed in many economic or econometric studies which take into account only macro elements like productivity; profit etc.

For the OCF firms such a process of outsourcing provides a new and more profitable **market space**. They earn more profits that too by an assured sale (by contract) to a customer abroad. Also the volumes are large than what they (OCF) can imagine in their domestic markets because the foreign customer DCF firm has global access to market.

It should be noted here that in this relationship between DCF and OCF, DCF is in a stronger position. It can have many OCF's in the same country or different

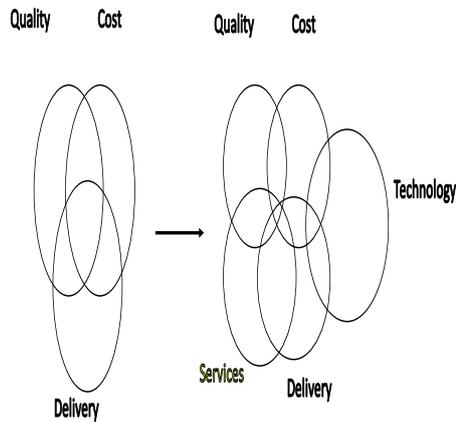
countries. It can dictate terms as it has the core strengths in the technologies for the products (technology as defined by Branscomb Ref.5) for the global market.

But OCF firm need not be and should not be in the same static position in which they were selected by the DCF firm and provide outsourced services as the “most obedient and loyal server”. That would have been a virtue in the 1980's. Not any more. Because the DCF firm in the global market is not a monopoly “emperor”. It is under continuous “attack” by its other competitors who may be number 2, 3, 4 even 10. That is the power of the modern technologies and innovation. A number 10 may spring surprises through its innovative and technological efforts (even incremental ones) and capture much of the market segment enjoyed by 1 to 9! Therefore DCF firm will look for not just a loyal and trusted OCF firm but also a firm which has S & T capabilities, which can think ahead and which can innovate **within the framework** of the product of DCF. It is like the Panchatantra story of Prince and the Monkey!

At this point let us look at a figure sourced from Radosevic's book Ref. 5

NEW REALITIES

Linear paths and standard S-curves are out!



With the detailed discussions we have had before it is easy to understand this figure. Earlier requirements of quality, cost, and schedule remain. But two more crucial elements are added.

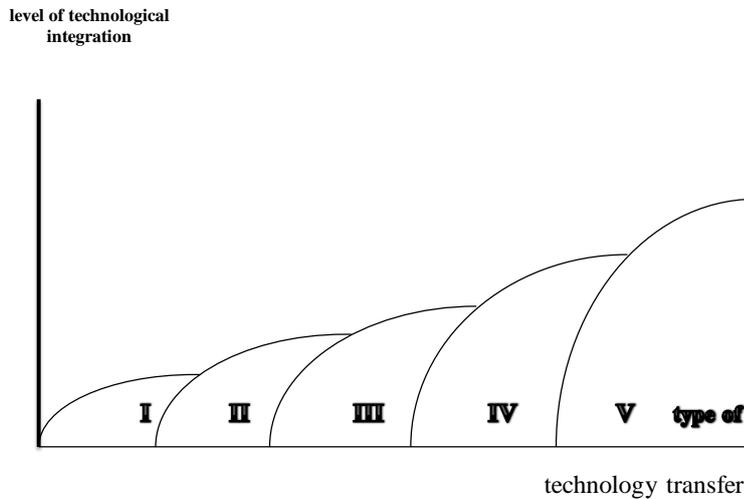
Those are elements which add to the technological capabilities to the OCF

firms. Instead of leaving them at an individual firm level to the “market forces” as it happens in India today due to faulty policies and poor implementation of even good policies, it is necessary to orchestrate the whole process in India with all the willing firms and all the willing colleges. Basic knowledge inputs for such a “technology intermediation effort” (See Ref. 18) has to be done by the State with sophisticated modern methods and flexible governance systems. Such actions will create the necessary innovation system, though at a bottom level to begin with.

But one cannot be satisfied with such a state of capability. One has to go forward.

Again to source a figure from Radosevic (Ref 12), it describes the evolutionary process of transformation of IT from mere outsourcing (intelligent though) to higher levels of capabilities.

Discontinuous character of technology learning within alliances



I	II	III	IV	V
Cost reductions; Standard quality	Quality improvements; Flexibility and response time	Product customization; Process improvements	Minor joint product developments	R & D co – operation; Major joint product developments
Cost cutting alliances		Process and product development alliances		Pre-competitive and product development alliances
First threshold level		Second threshold level		Third threshold level
Standard quality processor or contractor		Specialty subcontractor		Technologically integrated; Strong learning-by-exporting inputs

If the figure is read along with the table with the background of the

discussions so far (earlier), one can be clear about the various (more) challenging steps for the firms and therefore for the

participating academic and S & T institutions. All these steps have great challenges and opportunities for the elite, medium and private institutions / colleges. Govt. has a role to play as a facilitator – also through incentive / disincentive systems to make the better institutions to focus on these processes rather than being lost in so called “blue sky research” agenda set up by developed countries for themselves.

With the size of Indian human resource and domestic market, Indian firms and institutions have a great opportunity before them for creative challenges, more wealth and profit, as well as the excitement of achieving leadership position in the global markets in several areas.

But this cannot be done by hypes and hyperbolic policy statements.

Can be achieved only through orchestrated and sustained policies and implementation by Govt., firms, institutions, media and others over a period of 15 – 20 years (minimum gestation period).

Let me quote:

Observe calmly; secure our position; cope with affairs calmly; hide our capabilities and bide our time; be good

at maintaining a low profile; and never claim leadership.

AN OVERVIEW

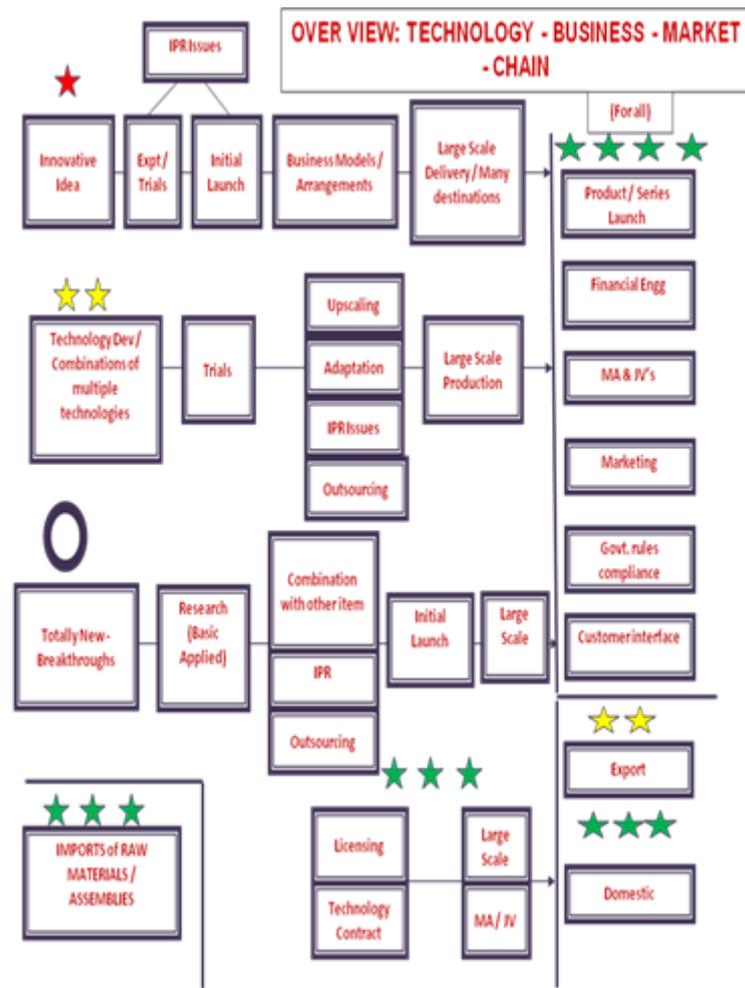
So far we have covered as to how we need to orient policies and procedures such as to acquire technological capabilities in the firms, academic and S & T institutions, governance systems etc. If the orientation is not suiting the demands of the globalization processes under way as well as the rapid growth of multiple technologies which are increasingly customer options oriented, the firms and institutions of that country will be left behind with serious implications in terms of denying better incomes, prosperity and well being of the bulk of the people.

Since many countries are in the race there is a need to catch up faster and be agile to changing situations.

As explained earlier there are no single point solutions, such as more of R & D or basic research means innovation and leadership; outsourcing or continual imports or continual merger and acquisitions abroad will do etc., will not suffice either. It is a multipronged attack depending upon the context along with, agile mid course corrections but having a clear overall strategic view of arriving at a

leadership position in order to achieve a respectable stature for interdependence in the world.

In the context of such a multipronged approach, an overview flow diagram of technology to market and customer as applicable to 2010 period is given in this text. This diagram is true for any country and has to be adapted sector by sector or even for sub sectors in order to derive practical insights. It can be used at a firm level too if it is big or a group of firms. It will require lots of inputs in terms assessment of current global situation and the context of firm / group / sector etc; technology foresight relevant to the sector; potentials for the firm / group / institution etc. It will be a knowledge intensive exercise. It can take several weeks to several months depending on the magnitude of the scope covered. For a country as a whole (like say India), it will take at least a year.



In that diagram, only a very broad brush impressionistic / intuitive (derived from experience) indicator is given in terms of rating as stars. For a particular sector or sub sector it may vary. But by and large for a macro view of the country's position in terms of capabilities at the various levels of the value chain from an idea to actual customer service, the star rating is reasonably correct.

On the right side of the figure is clubbed all tasks relating to reaching the market / customer service / meeting

special regulations, if any, in the country of market (foreign for exports or domestic) etc.

Post liberalization in 1991, the Indian private sector has progressed remarkably well in terms of achieving various targets for the elements in the right hand side in the competitive global market (i.e. export as well as domestic competition by imported goods or with foreign entities operating in India). They have done it despite the fact that governmental enabling systems are poor compared to their counterparts in the world. PSE's performance is not to their full potential because of the various constraints posed by the promoter owner that is, Govt. They are still under various bureaucratic and political controls. Once freed PSE's will also do well. Therefore all the elements in the right hand side except the bottom two elements is four star (out of five) for Indian companies. Bottom two elements of the right hand side are shown as EXPORT and DOMESTIC.

In EXPORTS India is still a small player. Indian Pharma firms, chemical firms etc do better, but most others are small. (See Ref 9 for a brief glimpse of global position of Indian Industry) Of course the issues are not merely that of science, technology and engineering. But they can also help to achieve better

competitiveness. Our assessment overall for Indian industry is two star out of five. Lot of work is needed.

Performance in meeting the domestic sector market is better. Indian domestic demand in high and is growing. Still the performance of the Indian companies in reaching the vast domestic market is still not very high; hence it gets three stars. Lot needs to be done, be it reaching IT and IT enabled systems to rural areas or doing special and quality products for rural and small town markets etc. They are yet to reach the real bulky base. Of course there are various constraints such as absence of electricity, other infrastructural inadequacies, poor governance leading to delays and corruption etc. But still there is a scope to improve.

For the right hand side elements there is very little interactions with Indian academic and S & T institutions. Even MBA institutions including elite ones do not participate and are mostly being happy with foreign case studies. Of course the academic institutions turn out the rich human resources of young qualified men and women who learn and adapt while in job.

We suggest that upscaling to five star status will require several endogenous

knowledge inputs and knowledge intermediation. Close partnership with academic and S & T institutions, of all types, not just elite ones, will broaden the gene pool of innovative ideas which will in turn help the companies doing business.

For example, good practicing technologists from the academic and S & T institutions along with experts from industries can visit many exports markets in which the Indian companies have entered. If planning and follow up exercises are done well each big company and a group of MSME's could have their own well informed 'think tanks' which can help the company to chart out new innovative paths to increase their market presence or to improve profits etc.

Now the question is who will make the first move given decades of respected (or suspicious) hiatus between the academia and corporate sector in India?

It is hoped that some of the listeners of the talk or readers of this paper will attempt: One is aware that it is not an easy task. But it is in the interest of all Indian people and also the main stake holders – the companies and the academia.

In the export sector, to graduate from two star to say four star and in the domestic sector to graduate from three star to five star are great challenges. For the

domestic sector the colleges spread all over India can do a great job, if companies / firms include them in partnership. The experience from TIFAC – CORE and other TIFAC projects mentioned earlier are good examples and forerunners for such partnerships. For the export sector, young persons now working in India having had a study or work experience abroad will be of great help.

Of course if State / Central governments take active interest – not for a central planning nor for supervisory control – but as a facilitator for technology and knowledge intermediation, the process will be accelerated. But such facilitating agencies should keep in mind the diversity, complexity and fast moving nature of globalization and technologies, so that they avoid single point guidelines – one shoe fit all type – which will appear excellent on paper and in air conditioned meeting rooms, but will fail in practice. This is the experience of the past several attempts by various central government departments including S & T departments. If such a mindset continues it is better not to do a facilitatory process!

Now moving leftward of the figure let us look at the bottom of the chain. They involve various tasks like licensing arrangements with principals abroad for manufacture and other aspects or having

long term contract with the outsourcing DCF firms, technology contracts of various forms including consultancy accreditations, project management of these elements etc and using these to start large scale production in India. Most companies in automobile sector, chemical sector, electronics etc use these processes. Since Central govt. controls have become minimal since the period of liberalization (post – 1991) PSE's also do well despite their governance constraints. As a part of large scale operations and depending on the needs of specific technologies or market access, mergers and acquisitions as well as joint ventures are done. Mostly Indian companies are very good in the process. Hence there is a three star.

Here again there is a good scope for partnership between academic / companies / firms and S & T institutions on the lines suggested above. Technology foresight, IPR searches, technology assessment and identifying areas of incremental improvements in the short and medium term and organizing technology acquisition or development of the same etc could be the tasks.

In the extreme left hand end one would notice the input elements for most of the companies – imports of raw materials / assemblies. Indian companies in the overall cannot be considered to be

excellent but are very good. Better technological knowledge coupled with market / business aspects can help them in competitiveness in terms of cost, quality and performance. This again is an excellent area for academic / S & T institutions to partner with industries. Each S & T institution or a group of them may specialize in select sectors. Many such groups in turn can network themselves as Knowledge / Technology Intermediation groups. There is a plenty of scope for knowledge / experience sharing between industries as well as partner institutions.

Let us go up in the chain second from the bottom. This is indicative of a line of technology development, production and marketing starting with new break through ideas for technology. Though there are occasional media hypes and misinformation from some S & T institutions, there are no such break through ideas coming from an Indian firm or institution which has tried to move rightward. We are still followers and everybody is conditioned to think whether it has been done elsewhere, even for basic science research! The review committees at most laboratories or at the funding agencies will ensure nothing break through can be proposed!

We leave this chain for a moment hoping for a better future. Hence shown as a big zero.

Third chain (upwards) from the bottom left hand extreme indicates some technology development mostly as adaptive or with some incremental value addition or combination of several existing technologies in a different configuration or process to derive a better product.

Firstly they go through various trials and then go through further steps. Since WTO regimes are in operation, IPR issues are critical. Some elements of the work may be outsourced by the Indian firm to others in India or abroad (eg getting a design for a high value leather good from France or Italy etc). Then the firm can enter into large scale production and go further right.

Indian companies have started making some presence in this chain: examples are in automobile sector – full systems and auto components, also in pharma; chemical etc. Still the total number of such companies are small. Most of companies prefer to adopt the bottom line of licensing, technology contract discussed earlier. Thus for this chain, we give two stars out of five.

Though currently the number of firms / companies involved in venturing

into this chain even for some of their product lines, is small now, it is a huge area of opportunity for academic and S & T institutions to partner with industries. Many more Indian firms / companies will venture when they see the initial adventures benefit the industries / firms, in terms of new markets, increased profits etc. Knowledge intensity required for this chain will provide new challenges for the academic and S & T institutions especially the ones which are already better equipped. But S & T / academic institutions under govt sector try to shun this chain, as they get substantial funds from Govt. which they can use for research of their own choice without the necessity of having pressures to meet targets and schedules. **With the slogan of investing more in S & T to increase the share of expenditure in S & T as percentage of GDP, merely to show the macro level statistics, will lead to a situation where most S & T / academic institutions which are already well funded by Govt. will shy away from taking the real challenges required to build technological capabilities of the Indian firms. If such a situation continues, even if our S & T / academic institutions invent some new technologies there would be no takers from the Indian firms / companies.** Then the inventors have to try to find foreign

companies who may take them but it is not going to be an easy process.

Therefore concentrating on this chain for various sectors and sub sectors by our academic / S & T institutions and working with Indian firms in their real problems and challenges will not only be profitable for India but also build up within the management of Indian firms a trust about the capabilities of Indian S & T / academic institutions. Then they will be ready to go towards the top chain in which they will start with an innovative idea from within their firms and especially from our academia and laboratories. **Today their (firms') trust level on academic national S & T laboratories is very low. Trust can build up only through real life positive examples.**

If the top chain gets populated with several success stories by Indian firms in the domestic and global markets with "Invented in India" brand, then India would have arrived at a respectable interdependence level in the global competitive market. It will then be innovative India.

The top chain as of now only has come episodic examples, those too being small ones. Most of them are due to the struggles of a few brave men and women in the difficult ecosystem of India. That is

why it is shown single star out of five star. India cannot afford to be in the same situation for another decade when she is really growing up her economy and becomes a reasonable size in global terms.

In order to upgrade the top chain, confidence in industry – academia partnership should be built up through the bottom most chain, third from bottom chain and then arrive at the top chain soon. (The break through chain can be in general forgotten or kept in abeyance for a decade or so till other chains function well).

If this chain approach is taken seriously first by academic and S & T institutions (national laboratories), then the firms / companies would respond. Then pressure can be built up on Govt. technologies funding agencies / schemes to modify the current straight jacketed and unrealistic rules.

Then the powerful Industry – Academia lobby which will be wide spread all over India, can then force the governance mechanisms to change in order to create a good national ecosystem for innovation (which is currently rated poor by global standards). India : The uneven innovator by Kirsten Bound, The Atlas of Ideas: Mapping the new geography of science published by DEMOS, first

published in the year 2007. ISBN 1 84180 171 2 (Ref 22)

GLOBAL LEVEL INNOVATIVE

INDIA

That brings us to the last section of this long paper / talk. It is best to refer to a book titled “Innovation Policy in a Global Economy” edited by Daniel Archibugi, Jenemy Howells, and Jonathan Michie published by Cambridge University Press (1999), Ref 23) transferred to digital printing in 2003. <http://www.cup.cam.ac.uk> and <http://www.cup.org> . It comprises twelve chapters by eminent experts. Each of the chapter brilliantly bring out the actual experiences, analyses thereof as well as suggestions for actions for the future. Especially in the context of the latter element it is an unusual book and is therefore useful for practitioners in firms, institutions and policy makers.

Chapter 2 of the book is titled “Technology Policy in the Learning Economy” by Bengt – Ake Lundvall. The author has effectively brought out the idea that world is past mere knowledge economy and in fact through operation of knowledge economy, another equally critical element has started dominating. That is, “learning”. In the words of the

author “The concept emphasizes that we today find ourselves in an economy in which the competitiveness of individuals, firms and entire systems of innovation reflects the ability to learn.” The author elaborates various aspects of the learning economy such as the changes in the structure of labour market and production, and the fact that the increasing proportion of output is knowledge and information. Te author further points out that “learning and especially learning new skills and competences is necessarily a social and interactive process....” And further elaborates the social dimension. Hence the learning economy cannot flourish in pure market economy and the author recalls Nobel prize winner Kenneth Arrow’s paradoxical observation “that people will only pay for knowledge they do not have – but that, on the other hand it is difficult to assess how much to pay when you do not know what you are getting for your money”.

The chapter -2 further explores the learning process and arrives at the need for TRUST, another difficult item to incorporate in an economic analysis. Again there is an Arrow quote “trust cannot be bought; and if it could, it would have no value whatsoever”.

It is good to read the whole book and especially Chapter -2. Other issues

discussed are: plan versus market – a dead issue?; competence and social equity; etc. then are given six steps in the formulation of a knowledge – oriented technology policy. They holistically cover many elements referred to in this talk (paper).

In its summary part of the chapter – 2 the author concludes: “..... in the learning economy the primary task of industrial and innovation policies will be to promote learning processes involving a interaction between sub – systems, organizations and individuals. This involves, among other things, ensuring good communication between knowledge producers such as universities and schools on the one hand, and firms, on the other. But it is even more important that firms, both on an individual basis and in an interplay with each other, invest in knowledge creation. It is also of crucial importance that the knowledge created in one firm is used to stimulate innovation in other firms. Particularly with respect to organizational renewal, it is imperative that firms are encouraged to learn from each other.”

These words emphasize what the current paper reiterates in various sections. They also further strengthen the need to address different chains described earlier in order to build trust between the firms and S & T / academic institutions. In turn

they will learn from each other and continue to innovate in the global economy and global knowledge society.

Let us all work for enjoying our participating in such a knowledge society and more importantly bring the benefits to all Indians.

It will, of course, require that we totally change our present mindsets and adjust ourselves to the demands of new paradigms unfolding rapidly in the globalizing world.
Thank you.

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Plastic: Waste to Fuel



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Abstract:

Plastics consumption has increased rapidly throughout the world. Approximately 40% of the plastics have life duration shorter than 1 month, thus there is a huge waste stream creating a serious environmental problem. Thermoplastic polymers make up a high proportion of waste and this amount is continuously increasing, thus posing a more serious environmental challenge because of their huge quantity and disposal problem as thermoplastics do not biodegrade for very long time. Different methods like land filling, incineration, gasification, recycling etc., are used to get rid of them. But by using most of these processes, the resources used to make the plastics are lost and no recovery can be made. In this world of continuously declining natural fuel sources, making of fuel from the waste plastic can be a very beneficial. Various methods like pyrolysis, fluidized catalytic cracking, thermal and catalytic cracking etc., can be used for generation of fuel from waste plastics. Plastics can even be used as fuel themselves in blast furnace with coal. So here is a brief description of the methods used to generate fuel from plastics, Waste Plastics.

Keywords: Plastics, incineration, waste, natural fuel, environmental challenge.

Introduction:

The huge population increase coupled with the improved living conditions of the people led to a dramatic increase of the consumption of plastics worldwide.

The chief usages of polymeric materials are in:

1. Packaging,
2. Household and domestic products,

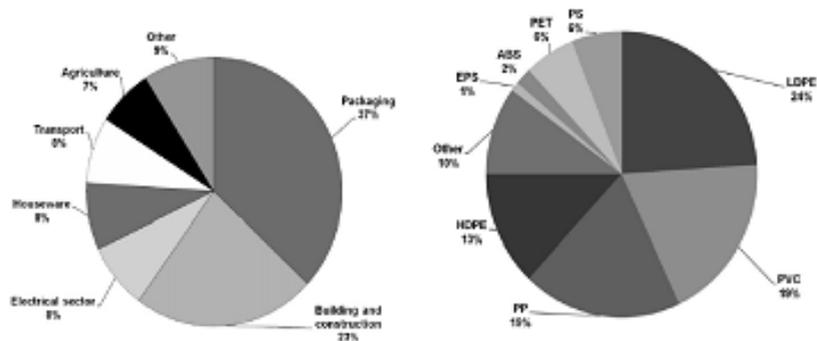


Figure: 1: Plastic Consumption, according to industry and polymer. UK⁵

3. Electrical and electronic goods,
4. Building and construction,
5. Automotive industries, etc...¹

Plastics consumption has increased rapidly throughout the world. The annual plastic consumption in United States was 30 million tons in 2006 and 48.8 million tons in Western Europe in 2003. In Asia, the consumption rate is less per person but growing faster than that of the US or Europe.²

Our modern society is unimaginable without plastics. Nowadays both the consumption and production of polymers are increasing, but the increasing amount of polymer wastes from them generates further environmental problems³. Approximately 40% of the waste plastics have life duration shorter than 1 month, thus there is a huge waste stream creating a serious environmental problem⁴.

Thermoplastic polymers make up a high proportion of waste and this amount is continuously increasing, posing a more serious environmental challenge because thermoplastics do not biodegrade for very long time¹. Plastic products, such as polyethylene terephthalate (PET), high-density polyethylene (HDPE), polyvinyl chloride (PVC), low-density polyethylene (LDPE), polypropylene (PP), polystyrene (PSI, polyurethane and polyphenols, make up 83% of the production of plastics⁵. See figure1.

MAJOR METHODS TO GET RID OF PLASTIC

WASTE:

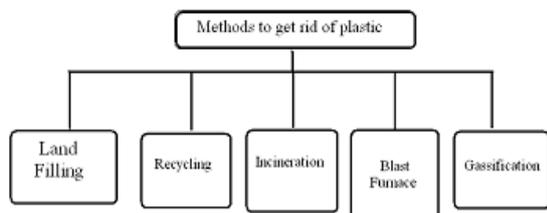


Figure: 2 Methods to get rid of Plastic⁵

1. Land Filling:

The disposal of solid tire wastes from human activity is a growing environmental problem for the modern society, especially in developing countries. This organic solid waste is non-biodegradable. One common way of disposal is land filling. Land filling for disposal of used tires is connected with some problems: it needs a considerable amount of space because the volume of tires cannot be compacted.

Dumped scrap tire in massive stockpiles is one of the possible causes of ideal breeding grounds for disease carrying mosquitoes and other vermin with the aid of rain water, which is deposited in the free space of the tire wall. Also, land filling is a potential danger because of the possibility of accidental fires with high emissions of hazardous gases.⁶

2. Recycling

Currently, however, only somewhere between 5 and 25% of plastic waste is being recycled. Recycling of plastics should be carried in such a manner to minimize the pollution during the process and to enhance the efficiency of the process and conserve the energy. Plastics recycling technologies have been historically divided into four general types -primary, secondary, tertiary and quaternary.

Primary recycling involves processing of a waste/scrap into a product with characteristics similar to those of original product.

Secondary recycling involves processing of waste/scrap plastics into materials that have characteristics different from those of original plastics product.

Tertiary recycling involves the production of basic chemicals and fuels from plastics waste/scrap as part of the municipal waste stream or as a segregated waste.

Quaternary recycling retrieves the energy content of waste/scrap plastics by burning / incineration. This process is not in use in India.⁷

Mechanical recycling processes are limited to thermoplastics and technical limitations for the treatment of mixed plastic wastes, together with the limited size of the market for recycled products, difficulties in maintaining product quality and fluctuations in the price.⁸

The problems associated with the recycling process are as follows:

- Many types of plastics are used hence it is difficult to segregate them for specific purpose.
- Plastics contain a wide range of fillers & additives.
- Many times plastic is associated with metal, glass etc.
- Sorting of plastic is technically difficult as well as expensive.
- Recycling of plastic degrades the quality of the end product

3. Incineration

Often practiced in developed economies is incineration with energy recovery. In this, waste is burnt, thereby significantly reducing the volume of waste requiring

disposal. Incineration with energy recovery is not an action specific to the packaging waste, but is relevant to municipal waste at large. If the overall goal of the waste management system is to minimise the disposal to landfills⁹, incineration can complement the recycling systems. Incineration with energy recovery is a feasible option in countries where material recycling is low and waste has a high calorific value.

In the case of India, incineration with energy recovery may not be a feasible option, considering the fact that material recycling of plastics is as high as 60%. This may not leave waste with much calorific value, thus making incineration with energy recovery a non-viable option.¹⁰

Due to the generation of unacceptable emissions of gases such as nitrous and sulphur oxides, dusts, and dioxins, incineration can no longer be an important mode of waste disposal.⁸

4. Blast furnace

Waste plastic may be used in place of coke and pulverized coal after forming into particles of the required size and

subsequently injected into the blast furnace. The injected plastic is broken down to form reducer gas ($\text{CO} + \text{H}_2$), which rises through the raw material in the furnace and reacts with the iron ore. The injection of chlorine-contained plastics such as PVC in the blast furnace generates hydrogen chloride. The limestone used in the blast furnace to control the composition of the slag neutralizes the hydrogen chloride in the furnace and decrease its concentration.

But substitution of coke with plastic is limited to approximately 40% wt only.⁹⁻¹¹

5. Gasification

Gasification is essentially thermal decomposition of organic matter under inert atmospheric conditions or in a limited supply of air. If the feed contains chlorinated compound like PVC then it is advisable to do gasification at a lower temperature to remove chlorine then the temperature is raised to convert higher hydrocarbons.

There are problems in controlling the combustion temperature and the quantity of unburned gases.¹²

In Europe, recycling rates for post-use plastic waste were as follows:

1. Incineration with energy recovery (14%),
2. Mechanical recycling (6%)
3. Feedstock or chemical recycling (0.3%).¹³

Different Steps involved before carrying out the above or the below mentioned process:



Figure: 3 Different Steps involved¹³

1. Collection:

When thinking about setting up a small-scale recycling enterprise, it is advisable to first carry out a survey to ascertain the types of plastics available for collection, the type of plastics used by manufacturers (who will be willing to buy the reclaimed

material), and the economic viability of collection.

The method of collection can vary. The following gives some ideas;

- House to house collection of plastics and other materials (e.g. paper).
- House to house collection of plastics only (but all types of polymer).
- House to house collection of certain objects only.
- Collection at a central point e.g. market or church.
- Collection from street boys in return for payment.
- Regular collection from shops, hotels, factories, etc.
- Purchase from scavengers on the municipal dump.
- Scavenging or collecting by oneself.

The method will depend upon the scale of the operation, the capital available for set-up, transport availability, etc.

2. Initial upgrading

Once the plastic has been collected, it will have to be cleaned and sorted. The techniques used will depend on the scale of the operation and the type of waste collected, but at the simplest level will involve hand washing and sorting of the plastic into the required groups. More sophisticated mechanical washers and solar drying can be used for larger operations.

Sorting of plastics can be by polymer type (thermoset or thermoplastic for example), by product (bottles, plastic sheeting, etc.), by colour, etc.

3. Size reduction techniques

Size reduction is required for several reasons; to reduce larger plastic waste to a size manageable for small machines, to make the material denser for storage and transportation, or to produce a product which is suitable for further processing.

There are several techniques commonly used for size reduction of plastics:

- *Cutting* is usually carried out for initial size reduction of large

objects. It can be carried out with scissors, shears, saw, etc.

- *Shredding* is suitable for smaller pieces. A typical shredder has a series of rotating blades driven by an electric motor, some form of grid for size grading and a collection bin. Materials are fed into the shredder via a hopper which is sited above the blade rotor. The product of shredding is a pile of coarse irregularly shaped plastic flakes which can then be further processed.
- *Agglomeration* is the process of pre-plasticising soft plastic by heating, rapid cooling to solidify the material and finally cutting into small pieces. This is usually carried out in a single machine. The product is coarse, irregular grain, often called crumbs. See figure 4.

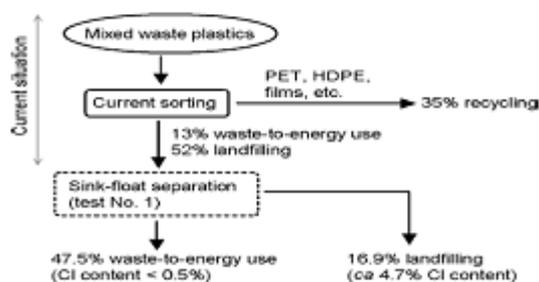


FIGURE: 4¹⁴

FUEL FROM PLASTIC:

Management of plastic wastes is a hot issue and currently about 90% of the plastic wastes are disposed in landfills and incineration, but both these applications are not environmental friendly and create other problems¹⁴. To avoid environmental problems and use plastic waste as a resource, alternative solutions are needed.

It can be converted into useful products for resource recovery. To overcome the current energy crises in the world, new energy resources should be explored among which waste high-density polyethylene could be used as raw material. One of the possible solutions is thermal/catalytic degradation of the plastic materials to obtain a useful and selective degradation product like fuel oil and laboratory chemicals¹⁵.

Energy recovery as fuel is a preferred option for utilizing plastic wastes when their potential recycling as raw material for product manufacturing is not possible because their physical properties have been damaged during long exposure to sunlight.¹⁶

It was found that the degradation process is a suitable technique for converting waste polymers into liquid hydrocarbons. The volatile products could be used as feedstock components, e.g. in refineries. Their further utilization for petrochemical purposes has not yet been solved. One possibility is a fuel-like application or mixing in fuels as a blending component. Before blending the high olefin content is to be saturated with hydrogen, or hydroisomerized. These steps result in a high quality synthetic diesel fuel, with high cetane number, and theoretically free from sulphur, nitrogen and metals. In practice these fractions generally have a very low heteroatom content, even if the raw material was pure and not waste, because most polymers contain, e.g. sulphur containing anti-flame or antioxidant additives, etc.¹⁷. See Figure 5.



Figure: 5¹⁷

A research-cum-demonstration plant was set up at Nagpur, Maharashtra for conversion of waste plastics into liquid fuel. The process adopted is based on random de-polymerization of waste plastics into liquid fuel in the presence of a catalyst. The entire process is undertaken in a closed reactor vessel followed by condensation, if required. Waste plastics while heating upto 270⁰C to 300⁰C convert into liquid-vapour state, which is collected in a condensation chamber in the form of liquid fuel while the tarry liquid waste is topped-down from the heating reactor vessel. The organic gas is generated which is vented due to lack of storage facility. However, the gas can be used in dual fuel diesel-generator set for generation of electricity. Process is as shown in the diagram above.¹⁷

India has been a favored dumping ground for plastic wastes, mostly from industrialized countries like Canada, Denmark, Germany, UK, the Netherlands, Japan, France and the United States. According to the Government of India import data, more than 59,000 tons and 61,000 tons of plastic waste have found its way into India in the years 1999 and 2000 respectively.¹⁸ See table 1.

Table 1¹⁹:

India is the fourth highest Asian importer of plastic waste.

Country	No. of Shipments	Total (kg)
Hong Kong	586	1,71,37,118.00
Philippines	58	24,45,200.00
Indonesia	50	22,48,443.00
India	11	9,98,046.00
Malaysia	7	2,54,935.00
China	6	95,746.00
Taiwan	6	1,56,453.00
Thailand	6	1,23,974.00
Korea	6	1,09,807.00
Japan	5	51,210.00
Singapore	6	71,437.00
Total	747	23,692,369.00

DIFFERENT WAYS: WASTE PLASTIC TO FUEL

1. Pyrolysis:

Pyrolysis provides an excellent alternative for the disposal of plastic wastes with the recovery of valuable transportation fuels like gasoline, kerosene and diesel.

- 1.1 Thermal pyrolysis of plastic yields a very broad compositional range of low-value mixture of liquid hydrocarbons
- 1.2 Catalytic pyrolysis yields a more narrow range of products, most suitable for transportation fuels.

Pyrolysis of waste plastic affords high rates of conversion into liquid fuels that can be used as feedstock in refinery²⁰. The advantage of pyrolysis is that the waste plastics do not have to be separated ahead of time, thereby, eliminating the labor-intensive step as required in the hydrolysis

and mechanical recycling methods. The production of transportation fuels from waste plastics is an emerging technological solution to the huge amount of waste plastics that cannot be economically recovered by conventional mechanical recycling processes. The pyrolysis of mixed plastics has been considered as an effective way to convert waste plastics into environmental and industrially useful hydrocarbon products.²¹

The mechanism of thermal degradation of waste plastic is very complex and includes, amongst others, the following reactions: chain fission, radical recombination, carbon-hydrogen bond fission, hydrogen abstraction, mild-chain α -scission, radical addition, etc.²¹

Example 1: Pyrolysis of waste from agricultural and packaging sector:

Selectively collected waste high-density polyethylene (HDPE) and polypropylene (PP) from agriculture and packaging sectors were used as raw materials. Both waste plastics were washed and shredded before pyrolysis. It is also clear that both plastic wastes have sulphur content (238

and 49 mg/kg respectively), while nitrogen, phosphorus and calcium additionally have been found only in the case of polypropylene (963 mg/kg, 47 mg/kg and 103 mg/kg). In all probability fertilizers (possibly superphosphate and ammoniumnitrate) can be accumulated in the surface of polyethylene agricultural wastes, which could not be removed by washing procedure. The super-phosphate and ammonium-nitrate are widely used fertilizers, in which generally are also calcium and sulphur containing other chemicals. See figure6.

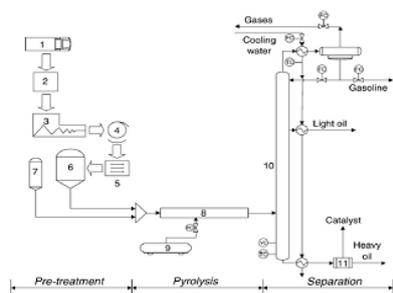


Figure: 6 Applied apparatus for pyrolysis of waste polymers
 1—Transportation, 2—Selective collection, 3—Shredding, 4—Washing, 5—Drying, 6—Waste storage, 7—Catalyst storage, 8—Reactor, 9—Heating gas storage, 10—Separation unit, 11—Catalyst filter

Pyrolysis of waste polymers was carried out in continuous reactor with feed rate of 9.0 kg/h at 520°C. As shown in the figure 6, plastics with suitable grain size had been stored in a raw material storage unit. Raw material was mixed with the catalyst (For supporting the more intensive cracking of C-C bonds of main polymer structure a commercial ZSM-5 catalyst was tested in concentration of 5.0%.) then

that mixture was fed in the reactor by an electrically heated extruder, where the polymer was preheated. The outside wall temperature of the feeder was 280°C in each case. The extruder was directly connected to the reactor in the beginning section. See table 2.

Table 2

The main properties of waste polyolefin.

	Polyethylene	Polypropylene
Source	Agricultural	Packaging
MFI, g/10 min	7.1	40.0
Density	0.965	0.905
S, mg/kg	238	35
N, mg/kg	963	No
P, mg/kg	47	No
Ca, mg/kg	103	No
Other impurities	No	No

Inside the gas heated reactor the waste polymer had melted and their carbon chain cracked into fragments with lower molecular weights. To reach better heat transfer the hydrocarbon flow had been driven by using special mixing equipment inside the reactor tube. For adjusting the temperature constant thermocouples and electronic PID controllers were used both in the extruder and pyrolysis reactor.

Table 4:

In the distillation column hydrocarbons were separated into different products: gases, gasoline, light and heavy oil. The column bottom temperature was 380°C.

Catalyst was separated from the bottom product by filtration in thermo-catalytic pyrolysis.

Gases from polypropylene pyrolysis consisted mainly of C₃ hydrocarbons both catalytic and non-catalytic cases (55.9% and 54.6%), in contrast to agricultural waste, where the C₂ (52.0% and 45.6%) and C₄ (31.7% and 25.5%) compounds were the most significant fractions. For these results basically the chemical structure of raw materials is blamed too. See table 3.

which resulted to high amount of propylene (30.0% and 30.1%) and propane (25.9% and 24.5%). Data also well demonstrates that the formation of alkenes was a bit higher than alkanes of the same carbon number.

The calculated heating values of gases were 45.9–46.6 MJ/kg, which is enough for high energy generation to heat consumption of pyrolysis.

It is well discernible that carbon-chain isomerization takes place in the presence

The structure of gasoline and light oil fractions.

Products	Gasoline				Light oil			
	HDPE	HDPE + catalyst	PP	PP + catalyst	HDPE	HDPE + catalyst	PP	PP + catalyst
n-Paraffin	49.6	33.9	18.8	8.3	49.2	35.5	14.4	7.9
i-Paraffin	3.0	20.4	41.1	51.4	3.3	15.4	47.1	52.1
Vinyl olefin	43.9	9.3	4.2	2.7	41.5	8.8	3.7	3.1
Vinylidene olefin	2.5	2.1	34.0	22.7	2.1	3.6	31.0	20.5
Vinylene olefin	1.0	32.6	14	12.9	3.9	35.2	3.4	14.5
Aromatic	0.0	1.7	0.5	2.0	0.0	1.5	0.4	1.9

Table 3:

The composition of gases obtained by plastic waste pyrolysis.

	HDPE	HDPE + catalyst	PP	PP + catalyst
Methane	3.1	2.5	4.2	4.8
Ethene	30.6	26.1	11.4	6.6
Ethane	21.4	19.5	7.3	6.4
Propene	8.9	8.9	30.0	30.1
Propane	4.3	6.8	25.9	24.5
Butene	17.1	14.6	11.8	9.5
Butane	14.6	10.9	9.4	6.2
i-Butane	0.0	10.7	0.0	11.9

The carbon chain of PP cracked in highest likelihood at the ramification of the chain,

of catalysts, but the yields of branched hydrocarbons were lower in the case of polyethylene than polypropylene. For the high level of α -olefins basically the α -scissions are blamed, which are the ruling reaction in thermal case. See table 4.

In catalytic case ions should be isomerized and result to branched hydrocarbons and internal olefins. The carbon frame isomerization effect was more notable in gasoline than that of light oil. When catalyst had been used, the concentration of branched compounds was 6.8

(polyethylene) and 1.3 (polypropylene) times more in gasoline related to the catalyst free pyrolysis, while the increase was only 4.6 (polypropylene) and 1.1 (polypropylene) times in light oil. Therefore the catalytic effect was more significant of smaller molecules. See table 5.

consumer polymer waste stream in North-Taiwan with the component of polyethylene (~62 wt.% PE+~38 wt. % HDPE+~24 wt.% LDPE), polypropylene (~34 wt.% PP), polyvinyl chloride (~3 wt.% PVC) and with about 1 wt.% polystyrene (PS) mixtures.

Typically, the content of waste plastic

The other properties of fractions pyrolyzed.

	HDPE			HDPE + catalyst			PP			PP + catalyst		
	Gasoline	Light oil	Heavy oil	Gasoline	Light oil	Heavy oil	Gasoline	Light oil	Heavy oil	Gasoline	Light oil	Heavy oil
Density, g/cm ³	0.765	0.832	0.865	0.758	0.821	0.849	0.751	0.819	0.850	0.745	0.819	0.810
RON	78	-	-	85	-	-	85	-	-	88	-	-
MON	71	-	-	76	-	-	73	-	-	79	-	-
Cetane number	-	69	-	-	62	-	-	65	-	-	63	-
Viscosity, mm ² /s	-	2.26	6.49	-	2.22	6.39	-	2.20	6.30	-	2.12	6.13
Flash point, °C	-	93	225	-	90	215	-	92	215	-	82	208
CFPP, °C	-	4	-	-	3	-	-	1	-	-	-4	-
S content, mg/kg	75	119	195	37	83	155	5	7	12	1	2	6
N content, mg/kg	627	720	996	382	475	782	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
P content, mg/kg	62	67	70	36	42	48	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Ca content, mg/kg	n.d.	n.d.	179	n.d.	n.d.	231	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Other impurities	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Boiling range, °C	23-209	110-359	320-660	25-211	113-353	318-646	23-216	115-353	321-650	24-210	107-359	315-640
Caloric value, MJ/kg	-	-	40.5	-	-	40.8	-	-	40.8	-	-	41.6
M, g/mol	119	237	-	112	230	-	112	233	-	102	223	-

The viscosity of light and heavy oil fractions was measured at 40 °C and 100 °C, respectively. The boiling point range of heavy oils was given using simulating distillation.

Table 5:

Their caloric values were about 41.0 MJ/kg, which is quite high to application of these fractions for energy producing.²²

Table 6:

Catalyst	Si/Al	Surface area (m ² /g)			Pore size (nm)	Commercial name
		BET ^a	Micropore	External		
FCC-R1 ^b	2.1	147	103	44	-	Equilibrium catalysts ^c
Silicalite	>1000 ^d	362	297	65	0.55 × 0.51	Synthesized in-house
HUSY	5.7	472	375	118	0.74	Ultrapabilised Y zeolite ^c
ZSM-5	17.5	375	257	118	0.55 × 0.51	ZSM-5 zeolite ^c
SAHA	2.6	268	21	247	3.28	Amorphous silica-alumina ^c

Example 2: Pyrolysis of hospital plastic waste:

The mixture of hospital waste plastics used in this study was obtained from post-

sample tested by element analysis was about:

84.84% C, 12.31% H, 2.72% Cl, 0.06% O, 0.07% N, and 0.13% S.

A three-zone heating furnace with digital controllers was used and the temperatures of the furnace in its upper, middle and

bottom zones were measured using three thermocouples. By these means the temperature of the pre-heated nitrogen below the distributor and catalyst particles

(See table 6) in the reaction volume could effectively controlled to within ± 1 °C. The polymer feed system was designed to avoid plugging the inlet tube with melted polymer and to eliminate air in the feeder. The feed system was connected to a nitrogen supply to evacuate polymer into the fluidized catalyst bed. See figure 7.

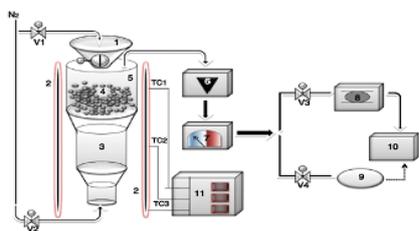


Figure 7: Schematic diagram of a catalytic fluidized-bed reactor system.²³

1. feeder, 2. furnace, 3. sintered distributor, 4. fluidized catalyst, 5. reactor, 6. condenser,
7. de-ionized water trap, 8. 16-loop automated sample system, 9. gas bag, 10. GC, and
11. digital controller for three-zone furnace.

Thus, commingled polymer particles were purged under nitrogen into the top of the reactor and allowed to drop freely into the fluidized bed. Volatile products leaving the reactor were passed through a glass-fiber filter to capture catalyst fines, followed by an ice-acetone condenser to collect any condensable liquid product.

A de-ionized water trap was placed in series after the condenser to catch any HCl produced by the degradation of PVC

component. A three-way valve was used after the condenser to route product either into a sample gas bag or to an automated sample valve system with 16 loops. The Tedlar bags, 15 L capacity, were used to collect time-averaged gaseous samples. The bags were replaced at intervals of 10 min. throughout the course of reaction.

Summary of the main products of post-consumer waste plastics degradation at reaction temperature of 390°C over various catalysts (fluidizing N₂ rate=570 ml min⁻¹, catalyst to plastic ratio=30 wt.% and catalyst particle size=125–180 µm).

It is also concluded that the use of this reaction system coped with a spent FCC equilibrium catalyst can be a better option

since it may lead to a cheaper process with valuable products and can be further used as an adequate approach for the catalytic recycling of plastic waste.²³ See table 7.

Table 7:

	Catalyst type				
	FCC-R1	Silicalite	HUSY	ZSM-5	SAHA
<i>Yield (wt.% feed)</i>					
Gaseous	82.4	13.5	85.6	88.3	84.1
Liquid ^a	3.8	1.4	3.3	3.4	3.6
Residue ^b	11.7	85.1	8.6	6.4	10.5
Involatle residue	9.3	83.2	4.1	4.9	8.4
Coke	2.4	1.9	4.5	1.5	2.1
HCl	2.1	1.4	2.5	1.9	1.8
Mass balance (%)	97.8	98.3	96.5	97.4	95.7
<i>Distribution of gaseous products (wt.% feed)</i>					
Light gases (C ₁ -C ₄)	24.0	6.8	35.7	52.7	30.2
Gasoline (C ₅ -C ₉)	54.8	6.2	48.4	34.5	52.4
Styrene	0.7	0.1	0.5	0.6	0.8
BTX ^c	1.6	0.4	1.0	0.5	0.7

^a Condensate in condenser and captured in filter.

^b Coke and involatile products.

^c Benzene, toluene and xylene.

Example 3: Pyrolysis of motorcycle tyre waste:

A variety of scrap tires are available in the modern society. These are bicycle and rickshaw tires, motorcycle and auto-rickshaw tires, car and taxi tires, microbus and jeep tires, tractor tires, bus and truck tires. Tires contain vulcanized rubber in addition to the rubberized fabric with reinforcing textile cords, steel or fabric belts, and steel-wire reinforcing beads. Other components in the tire are: carbon black, extender oil, which is a mixture of aromatic hydrocarbons, sulphur, accelerator, typically an organo-sulphur compound, zinc oxide, and stearic acid.

There are many different manufacturers and countless different formulations available all over the world; the composition of the tire varies depending on the tire grade and manufacturers. Consequently, the tire pyrolysis products may also vary in terms of yield and chemical composition depending on the source and grade of the tires.

Very different experimental procedures have been used to obtain liquid products from automotive tire wastes by pyrolysis technology including fixed-bed reactors, fluidized-bed pyrolysis units, vacuum pyrolysis units, spouted-bed reactors, etc., ranging from laboratory to commercial scale plants.

The Indian made “MRF” brands of motorcycle tires, which are mostly consumed in Bangladesh, has been taken into consideration as feedstock. The main components of tires such as rubber, fillers like carbon black, steel, sulfur, zinc oxide, processing oil, vulcanization accelerators, etc. are heterogeneously distributed over the cross-section.

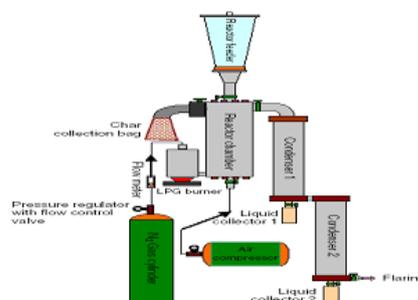


Figure: 8 Schematic diagram of the fixed-bed, re-tube heating pyrolysis system²⁴

The experimental unit consists of eight major components: (1) a fixed-bed re-tube heating reactor chamber with a power system; (2) a gravity feed type reactor feeder; (3) two ice cooled condensers, each of them having a liquid collecting glass bottle; (4) an N₂ gas cylinder with a pressure regulator, a flow control valve

and a gas flow meter; (5) an N₂ gas pre-heater with LPG burner; (6) an air compressor; (7) char collecting bag; and (8) Ktype (chromel–alumel) thermocouples, whose measurement accuracy is $\pm 2.5^{\circ}\text{C}$ with a temperature controller. At a distance of 30 mm from the closed bottom of the reactor, a distributor plate was fitted to support the feedstock. See figure 8. The distributor plate was made of stainless-steel plate having 150 holes of 3 mm diameter. The N₂ gas inlet was 20 mm below the distributor plate. Eight equally spaced stainless steel, 10 mm diameter re-tubes containing insulated electric coil of a total capacity 1.60 kW were fixed inside the reactor. The re-tubes and pre-heated N₂ gas provided uniform heating across the cross-section of the reactor chamber. The reactor was thermally insulated with asbestos cylinder. The reactor height from the distributor to the gas exit was 270 mm and its diameter was 100 mm, which provided an apparent vapor residence time of 5 s.

Three types of products are usually obtained from pyrolysis of tire rubber: solid char, liquid, and gas. The product distributions obtained from pyrolysis of prepared representative sample for temperature range of 375–575°C at every

50°C, feedstock size of 4 cm³ and vapor residence time of 5 s. See figure 9.

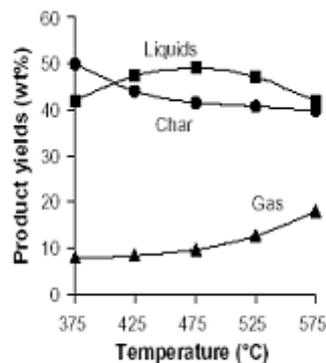


Figure: 9 Effect of temperature on product yields^{2,3}

The pyrolytic liquids obtained from pyrolysis of motorcycle tire wastes, which are oily organic compounds, appears dark brown with a strong acrid smell. Careful handling of the liquids is required since it reacts easily with human skins, leaving permanent yellowish brown marks and an acrid smell for a few days, which is difficult to remove by detergent.

The fuel properties of the pyrolytic liquids in comparison to commercial automotive No. 2 diesel, which is mostly consumed in Bangladesh, are: See table 8.

Analyses	Motorcycle tire derived liquids	Commercial automotive No. 2 diesel
<i>Elemental (wt.%)</i>		
C	85.86	84-87
H	9.15	12.80-15.70
C/H	9.38	5.35-6.80
N	0.65	65-3000 ppm
S	1.25	1100-7000 ppm ^a
Ash	0.22	0.0
O	2.87	0.0
H/C molar ratio	1.27	1.76-2.24
O/C molar ratio	0.025	-
Empirical formula	CH _{1.27} O _{0.025} N _{0.0065}	-
Density (kg/m ³)	957	820-860
Viscosity (cSt)	4.75 ^b	2.0-4.5 ^c
Flash point (°C)	≤32	>55
Pour point (°C)	-6	-40 to -30
Moisture (wt.%)	N/A	≈80 ppm
pH value	4.40	-
GCV (MJ/kg)	42.00	44.00-46.00

^a Valid for legislation requirements of Bangladesh.

^b At a temperature of 30 °C.

^c At a temperature of 40 °C.

Table 8:

The main inferences from pyrolysis of motorcycle tire waste are as follows:

1. The main rubber components in the present motorcycle tire waste are NR and SBR. The motorcycle tire rubber formulation comparatively use larger amount of inorganic materials as additives consequently energy content of the solid tire waste is lower than that of car and truck tire wastes.
2. The optimum liquid yield conditions for the fixed-bed re-tube heating reactor system are: operating temperature 475°C, feed size 4 cm³ and apparent vapor residence time 5 s. The main effects of operating conditions on the product distributions are that:

(i) The lower temperature and larger feed size favor incomplete decomposition, which increase in char yields and decrease in the liquid and gas yields,

(ii) The higher temperature and longer residence time contributes to secondary reactions results in more gaseous products with the expense of liquids while char yields remain almost constant.

3. The fuel properties of the pyrolysis liquids such as density, viscosity, GCV, carbon and hydrogen contents are found almost comparable to those of the commercial automotive diesel fuels but higher sulphur content and lower ash point are problematic. The pyrolytic liquids may be used as diesel fuel or heating oils after the upgrading such as desulphurization and dehydrogenation or blending them with petroleum refinery streams.
4. The pyrolytic liquids abundantly contain olenes, specially limonene and light aromatics, which have higher market values as chemical feedstock than their use as fuels.

5. However, further studies are necessary to utilize pyrolytic liquids as liquid fuels or chemical feedstock.⁶

2. Furnace:

The possibility of using waste plastics as a source of secondary fuel in a blast furnace has been of recent interest. The success of this process, however, will be critically dependent upon the optimization of operating systems. For instance, the supply of waste plastics must be reliable as well as economically attractive compared with conventional secondary fuels such as heavy oil, natural gas and pulverized coal.

Example: 1 PE as fuel for furnace:

Considering that in volume-wise PE makes up the largest portion in waste plastics, recycled PE was used as a representative. The bulky samples, obtained from local recycling center, were cleaned and dewatered before use, and exposed to liquid nitrogen for easier fracture in a ball mill. Thus, prepared pellets were classified into three types based on the final particle size (1.0–1.5, 3.0–5.0, and 8.0–10.0 mm)

and were stored in a desiccator for further use.

Figure 10 shows a schematic of a simulated blast furnace, named as *hot model*. Three LPG type gas heaters were used to blow hot air through the blow-pipe, and by this set up the temperature could be efficiently controlled in the range of 900–1100°C. Oxygen could be also injected simultaneously with hot air. In the upper part of the blast, a coke injection chamber was installed, and blast could be operated continuously for 30 min with one fill-up. Upon reaching the preset temperature, waste plastics and/or pulverized coal (size is about 75mm) were injected at a rate of 45 kg/h through the side of the blow-pipe.

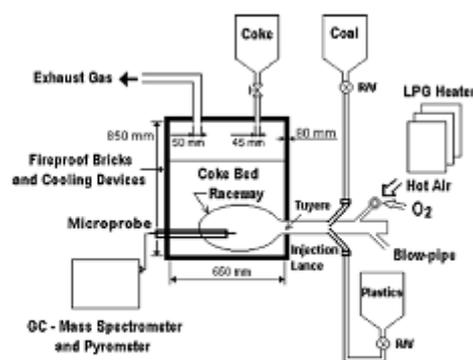


Figure: 10 Schematic Diagram of Blast Furnace²⁵

PE thermally decomposes into oily liquid and gas phase successively. In Figure 11, thermogravimetric results for commercial

low-density polyethylene (LDPE) and waste PE are shown. Detectable weight decrease starts from 300°C followed by fast thermal decomposition that ends around 400°C. The overall decomposition behavior for both samples were similar; however the inflection points of 50% of weight loss are, respectively, about 392 and 385°C for commercial LDPE and recycled PE, and this may be ascribed to more porous structure of recycled PE.

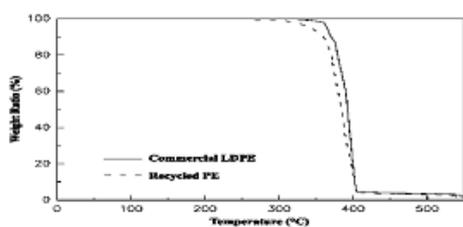


Figure: 11 TG curves for commercial LDPE and recycled PE ²⁵

It was found that with the increase of both blast temperature and the level of oxygen enrichment, and with the decrease of particle size, the combustion of waste PE occurred at shorter distance from the tuyere (figure 12). This strongly suggests that the combustibility of waste plastics can be improved by controlling these variables. Lastly the combustion behavior of the mixture of pulverized coal and waste PE was investigated. Although the efficiency of coal combustion was found to decrease with the addition of plastics, the combustion efficiency of the mixture

could be comparable at longer distance from the tuyere. ^[26]

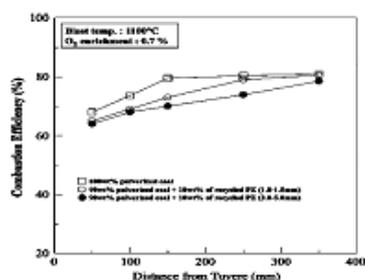


Figure: 12 Combustion behaviors of pure pulverized coal and mixtures of recycled plastics and pulverized coal ²⁶

Other methods that can be used are:

3. Thermal and Catalytic Process:

Thermal or catalytic cracking of waste plastics is one of the possible methods of their utilization¹⁻⁸. As a result of the cracking at 400°C or higher process temperature some quantities of hydrocarbon mixtures in the form of gas, liquid products (gasoline and diesel fuel boiling range) as well as higher boiling liquid residue or solid can be obtained^{1,6,8}. All these products can be used as fuels or fuel components. Especially liquid products of gasoline and diesel fuel boiling range can be applied as components of engine fuels. It is however necessary to remember that products of cracking or pyrolysis of polyolefines are highly unsaturated and therefore they have to be further submitted to hydrogenation and skeletal isomerization if they are to be

applied as engine fuels. Application of cracking or hydrocracking catalyst and higher process temperature can enlarge conversion of waste plastics. The main goal of application of hydrocracking catalyst and hydrogen is hydrocracking of plastics and hydrogenation of olefins in process products.

4. Fluidized Catalytic Cracking:

A more interesting approach, however, is that of adding waste polymers into the usual feed-stocks of the process of fluid catalytic cracking of hydrocarbons (FCC) because, under standard process conditions, a large number of plastics, including polyolefins, can be dissolved into vacuum gas oils (VGO) and in this way, they can be converted into a mixture of hydrocarbon compounds. The idea has been tested with different plastics and laboratory conditions.

Conclusion:

Thus hereby we can conclude that, plastics can be well converted to fuel by either of the above said processes. The low molecular weight hydrocarbon obtained can be a good source of fuel. Plastics like PP, PE, PS, rubber, etc can be used for the purpose. It is, but important that the parameters of the process be well known and the process be carried out properly. Or

else the yield of the process will change. Hydrocarbon polymers can be as said, easily used as fuel source, but when chlorinated polymers like PVC, PVDC, etc., are to be used, it is important that the process is able to handle the liberated HCl gas in an environmental friendly and non-hazardous manner.

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Green Technology: Overview on Biodiesel



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Abstract:

Petroleum-derived diesel which is increasingly called as petrodiesel is generally used as liquid fuel in diesel engines. But it is obtained from crude oil which is one of the non-renewable source of energy and it is hazardous to the environment also due to emission of gases such as carbon monoxide during combustion. Because of its non-renewable origin its sources are decreasing whereas its prices are increasing day by day so we have to search for an alternative which can be used as replacement for petrodiesel in future. One such alternative is Biodiesel which can directly replace petrodiesel. Biodiesel refers to vegetable oil or fat-based diesel fuel formed by transesterification reaction and consisting of long oil alkyl esters mainly methyl esters. It is clean burning, biodegradable, non-toxic, environmental friendly. Jatropha is the main feedstock for biodiesel production. Currently biodiesel production is done by homogenous base catalysis reaction, but by new emerging technology for biodiesel production and its environmental friendly nature it will become one of the major energy source in future.

Keywords: biodiesel, transesterification, supercritical methods, blending.

Introduction:

As energy demand continues to increase and reserves of fossil fuels shrink, the diversification of energy sources becomes increasingly important.

Several studies have presented promising methods that make use of triglycerides as an alternative fuel for diesel engine. The higher molecular weight, higher viscosity, poor cold flow properties, are

the main impediments to using vegetable oil or vegetable oil blend, directly as fuel. Hence vegetable oil derivatives, mainly methyl esters, have become popular biofuel and it is known as biodiesel. [4], [11]

Biodiesel:

Biodiesel refers to vegetable oil or fat-based diesel fuel formed by transesterification reaction and consisting of long oil alkyl (methyl, propyl or ethyl) esters. [13]

3. Biodiesel Worldwide:

3.1. Global Scenario: Several countries especially United State and members of European Union are actively supporting the production of biodiesel from the agriculture sector. In 2006, nearly 6.5 billion liters of biodiesel was produced globally. However, by the year

2020, it is predicted that biodiesel production from Brazil, China, India and some South East Asia countries such as Malaysia and Indonesia could contribute as much as 20%. [06]

3.2. Indian Scenario: India imports more than 40% of its edible oil requirement and hence non-edible oils are used for the development of biodiesel. India is a agrarian nation and has rich plant biodiversity which can support the development of biodiesel. Common non-edible oil bearing plants and trees include neem, karanja, mahua, jatropha, etc. where Jatropha curcas and pongamia pinnata (Karanja) are gaining prominence as feed-stock for biodiesel. Jathropha carcus is main raw material for biodiesel production. [07], [08], [20]

4. Biodiesel, petrodiesel and blends of biodiesel : [1]

4.1. Table 1 - Difference between biodiesel and petrodiesel

Biodiesel	Petrodiesel
Biodiesel is produced from vegetable oils by converting the triglyceride oils to methyl (or ethyl) esters via a process known as transesterification.	Petroleum diesel, in contrast, is made up of hundreds of different hydrocarbon chains (roughly in the range of 14-18 carbons in length),

	with residues of sulfur and crude oil remaining and obtained from crude oil.
Better lubricity. The higher lubricity enable the engine to work in a smoother manner and because it works better it reduce the physical deterioration of the engine.	Less lubricity.
Lower vapor pressure and flammability than their petroleum.	Higher vapor pressure and flammability
Cleaner Burning	Not clear burning
Biodegrades much faster than petrodiesel.	Biodegrades less faster than biodiesel
Higher lubricity and cetane than petrodiesel. Because of higher cetane rating engine noise and ignition cocking get reduced.	Lower lubricity and cetane than Biodiesel.
Formed from vegetable oil resources which are infinitely grown and produced as compared to crude oil resources which are limited.	Formed from crude oil resources which are limited in nature as compared to vegetable oil.
Supporting agriculture industry.	Non supporting to agriculture industry.
Flash point = 150 ⁰ c	Flash point = 77 ⁰ c

4.2. Biodiesel Blends :

The level of blending with petroleum diesel is referred as Bxx, where xx indicates the amount of biodiesel in the

blend (i.e. B10 blend is 10% biodiesel and 90% diesel) ^[07]

5. Properties of Biodiesel : ^[2]

Table 2 - PROPERTIES OF BIODIESEL

Specific gravity	0.87-0.89
Kinematic viscosity at 40 ⁰ c	3.7-5.8
Cetane number	46-70
Higher heating value (btu / lb)	16928-17996
Sulphur wt %	0.0-0.0024
Cloud point (⁰ c)	-11 to 16
Pour point (⁰ c)	-15 to 13
Iodine number	60-136
Lower heating value (btu / lb)	15700-16735
Density at 90 ⁰ c	~0.900 gm/cm ³
Flash point (⁰ c)	130 ⁰ c(min)
Methanol (% wt)	0.3
Free glycerin (wt %)	0.020
Total glycerin (wt %)	0.25

6. Biodiesel production :

Process description of production of biodiesel :

6.1.1. The first step in the recovery of oil from oil seed. "crush" the seeds and then to separate oil from the residual seed material (meal).

6.1.2. The pretreated oils and fats are then mixed with alcohol and a catalyst.

6.1.3. KOH / NaOH is mixed with methanol in catalytic reactor (for 10 min) until KOH has completely dissolve and solution becomes potassium methoxide.

6.1.4. Then vegetable oil mixed for 60 minutes. i.e esterification process, then

it transfer into settling tank where it settle for 6-18 hrs.

6.1.5. After this glycerin is removed from the bottom of settling tank by draining or pumped out into glycerin container.

6.1.6. From upper part of settling tank, biodiesel is removed out which is go for washing.

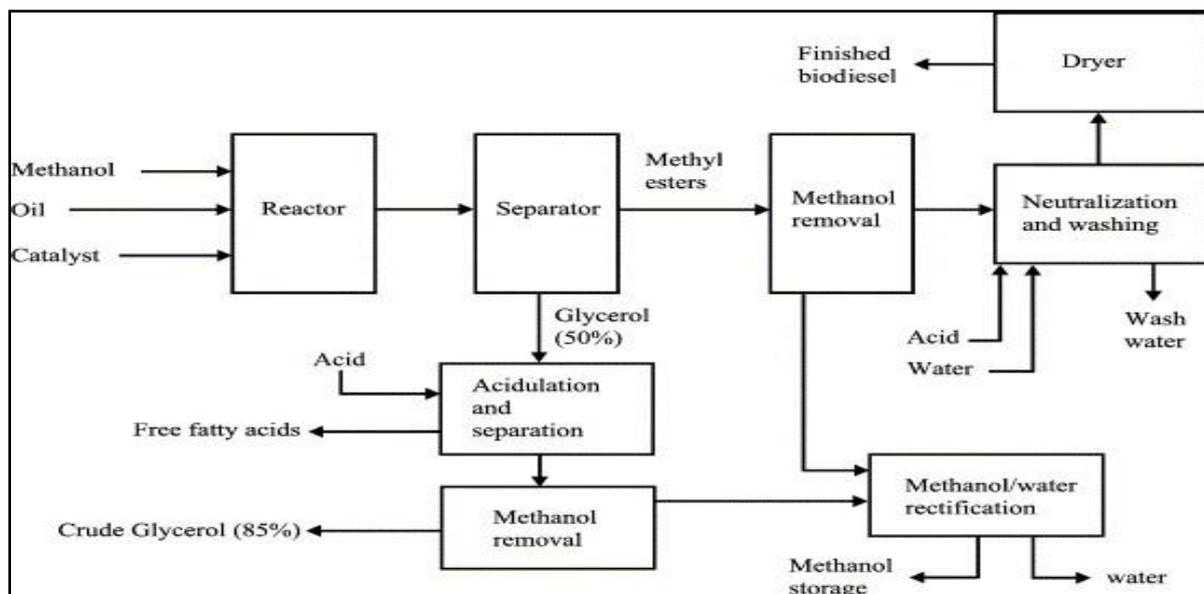
6.1.7. Excess methanol in biodiesel is removed using either vaccum or heating.

6.1.8. Acidic water washing is given (tannic or acetic acid) to remove excess catalyst.

6.1.9. Again separation is carried out and water is removed from the bottom.

6.1.10. Then product (biodiesel) is dried using heat / stirring / aeration. ^{[01], [17]}

Fig. 1 – Block Flow Diagram for biodiesel production



Transestrification:

Transesterification is the process of exchanging the organic group R" of an [ester](#) with the organic group R' of an

[alcohol](#). These reactions are often [catalyzed](#) by the addition of an [acid](#) or [base](#) catalyst. Nowadays enzymatic catalyst are also used. ^{[05], [06]}

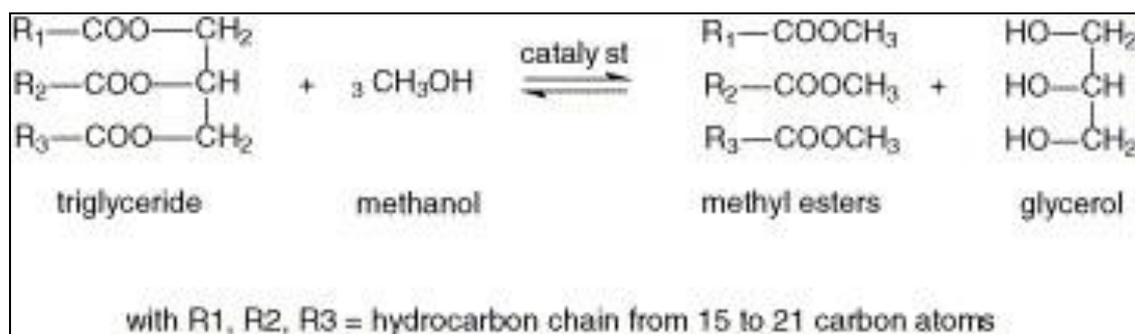


Fig 2 - Transesterification Reaction

Process variable in transesterification:

6.3.1. Reaction temperature : Maximum yield of biodiesel obtained at 60-80^o c. As oil temperature increases the % oil to biodiesel conversion increases, Biodiesel recovery increases. Maximum operating temperature is 60^o C because at higher temperatures methanol loss can occur.

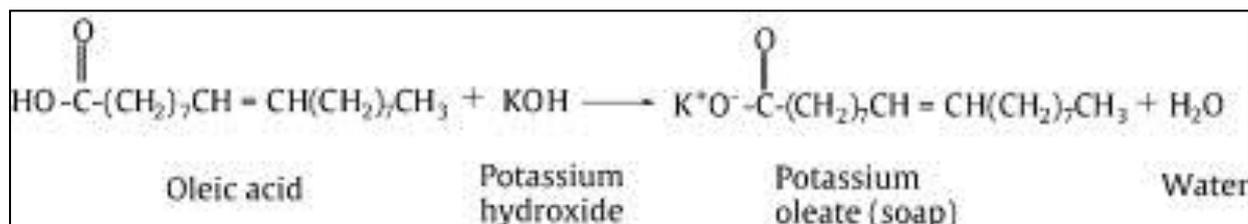
6.3.2. Ratio of alcohol to oil : At molar ratio 6:1 yield obtained is more than 98%. At theoretical stoichiometric ratio 3 : 1 the yield of ester decreases to 82%. With higher molar ratio, conversion increases but recovery decreases due to poor separation of glycerin.

6.3.3. Type and concentration of catalyst : Addition of catalyst with 0.5-1 by wt% yields 94-99% conversion of vegetable oil into ester.

6.3.4. Intensity of mixing and purity of reactant

6.3.5. A small amount of water (0.1%) in the transesterification reaction would decrease the ester conversion from vegetable oil. [1], [21]

6.3.6. Free fatty acids (FFAs) content after acid esterification should be minimal or otherwise less than 2% FFAs. These FFAs react with the alkaline catalyst to produce soaps instead of esters. [01], [06], [19]

Fig 3 - Reaction of fatty acid with alkaline catalyst (soap formation)^[06]

7. Biodiesel Production from Algae :

While a number of bio-feedstock are currently being experimented for biodiesel production, algae have emerged as one of the most promising sources for biodiesel production. Algae yields could reach a high of 50 T of biodiesel per hectare year against 2T for competing feedstock such as jatropha. Oil content of some microalgae exceeds 80% of the dry weight of algae biomass. Another important advantage of microalgae is that, unlike other crops, they grow extremely rapidly and commonly double their biomass within 24 hrs. ^[03]

8. Stability of Biodiesel :

Oxidation of biodiesel by contact with air and metal surface results in the formation of hydroperoxide. These induce free radical chain reaction that leads to decomposition into low molecular highly oxidized species (aldehyde, ketone, acid) and high M.W polymeric material (gums). These gums causes poor combustion and other engine problem such as deposits on injectors and pistons & fuel-filter plugging.

Two pronged approaches have been adopted for improving oxidation

stability of Jatropha biodiesel. First route deals with the doping of Jatropha methyl esters with stabilizer or antioxidants. Among stabilizers utilized in industry phenolic antioxidants are most important. ^[06]

As antioxidants are costly chemicals. Therefore, another method is blending. For example, blend Jatropha oil methyl ester with palm oil methyl ester, which has good oxidation stability. The reason for good stability is the resistance to autoxidation, which was primarily due to the presence of saturated fatty acids. Jatropha has mainly unsaturated fatty acids like linoleic acid, oleic acid etc. Jatropha biodiesel, when blended with palm methyl ester leads to a composition having efficient and improved low temperature property as well as good oxidation stability. The feedstock for the synthesis of biodiesel must have a suitable combination of saturated as well as unsaturated fatty compounds to achieve improved oxidation stability and low temperature properties. ^{[11], [23]}

9. Advantages of Biodiesel :

9.1 Produced from renewable energy sources such as vegetable oil, fats etc. so biodegradable in nature.

9.2. Biodiesel contains oxygen, so there is an increased efficiency of combustion.

9.3. Carbon monoxide gas is a toxic byproduct of all hydrocarbon combustion that is also reduced by increasing the oxygen content of the fuel. More complete oxidation of the fuel results in more complete combustion to carbon dioxide rather than leading to the formation of carbon monoxide.

9.4. Biodiesel helps to reduce Greenhouse Gases. The carbon dioxide released this year from burning vegetable oil Biodiesels, in effect, will be recaptured next year by crops growing in fields to produce more vegetable oil starting material.

9.5. The absence of sulfur means a reduction in the formation of acid rain by sulfate emissions that generate sulfuric acid in our atmosphere.^[01]

Table 3 - Emission data for 100% biodiesel and biodiesel blends is given in table

Emmision	B ₁₀₀	B ₂₀
REGULATED EMISSION :		
Total unburned hydrocarbon	-93%	-30%
CO	-50%	-20%
Particulate matter	-30%	-22%
NO _x	+13%	+2%
NON REGULATED EMISSION :		
sulphate	-100%	-20%
PAH	-80%	-13%

[21]

10. Applications of biodiesel:

10.1. Biodiesel is used as a fuel.^[01]

10.2. Biodiesel is used as a green solvent for polymerization.^[12]

10.3. Dissolution of waste plastic in biodiesel is also possible.^[09]

11. Cost of biodiesel :

Raw material and production cost are keeping the retail price of biodiesel too high. The recovery of higher quality glycerol, a byproduct which is required for many other processes would also contribute to substantially reducing production costs. The high cost of refined vegetable oils, currently used for the biodiesel production with the conventional base catalytic method, is the main reason for this impediment. The cost of refined vegetable oils contributed to nearly 80% of the overall biodiesel production cost. In order to overcome this limitation, biodiesel manufacturer are focusing their attention on using low-cost feedstock such as waste cooking oil in order to ensure economic viability in biodiesel production.^[06]

12. Disadvantages of biodiesel:

12.1. NO_x emissions are higher which causes ozone layer destruction.

12.2. Engine performance (fuel economy, torque and power) is less than of diesel 8% to 15% because of the lower energy content of biodiesel.

12.3. Since its pour point and cloud point is around (-10)⁰c it solidifies at that temperature during winter in European and American countries.^[01],^[25]

13. Recent methods of biodiesel production :

13.1. Reaction with supercritical methanol:

A non-catalytic biodiesel production route with supercritical methanol has been developed that allows a simple process and high yield because of simultaneous transesterification of triglycerides and methyl esterification of fatty acids. In the conventional transesterification of fats and vegetable oils for biodiesel production, free fatty acids and water always produce negative effects since the presence of free fatty acids and water causes soap formation, consumes catalyst, and reduces catalyst effectiveness. The presence of water positively affected the formation of methyl esters in supercritical methanol method. Supercritical methanol is believed to

solve the problems associated with the two-phase nature of normal methanol / oil mixtures by forming a single phase as a result of the lower value of the dielectric constant of methanol in the supercritical state. As a result, the reaction was found to be completed in a very short time.^[18]

13.2. Synthesis of biodiesel via supercritical methyl acetate transesterification:

The use of methyl acetate instead of methanol for supercritical synthesis of

glycerol-free biodiesel from vegetable oils is a new process where byproduct triacetin is formed. The production of triacetin is advantageous not only because it avoids that of glycerol but also because it was demonstrated that mixtures of FAME and triacetin obtained by this process are suitable as biodiesel fuel. The overall biodiesel production must then account not only for the FAME but also for the triacetin content.^{[14], [22], [24]}

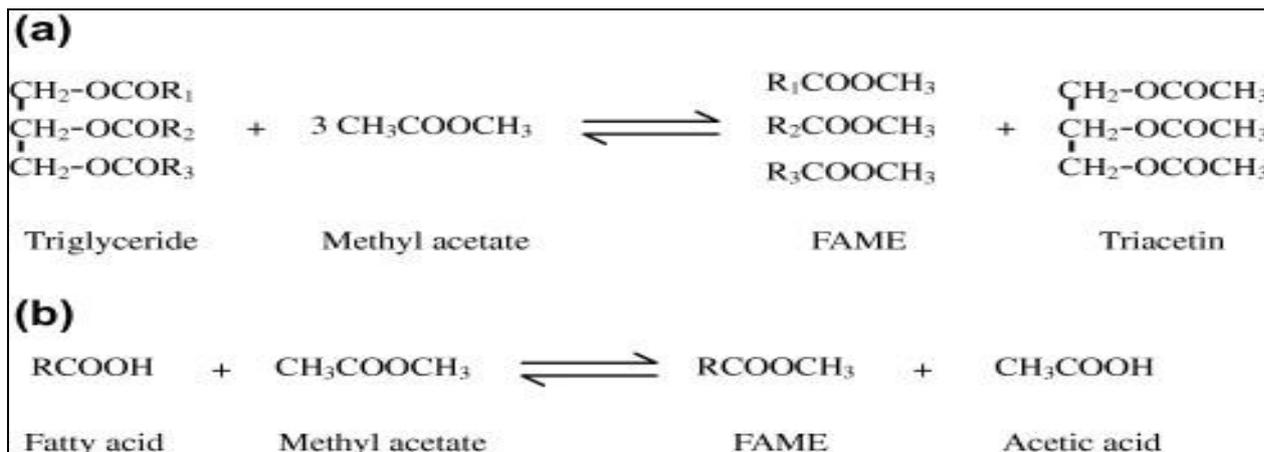


Fig 4 – biodiesel production with supercritical methyl acetate.^[22]

13.3. Catalyst-free production of biodiesel using supercritical dimethyl carbonate :

Supercritical Dimethyl carbonate is used as a potential reactant for biodiesel production in this process, glycerol carbonate was produced as one of the byproducts. It is reported that this

product has higher economic value than the abundantly available glycerol because it can be used as the raw materials for paint, dyes and adhesives and as a new source of new polymeric materials as well as a part of cosmetic composition and emulsifier.^{[14],[15]}

13.4. Oscillatory flow reactor (OFR) for transesterification reaction.^[06]

13.5. Ultrasound technology in transesterification reaction.^[06]

13.6. Co-solvent^[06]

14. Conclusion:

In recent years, biodiesel has become more attractive as an alternative fuel for diesel engines because of its environmental benefits and the fact that it is made from renewable resources. Currently, the alkali-catalyzed method is the most common and commercially available process for biodiesel production. However, water and free fatty acids (FFA) in oils / fats result in reducing the catalytic activity, thus, decreasing the yield and complicating the purification process. This prevented the use of waste vegetable oil as a reactant for biodiesel production which can reduce biodiesel production cost as compared to production from refined oil. Nevertheless, recent advances in technologies such as supercritical fluids, heterogeneous catalysts, and co-solvents have shown high potential in overcoming the limitations. But these are on a laboratory scale and if they go on industrial scale biodiesel production costs are reduced. Whereas on the other

side petrodiesel is obtained from crude oil whose resources are depleting day by day. Because of this it is obvious that petrodiesel price will increase in the future. But because of the above techniques biodiesel cost may decrease in future & if this is possible, because of its environmental benefits and lower cost it will substitute petrodiesel to large extent.^{[02], [06]}

15. Acknowledgement:

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Polymeric Solar Cells: Basics And Methods To Improve Morphology Of Spin Coated Films



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ABSTRACT

The following review paper contains the basic principle behind working of the solar cell. The present day PSC are made of electron donating (conjugated polymer) and electron accepting molecules(usually fullerene and its derivatives). The concept of the bulk heterojunction has resulted into great improvement in the efficiency of the PSC. In order to control the morphology and to improve the efficiency of the PSC processes like thermal annealing, solvent annealing and choice different solvents are being adopted by researchers. The reasearch carried out by Yang and D Chirvase are described in this paper.

1. INTRODUCTION

There has been a tremendous increase in the demand for energy in the last 30 or 40 years. In the year 2008 the worldwide energy consumption was around 15TW [1] and it will rise approximately to 30TW in the year 2050 [2]. The rapidly increasing energy demand and population has widened the gap between the supply and demand of energy. Use of the fossil fuels for energy production is posing a threat to the environment and also they are becoming less day by day. The requirement of a clean and cheap energy resource is necessary. Sun is the biggest source of energy to the earth. The first efficient solar cell was reported at the Bells Lab in 1954 and from the mid 1960's to the mid of 1980's there was focus on improving the efficiency to produce more power. Crystalline silicon is used in 90% of the photovoltaics used today. The other materials used are cadmium telluride (CdTe), copper indium gallium arsenide(CIGS), etc. However only about 0.1% of the total electricity generated in the world is supplied from PV installations. The primary reasons are the high cost of raw materials and processing, and the difficulty in fabrication and installation of the PV systems. Today, solar cells based on organic molecules and polymers are considered as a promising

alternatives to the inorganic counterparts. Some of the advantages of the organic PV's are the low fabrication cost of the large area devices, low specific weight, mechanical flexibility and easy tunability of chemical properties of the organic molecules. In spite of these advantages the polymer solar cells (PSC) aren't commercial yet due to their low efficiencies. PSC's having efficiencies 4-5% have been reported. It is widely believed that the efficiency barrier of 10% is to be crossed for commercialisation of PSC's. [M.C. Scharber, 2006].

2. WHAT ARE POLYMER SOLAR CELLS?

A polymeric solar cell is a device using a conjugated polymer (electron donating component) and/or an acceptor molecule as the photoactive layer of the cell. The active components are solution processible, and can be spin coated, printed, roll to roll printing or vacuum evaporated on a glass or a plastic substrate precoated with a transparent electrode, usually ITO (indium tin oxide). The four basic steps in the working of the polymer solar cell are:

- Absorption of light
- Charge transfer and separation of the opposite charges
- Charge transport

- Charge collection. [Rene Janssen]

2.1 Device architectures

2.1.1 Single layer Devices

The simplest used organic semiconductor device is the metal–insulator-metal (MIM) tunnel diode with metal electrodes of asymmetrical workfunction. Under forward bias, holes from the high workfunction metal and electrons from the low workfunction metal are injected into a thin film of a single-component organic semiconductor. Because of the asymmetry of the work function of the cathode and the anode, forward bias currents for a single carrier type material are orders of magnitude larger than reverse bias currents at low voltages. Improvement was reported for the devices using a Schottky contact that forms between the conjugated polymer and the metal electrode. [C.J. Brabec, N.S. Sariciftci, J.C. Hummelen, 2001]. However, only photoexcitations generated close to the depletion region W of the Schottky contact may lead to separated charge carriers as a result of the limited exciton diffusion length. Therefore, only a small region denoted as the active zone contributes to photocurrent generation, as illustrated in Fig. 1. [Harald Hoppe, N. Serdar Sariciftci, 2007]

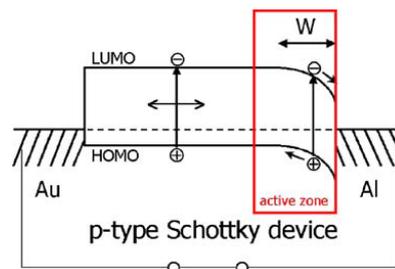


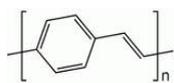
Fig. 1. The active zone for the single layer device [Harald Hoppe, N. Serdar Sariciftci, 2007]

2.2.2 Bilayer devices

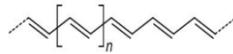
These devices use the concept of donor and acceptor molecules. When light is incident on the PSC, it results in the formation of excitons (Coulombically bound electron hole pair). In a two layer device these excitons can be generated in either layer. These excitons can diffuse towards the interface where they dissociate into free electron and free hole. The dissociation is said to be efficient at the interface because of the materials have different electron affinities and ionization potentials, where electron is accepted by the material having the more electron affinity and the hole by the material with a low ionization potential. However the exciton diffusion lengths happen to be at least 10 times (5 to 20nm) smaller than the optical absorption depth, thus limiting the efficiency of charge collection [J.J.M. Halls, C.A. Walsh, 1995]. Different types

of donors and acceptors are shown in Fig. 2. Inorganic semiconductors generally have a high dielectric constant and a low exciton binding energy (for GaAs the exciton binding energy is 4 meV). Hence, the thermal energy at room temperature ($kBT = 0.025$ eV) is sufficient to dissociate the exciton created by absorption of a photon into a positive and negative charge carrier. The formed electrons and holes are easily transported as a result of the high mobility of the charge carriers and the internal field of the p-n junction. Organic materials have a lower dielectric constant and the exciton binding energy is larger than for inorganic semiconductors [Rene Janssen].

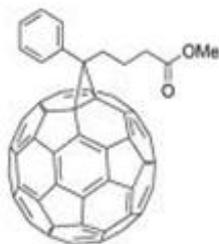
When the donor molecule absorbs light, an electron in the HOMO is excited and is transferred to the LUMO of the acceptor molecule.



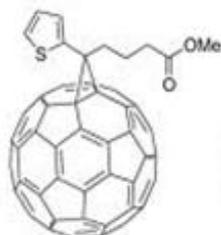
poly(p-phenylenevinylene)



polyacetylene



PCBM



ThCBM

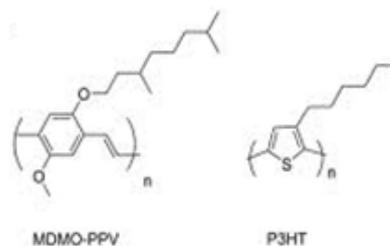


Fig. 2. Structures of electron acceptors (PCBM, ThCBM) and electron donors (Polyacetylene, PPV, P3HT, MDMO-PPV)

As mentioned above the driving force for the electron transfer is the difference in the ionization potential of the donor and the electron affinity of the acceptor, minus the Coloumb correlations. As a result of photoinduced charge transfer the, positively charged hole remains on the donor and the acceptor gets a unit negative charge. This photoinduced charge transfer between conjugated polymers as donor and fullerenes as acceptor takes place within less than 50 fs. Since all competing processes like photoluminescence (\sim ns) and back transfer and thus recombination of the charge (\sim μ s) take place on a much larger timescale, the charge separation process is highly efficient and metastable [Harald Hoppe, N. Serdar Sariciftci, 2007]. This process is as shown in the Fig. 3.

[Rene

Janssen].

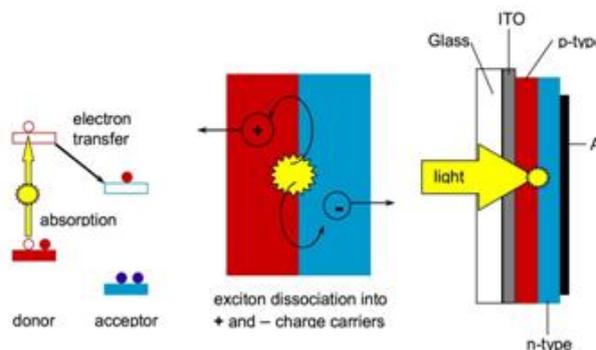


Fig. 3. Schematic diagram of working of PSC

After the separation of the charges it is necessary to transport the charges to the electrodes. Thus there is requirement of percolation path. In bilayer devices, charge carriers can be dissociated at the donor-acceptor material heterojunction. Only excitons generated within diffusion distance to the interface can contribute to the photocurrent. The donor carries the holes whereas the acceptor carries the electrons. However there are great chances of recombination of charges and thus a decrease in the efficiency of the PSC.

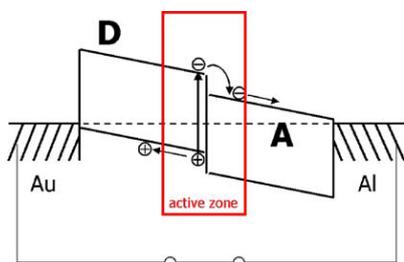


Fig. 4 active zone for the bilayer device

2.2.3 Bulk heterojunction device (BHJ)

The improvement in the transport of the separated charges to the respective electrodes was reported for bulk heterojunction devices.

In the BHJ the donor and the acceptor molecules are intimately blended, so that the excitons do not need to travel much to reach to the heterojunctions. Thus this decreases the probability of the recombination and in turn improving the efficiency of the cell. Consequently the BHJ concept led to the improvement in the photocurrent and there are reports of upto 5% power conversion efficiencies with these type of cells [Harald Hoppe, N. Serdar Sariciftci, 2007]. The following diagram (Fig. 5)[Rene Janssen] will give the idea of the BHJ.

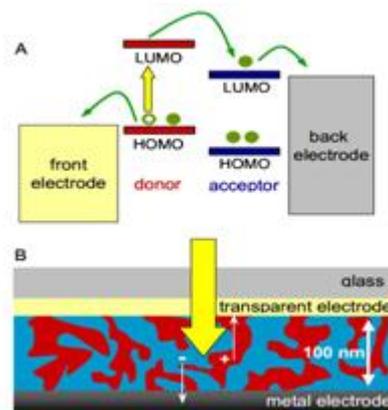


Fig. 5 Bulk heterojunction

Along with the efficient charge separation, this type of morphology also leads to the formation of good percolation paths for the electrons and the holes to travel to the respective electrodes. Since the polymer solar cells are solution processed, mostly spin coated, the morphology of the BHJ strongly depends on the type of solvent and the acceptor-donor combination used.

We will be focusing on comparing the morphologies reported for different

solvents like xylene, o-dichlorobenzene (o-DCB), chlorobenzene, THF mainly for P3HT/PCBM and MEH-PPV/buckminsterfullerene (C_{60}) systems. We will also look at the ways of improving the nanomorphology of the same.

3. MEH-PPV/ C_{60} : Morphology dependence on solvent and the C_{60} composition

It has recently been elucidated that the conformation of polymer chains can be controlled by the selection of the organic solvents, by the concentration of the polymer solution, and by the rotational speed of the spin-casting process. The resulting polymer morphology in the thin film plays an important role in controlling both the material and the device characteristics, such as the absorption and emission spectra, the device turn-on voltage, and the energy barrier height between the polymer/metal interfaces. Yang *et al* studied the morphology of the MEH-PPV/ C_{60} system using THF (non aromatic solvent) and xylene and o-DCB (aromatic solvents). He has, for pure MEH-PPV device reported that the device made with THF always has a smaller photocurrent than the device made with a similar film thickness but processed with xylene. On blending with the C_{60} , the photocurrent of the composite increases

rapidly. Also with the change in the concentration of the C_{60} component the photocurrent of the device increases (refer Fig.6). This enhanced photo response was attributed to the effective separation of the charge carriers by photoinduced charge transfer process. [Jie Liu, Yijian Shi, and Yang Yang, 2001].

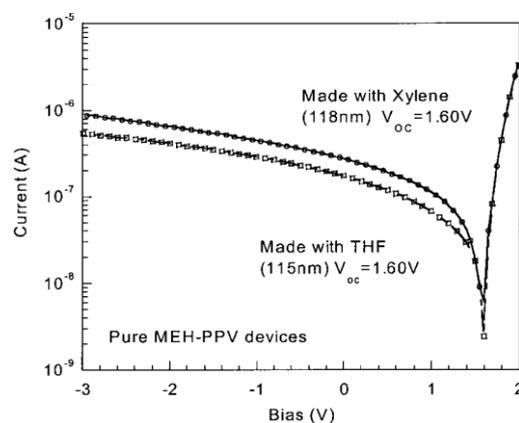


Fig. 6 (a)

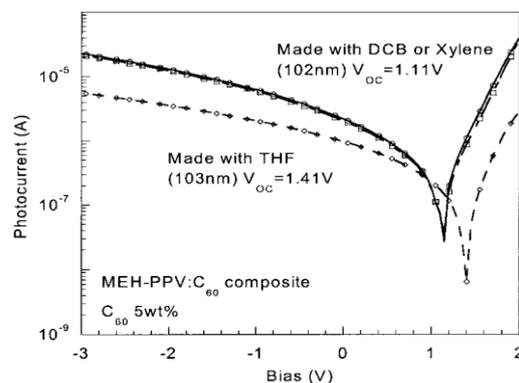


Fig. 6 (b)

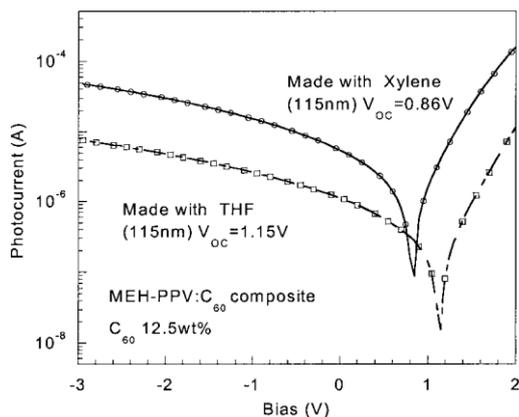


Fig. 6 (c)

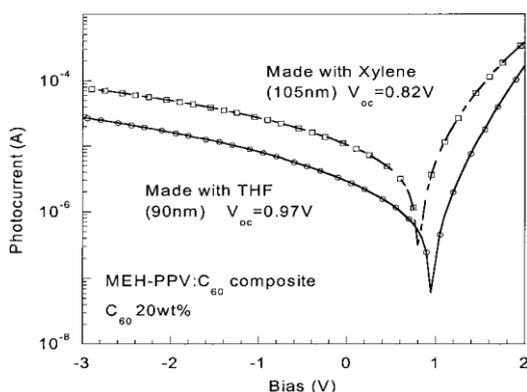


Fig. 6 (d)

Fig. 6 Graphs for MEH-PPV/C60 system with different solvents and different concentrations of C60

The above graphs were reported by Yang and associates.

Solvation-induced morphology results into different arrangements of polymer chains. For aromatic solvents, such as xylene, the solvent molecules preferentially solvate the p-electron conjugated segments and result in a conformation that has better $\pi - \pi$ stacking and subsequently better electrical conduction. On the other hand, non-aromatic solvents, such as THF, preferentially solvate the non-conjugated

segments of the polymer and result in a polymer conformation with a lower electrical conductivity [Y. Shi, J. Liu, Y. Yang, 2000], [J. Liu, Y. Shi, L. Ma, Y. Yang, 2001].

Yang et al suggested that due to the solvation effect, a photovoltaic device made from an MEH-PPV:C60 composite using xylene or DCB should have a better (more direct) contact between the p-electron conjugated segments of the polymer and the C60 molecules. When using THF, the possibility of direct contact between the conjugated segments of MEH-PPV and the C60 molecules is dramatically reduced by the presence of non-conductive side-chain groups between them. Since the side-chain groups have a dimension of several angstroms, which is comparable to the diffusion length of the charge carriers, it is most likely that both the intrinsic forward transfer process and the charge diffusion process are hindered in films fabricated with THF or chloroform. The incorporation of C60 into MEH-PPV can lower the open-circuit voltage in comparison to the pure MEH-PPV device because part of the available difference in potential energy is taken up internally during the CT within the MEH-PPV and C60 composite. [Jie Liu, Yijian Shi, and Yang Yang, 2001].

The following are AFM of MEH-PPV/C60 system, taken from [Jie Liu, Yijian Shi, and Yang Yang, 2001].

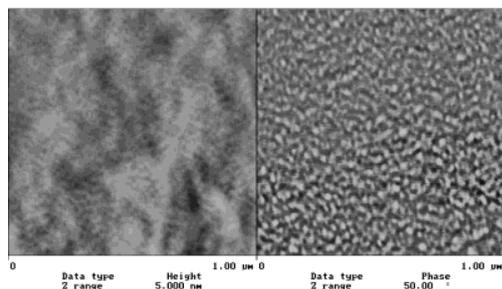


Fig. 7 (a)

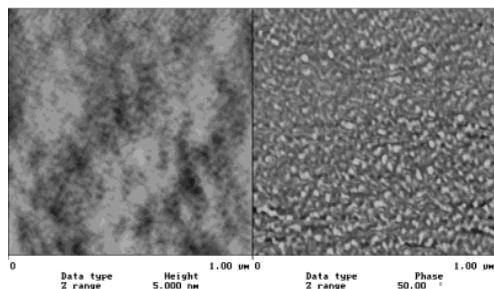


Fig. 7 (b)

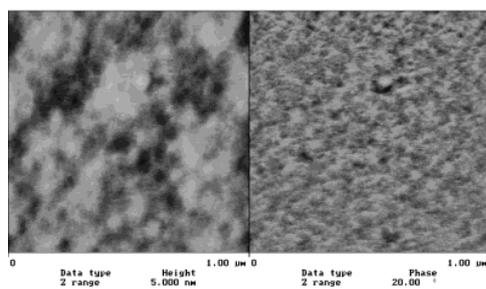


Fig. 7 (c)

Fig. 7 AFM of MEH-PPV/C60(20 wt%) with (a) Xylene, (b) o-DCB, (c) THF

4. Thermal annealing of P3HT:PCBM system

The process of thermal annealing has been demonstrated to considerably increase the

efficiency of P3HT based light emitting diodes and solar cells. As a result of heating, the morphological structure of the organic active layer can be improved by reducing the free volume and the density of defects at the interface during evaporation of the solvent and by enhancing interchain interactions. In a bilayer structure, interdiffusion between the donor and the acceptor was observed. In this way, the acceptor molecule may enter the exciton diffusion radius of the polymer, resulting in a highly efficient charge separation. Thermal annealing of polymer–polymer donor–acceptor blends with subsequent exposure to solvent vapour led to a significant increase of the charge carrier photogeneration efficiency [D Chirvase, J Parisi, J C Hummelen and V Dyakonov, 2004].

4.1. Improvement in absorption

As a result of enhanced P3HT crystallization upon thermal annealing, the P3HT absorption shows significant improvement. The effect of thermal annealing on polymer crystallization is discussed in the following section. Fig. 8 shows the UV-Vis absorption spectra obtained for P3HT : PCBM thin films (thickness 80 nm; PCBM conc. = 50 wt%) before and after annealing at different temperatures (70, 110, 130 and 150 uC for

10 min).⁴⁵ The absorption enhancement seems to saturate at 110 uC after which increasing the annealing temperature has no positive effect on absorbance [Gang Li, Vishal Shrotriya, Yan Yao, Jinsong Huang and Yang Yang, 2007]

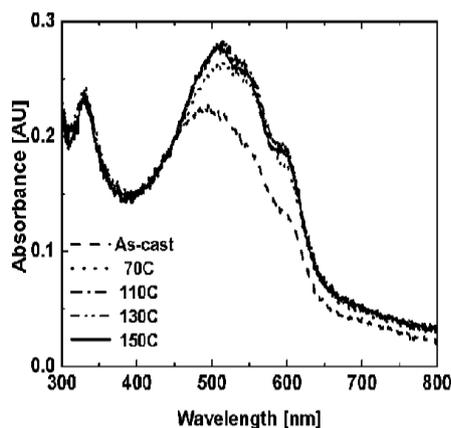
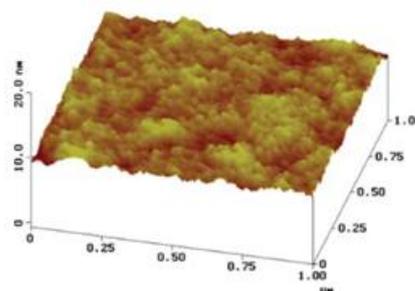


Fig. 8 UV-Vis absorption spectra obtained for P3HT : PCBM thin films (80 nm, with PCBM conc. = 50 wt%) before and after annealing at different temperatures.

4.2 Changes in Morphology

The BHJ structure basically consists of 3-D interpenetrating networks of donor and acceptor materials. The morphology of the polymer blend layer and the metal/polymer interface properties play important roles in determining device performance. The surface of the as-cast film is very smooth

with rms roughness (drms) of 0.377 nm. After undergoing thermal treatment the drms first increases up to 110 C and then decreases. The film texture also changes after annealing. The film annealed at 110 C shows a much coarser texture with broad hill-like features compared to the other films. Higher film roughness gives higher device efficiency. However, the surface area of the roughest film is only about 0.1% more than that of a completely flat surface. Therefore the increased surface roughness probably does not play any direct role in efficiency improvement. Instead, higher surface roughness is more likely a signature of annealing enhanced ordered structure formation in the polymer film. Higher absorption and increase in the charge carrier mobility due to ordering are the most likely reasons for efficiency enhancement. (fig .9)



(a) As-cast

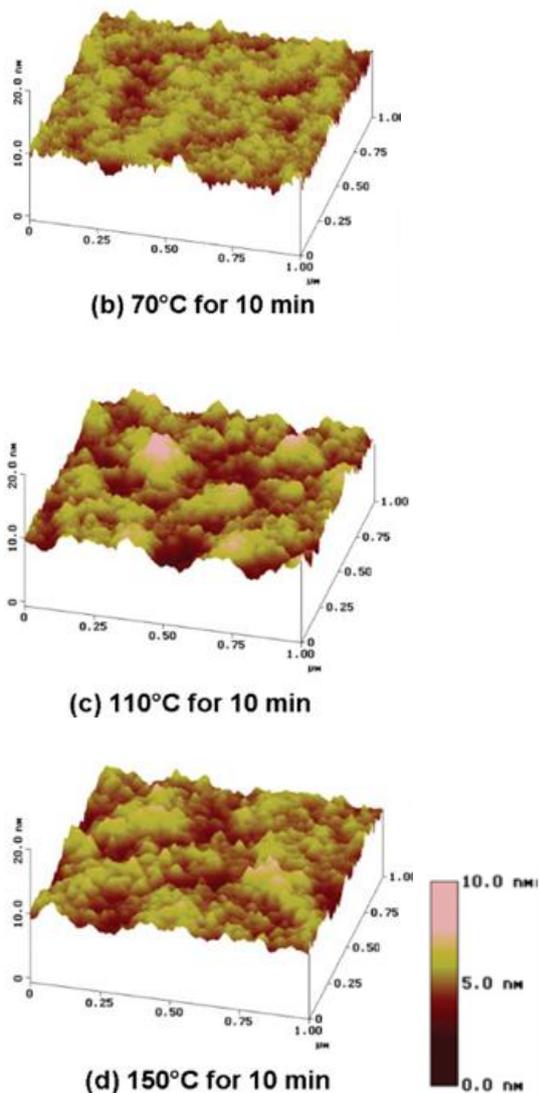


Fig. 9 AFM height images of the P3HT : PCBM surface (a) before annealing, and after annealing at (b) 70 °C, (c) 110 °C, and (d) 150 °C for 10 min

5. Solvent annealing of P3HT/PCBM system

Instead of recovering the RR-P3HT crystallinity (ordering) which is lost during the fast solvent removing (fast spin-coating) process, this approach aims at

maintaining the polymer ordering during the film formation stage. Reducing the solvent removal speed, results in self-organization in polymer chains by controlling the active polymer layer growth rate from solution to the solid state. The intrinsic polymer selforganization capability gives higher absorption, higher carrier mobility, and balanced carrier transport.

5.1 Effect on absorption spectrum [Gang Li, Vishal Shrotriya, Yan Yao, Jinsong Huanga and Yang Yang, 2007]

The absorption in the red region for the slow-grown film is significantly stronger compared to that of the fast-grown film. The three vibronic absorption features are the most prominent reported in the literature, indicating strong interchain–interlayer interactions of RR-P3HT chains, as well as well-maintained polymer ordering in the blend films. After annealing at 110 uC for 20 min, the absorbance of the fast-grown film shows a significant increase and the vibronic features become clearer, indicating a partial recovery of ordering. For the slow-grown film, the absorption spectra show no significant differences before and after thermal annealing.

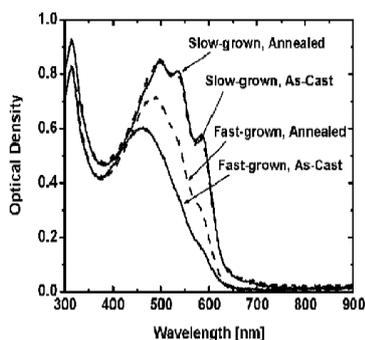
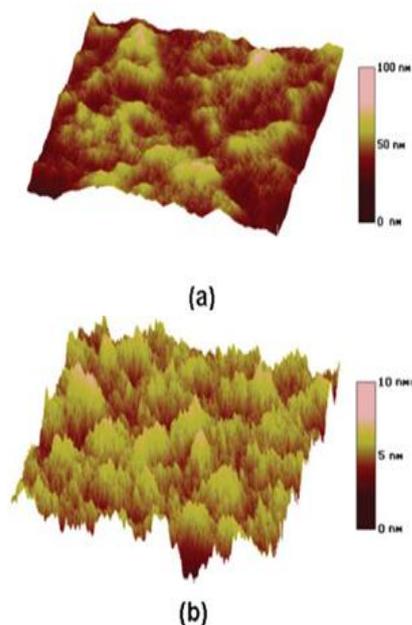


Fig. 10 UV-Vis absorption spectra for slow- and fast-grown P3HT:PCBM films, before and after thermal annealing at 110 uC for 20 minutes.

5.2 *Effect on the morphology* [Gang Li, Vishal Shrotriya, Yan Yao, Jinsong Huang and Yang Yang, 2007]

The AFM height and phase images (Fig. 11) show that the slow-grown film (a) has drms 9.5 nm, whereas the fast-grown film (b) has a very smooth surface with drms 0.87 nm. The peak to valley height of the slow grown film is about 100 nm, corresponding to 50% of the mean thickness (210 nm). The phase image of the fast-grown film (d) shows coarse chain-like (fibrillar) features running across the surface. These fibrillar features are assigned to the domains of pure P3HT crystallites. The region between these features is a disorder zone which harbors structural defects like chain ends and folds as well as tie segments.⁵⁴ PCBM molecules suppress the formation of P3HT

crystallites in the fast-grown films and most of the film consists of mixed domains which are amorphous in nature. For the slow-grown film (c), the crystalline domains of pure P3HT chains are denser. They have a strong tendency to form an interconnecting network and are distributed more uniformly throughout the film. The separation distance between the features is also less, which suggests tighter packing of P3HT crystallites in the slow-grown film. The separation distance between surface features in the slow-grown film (~28 nm) is smaller than that in the fast-grown film (~55 nm). P3HT chains get more time to self-organize into a more ordered structure during very slow growth. As a result, the regions of mixed P3HT/PCBM domains will reduce.



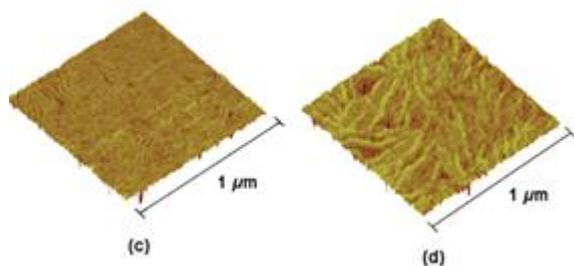


Fig. 11 AFM images for different growth rate of polymer active layer. Height images for (a) slow- and (b) fast-grown films. Phase images for (c) slow- and (d) fast-grown films.

The EQE for the device with a fast-grown film shows a maximum of 19% at a wavelength of 350 nm. On the other hand, for the device with a slow-grown film, the EQE maximum increases by more than three times to 63% at 500 nm (fig. 12).

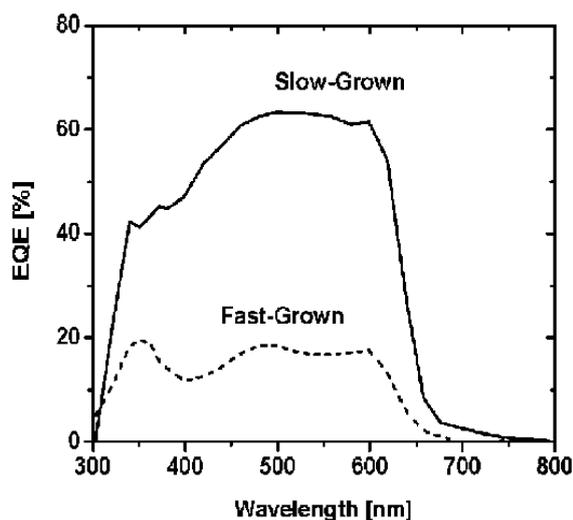


Fig. 12 EQE for P3HT : PCBM solar cells for two types of active layers: slow-grown and fast-grown.

Conclusion

In this paper we have seen the basic working of the solar cell and the various techniques that have a major effect on the morphology of the cell and hence a major effect on the efficiency of the polymeric solar cell.

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Glycolysis of waste PET using Zeolites as a Catalyst

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ABSTRACT:

Polyethylene terephthalate (PET) bottle waste can be depolymerized using excess of ethylene glycol (EG) in the presence of zeolites, b-zeolite and Y-zeolite as transesterification catalyst. The glycolysis reaction can be carried out under reflux in excess of ethylene glycol for up to 8hrs. The product of glycolysis was mainly the virtual monomer, bis(2-hydroxyethyl) terephthalate (BHET) admixed with dimer as residue. The BHET obtained will be in pure crystalline form. Influence of the reaction time, PET: EG ratio, type, and concentration of catalyst on the yield of the glycolysis products were investigated. The yield of BHET monomer will be more than 60%, which is comparable with the conventionally used heavy metal catalysts such as zinc acetate and lead acetate. Melting point of zeolite is much greater than oligomer. So the oligomer+zeolite mixture can be separated by heating it to the melting point of oligomer followed by solid-liquid separation. This process of glycolysis of PET is economically viable and the catalysts are environment friendly.

Key words: polyester; recycling; monomers; oligomers; zeolites.

1. INTRODUCTION:

Polyethylene terephthalate (PET) is one of the most valuable versatile engineering plastics which are used in the manufacturing of soft drinks bottles. With increasing application and decreasing prices, PET became the symbol of disposability in consumerism and hence a noxious material of concern in the relatively recent environmental protection issue, as it is resistant to atmospheric and biological agents. Therefore the necessity of finding a simple economic route for the recycling of waste PET is an important practice for suitable recycling and contributes to the conservation of raw petrochemical products and energy¹. The amount of plastic production has been increasing significantly year by year, with uses including fiber, packing, container, building materials, etc. Plastics offer a tremendous convenience for our life. However, the proliferation of plastic uses has raised waste disposal issues. In recent years, disposal of waste materials has come into focus as an environmental problem that affects everyone. PET resin, a common form of plastics, has excellent characteristic features such as thermal stability, clarity, transparency, light, and is processible. The amount of PET consumption has rising each year, used for producing fibers, textiles, video and audio

tapes, food packing and containers. With the increasing of PET consumption, its recycling has received considerable attention for the ecological and economic considerations².

There are two distinct approaches to the recycling of postconsumer polyester waste. It may be reused directly through **physical reprocessing** of grinding, melting, and reforming⁴.

Chemical Depolymerization of PET can be done by using several methods such as hydrolysis, methanolysis, aminolysis, glycolysis etc. **Hydrolysis** of PET can be carried out by water, acid or alkali under pressure. The ultimate products are terephthalic acid (TPA) and ethylene glycol (EG). During **Methanolysis**, PET waste is treated with methanol under pressure to recover dimethyl terephthalate (DMT) and ethylene glycol (EG) in the presence of catalyst. **Aminolysis** is the reaction of PET with different aqueous amine solutions to yield the corresponding diamides of TPA and EG³.

Glycolysis of PET can produce the BHET monomer, which has been widely used in the production of unsaturated polyesters and rigid or flexible polyurethanes, the glycolysis process was chosen for further investigation in our study. This process is very sluggish without a catalyst. So

depolymerization of PET with ethylene glycol (EG) must be done in the presence of catalyst. Glycolysis proceeding under the influence of EG is the true reverse reaction to the polycondensation of PET, reproducing the BHET monomer. Usually a partial hydrolysis of the PET wastes with EG is applied to obtain a low molecular mixture of oligomers and BHET. The mixture is re-circulated to the PET synthesis process or used in the synthesis of co-polyesters⁹ (see Figure 1)

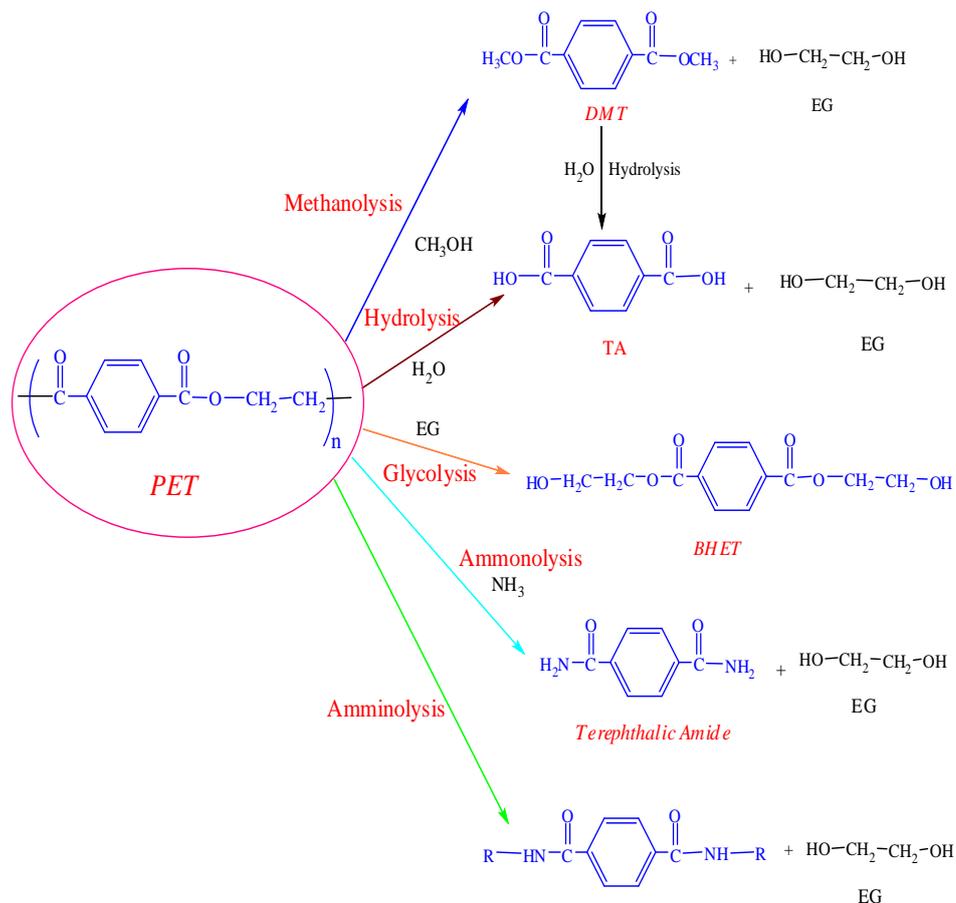


Fig. 1: Schematic representation of various methods of chemical depolymerization of PET.

*from ref no. 4

2. Glycolysis of PET waste:

The PET fiber waste is treated with ethylene glycol at a molar ratio of 1 : 6 (PET : EG) under reflux in the presence of different catalysts for time periods up to 8 hrs. Various catalysts are used in this process concentrations ranging between 0.3 and 1% (w/w). At the end of the reaction, distilled water is added in excess to the reaction mixture with vigorous agitation. The glycolyzed product is obtained as a residue after filtration. The filtrate contains unreacted ethylene glycol, bis-2-hydroxyethylene terephthalate (BHET), and small quantities of a few water-soluble oligomers. White crystals of BHET were obtained by first concentrating the filtrate by boiling and then chilling it. The glycolyzed residue is then boiled with water to extract any remaining BHET. White crystalline powder of BHET is purified by repeated crystallization from water, dried in an oven at 80⁰C and weighed to estimate the yield⁵. (see Table 1)(see Figure 2)

Table 1: Chemicals used in glycolysis

Chemicals	Molecular formula	Molecular weight	Density (g/cm ³) at 20 ⁰ C	Melting point (⁰ C)	Water solubility at 90 ⁰ C
PET	(C ₁₀ H ₈ O ₄) _n	192	1.4	240-270	Insoluble
EG	C ₂ H ₆ O ₂	62	1.113	-12.9	Miscible in all proportion
Water	H ₂ O	18	1.0	0	-
BHET	C ₁₂ H ₁₄ O ₆	254		109-112	Soluble

*from Material Safety Data Sheet on internet

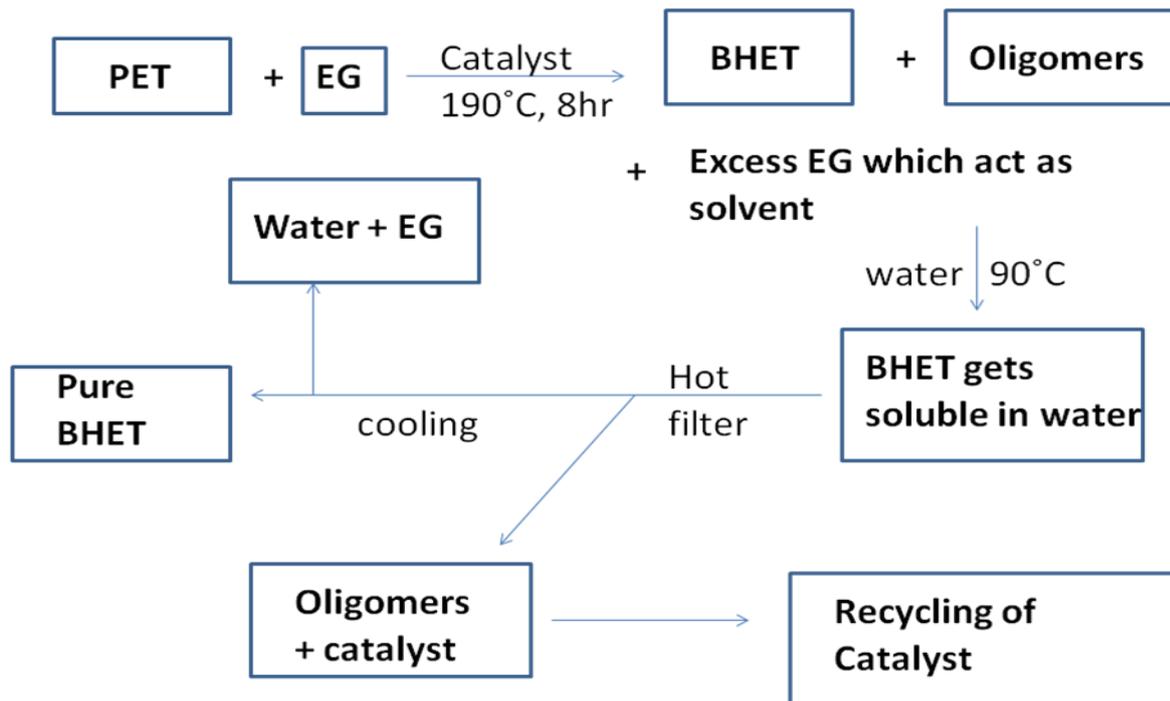


Fig. 2: Schematic representation of Glycolysis of PET. (*drawn by ourselves)

2.1 Reaction mechanism: (see Figure 3)

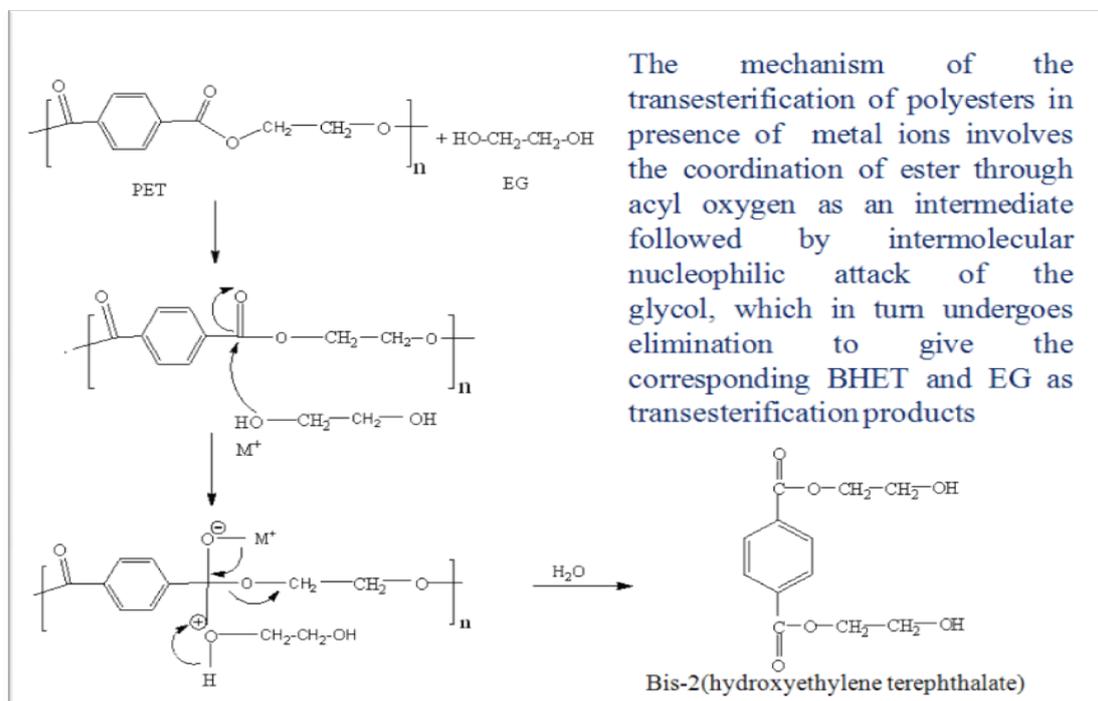


Fig. 3: Schematic representation of reaction mechanism. (*from internet google images)

3. Catalysts used for glycolysis:

Glycolysis of polyester is carried out **conventionally** at atmospheric condition using different types of metal catalysts like zinc acetate, lead acetate, titanium phosphate, solid super acids etc. The simple chemicals such as glacial acetic acid or salts of simple metal cations lithium, sodium, and potassium are found to be capable of depolymerizing PET fiber waste through glycolysis. Although the BHET yields are little less compared to the conventional catalysts such as zinc acetate, considering the environmental safety factors, the chemicals used stand better acceptance for the depolymerization reaction. Thus, glycolysis has been made possible with cheap, ecofriendly, and almost equally effective catalysts without the requirement of a pressure reaction^{5, 10}. (See Table 2)

Table 2: Effect of various catalysts on glycolysis of PET

Catalyst	BHET yield for 0.5 % conc. of catalyst	BHET yield for 1.0 % conc. of catalyst
Zinc acetate	67.63	61.31
Sodium bicarbonate	66.22	63.78
Lead acetate	65.91	62.18
Sodium sulphate	65.72	60
Sodium carbonate	65.43	62.18
Potassium sulphate	64.42	60
Lithium hydroxide	63.5	54.07
Acetic acid	62.42	57
β- zeolite	60	66
Y- zeolite	58	65

*from reference no. 4,5,10

3.1 Disadvantages of conventional catalyst:

1. Zinc and lead both are heavy metal cations that cause pollution due to their nonbiodegradable and toxic nature.
2. The heavy metals possess a tendency to accumulate in the living organisms over a period of time.
3. High exposure level affects the central nervous system.
4. Affects the aquatic animals.
5. The permissible limits of Pb and Zn cations in the effluent discharged to the Surface water are 0.1 and 5 ppm, respectively and Separation of catalyst is difficult.

To overcome these disadvantages of conventional catalysts simple chemicals such as glacial acetic acid or salts of simple metal cations lithium, sodium, and potassium can be used.

But these catalysts also have some disadvantages such as

1. Separation of catalyst is difficult.
2. Little low yield of BHET as compared to conventional catalysts.

3.2 Disadvantages of catalyst recovery techniques:

1. The cost of these techniques is very high.
2. The amount of catalyst used in the reaction is very small in proportion **but the recovery or recycling of it is very expensive as compared to the cost of the catalyst.**

3.3 Various separation techniques for the Water and EG mixture:

1. Vacuum distillation to separate water from the mixture.
2. Liquid-liquid extraction to separate EG by using solvents like Hexane, DMC etc.
3. Reverse osmosis.

To get rid of these conventional as well as simple chemical catalysts **zeolites as a catalyst** can be used.

4. Glycolysis using Zeolites as catalyst:

The **mechanism** we are proposing is the **Solvent Free Reaction for the glycolysis of waste PET**. In this reaction, EG itself acts as a solvent as well as take part in the reaction.

A solvent-free or solid state reaction may be carried out using the reactants alone or incorporating them in clays, zeolites,

silica, alumina or other matrices. Thermal process or irradiation with UV, microwave or ultrasound can be employed to bring about the reaction.

Initially, the reaction mixture is biphasic, one solid phase (PET) and a liquid phase (EG). When the chemical structure of polyesters (molecular weight and compositions) allows their solubilization, they pass into solution due to the presence of terephthalic moieties and lowering the EG concentration, due to the introduction of polyesters. The solubilization of polyesters is maximum at 196⁰C. The PET weight (%) loss is higher at higher temperatures.

4.1 Advantages of solvent free reaction:

1. These reactions occur more efficiently and with more selectivity compared to reactions carried out in solvents.
2. Such reactions are simple to handle, reduce pollution, comparatively cheaper to operate and are especially important in industry.
3. It is believed that solvent free organic synthesis and transformations are industrially useful and largely green.

4. Ease of purification.
5. High reaction rate (due to high concentration of reactant).
6. Bring down handling costs due to simplification of experimental procedure, work up technique and saving in labour. These would be especially important during industrial production.

4.2 Zeolites (as a catalyst):

Zeolites are naturally occurring crystalline aluminosilicates wherein Si⁴⁺ and Al³⁺ atoms are tetra coordinated, shared with oxide ions. This feature develops a negative charge on the aluminum atom and demands the existence of counter-ion to reach neutrality of crystalline structure outside the framework when protons (H⁺) are used; these materials act as Bronstead acids. Such zwitter ionic character is responsible for the unique chemistry of these materials. Zeolites have the ability to act as catalysts for chemical reactions which take place within the internal cavities. Zeolites find major uses in petroleum cracking, ion-exchange (water softening and purification), and in the separation and removal of gases and solvents. They are often referred to as molecular sieves. (see Figure 4)

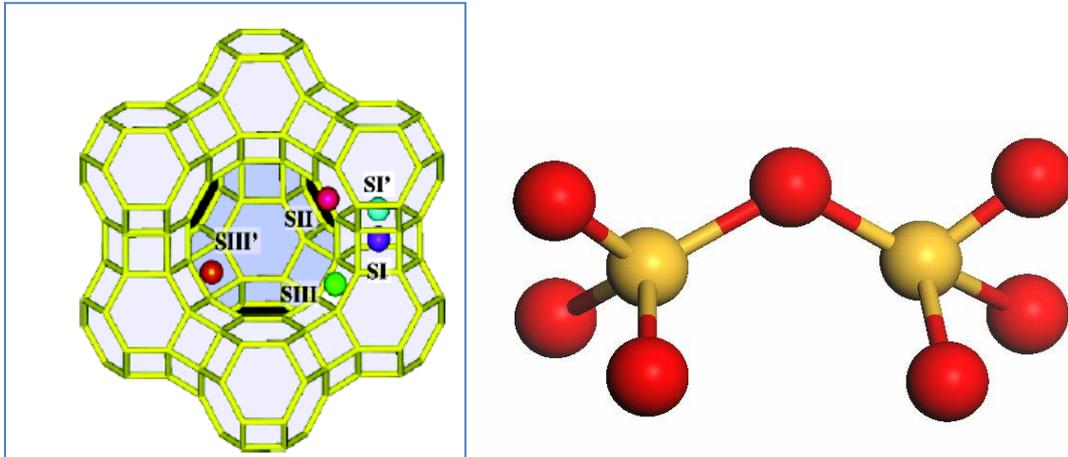


Fig. 4: Molecular structure of Zeolites. (*from internet google images)

For each Al, a negative charge is created. The negative charge is compensated by cation.

- Highly porous (high surface area)
- Cations are exchangeable.
- The zeolite has cages.
- Sharply defined pore structures:
 - Shape selective
 - Molecular sieves
- The aluminum sites are very acidic.

The Zeolites which we are considering are,

1. β -zeolite:

- Na form, $\text{SiO}_2/\text{AlO}_2$ ratio= 1:5 powder.

- It has lower Si/Al ratio and less active sites, hence it cannot solubilize PET as fast as Y-zeolite.

2. Y- zeolite:

- H form, $\text{SiO}_2/\text{AlO}_2$ ratio= 4:5.
- Y-zeolites have high Si/Al ratio and large mesopore surface since it has high hydrothermal stability and suitable acidic and porous properties for catalytic reactions.
- This directly affects the ion exchange equilibrium providing major part of the surface area and the active sites.

- The number and strength of active sites present in Y-zeolite are the crucial parameters for solubilization of PET and thus it helps in depolymerization of PET in a shorter time.

giving 58% yield of BHET, whereas in the case of β -zeolite, the yield of BHET even after 7 hr is 65% using 1% (w/w) concentration of β -zeolite and 1:6 PET:EG ratio⁴.(see Table 3)

Table 3: Material analysis for the reaction

Basis: Given weight of PET is 10.00g.

At the very initial stage (2 hr), glycolysis proceeds at a high rate for the Y-zeolite

Chemicals	Given Weight	Molar ratio	Number of moles	Final Weight
PET	10.00g	1	0.052	-
EG	19.31g	6(excess)	0.312	-
BHET	-	-	-	6.5g
Water	700.00g(excess)	Excess	Excess	-
Oligomers	-	-	-	3.5g
Catalyst(Zeolites)	0.1g	1% of PET	-	As per separation

*from reference no.4

4.3 Advantages of zeolites:

1. Zeolites are naturally occurring crystalline aluminosilicates.
2. They act as Bronstead acids.
3. It plays a significant role in reducing toxic impact of conventional catalysts on the environment.
4. Zeolites contribute to a cleaner, safer environment in a number of ways.

4.4 Separation of zeolite catalyst:

1. Melting point of zeolite is much greater than oligomer. So the oligomer + zeolite mixture can be separated by heating it to the melting point of oligomer. At this temperature oligomer will melt and can be separated by solid liquid separation i.e. filtration. Zeolite can be recovered after separation.
2. But the energy requirement for this separation is very high. So this process of separation is very expensive as compared to the cost of zeolite and the activity of the zeolite will decrease by the repetitive use.

5. Uses of BHET and Oligomers:

1. The purified BHET is converted to different fatty amide derivatives to obtain quaternary ammonium compounds that have a potential for use as softener in the textile finishing process. Application of these synthesized compounds is carried out on cotton fabric; they are evaluated for performance and are found to give good results. The chemicals used during depolymerization and reuse of PET are inexpensive and comparatively less harmful to the environment, and thus offer advantages in the chemical recycling of polyester waste fibers.
2. BHET produced in this way may be used alone or together with other monomers for the production of PET or aromatic copolyesters. BHET obtained from industrial PET waste can be used for various products.
3. Oligomer fractions can be used to prepare PET by adding TA to it.

6. CONCLUSION:

The most advantageous method for the recycling of PET is the Glycolysis. Zeolites used as a catalyst can give good yield as well as good recovery. It is

ecofriendly process as well as economical. This process will serve the purpose of future need of recycling of waste PET. This process will reduce the hazards of conventional catalyst.

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BIOCHAR AND THE FOURTH GENERATION BIOFUEL

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Abstract

Biochar (also known as black carbon) is charcoal created by pyrolysis of biomass. It is a way of carbon capture from the atmosphere and storage in the soil for many years. The CO₂ released into the atmosphere by burning fossil fuels can be trapped and stored in the ground thereby not only reducing the greenhouse gas levels in the atmosphere but also improving soil fertility and water quality benefiting agricultural productivity in the process.

Currently Biochar projects are present on a small scale as those two points continue to be researched on to prove their large scale use. However Biochar offers a grand opportunity of reducing carbon in the atmosphere along with providing a renewable energy source in the form of biofuel. Hence it is an attractive proposition.

Keywords: Pyrolysis, Biochar, carbon-negative energy, fourth-generation biofuel

Introduction

What is Biochar?

Soils have the ability to absorb carbon dioxide and influence its concentration in the atmosphere. Biochar can be used to increase the ability of soils to sequester carbon and simultaneously improve soil health^[1]. The goal of this paper is to introduce the concept and origins of Biochar, discuss its production process, potential uses, and the benefits and costs of Biochar in its key roles in agriculture and climate change mitigation^[2]

The manufacturing process –

Pyrolysis:

Pyrolysis is the direct thermal decomposition of biomass in the absence of oxygen to obtain an array of solid (Biochar), liquid (bio-oil) and gas (syngas) (which is the biofuel) products. The specific yield from the pyrolysis is dependent on process conditions, and can be optimized to produce either energy or Biochar.

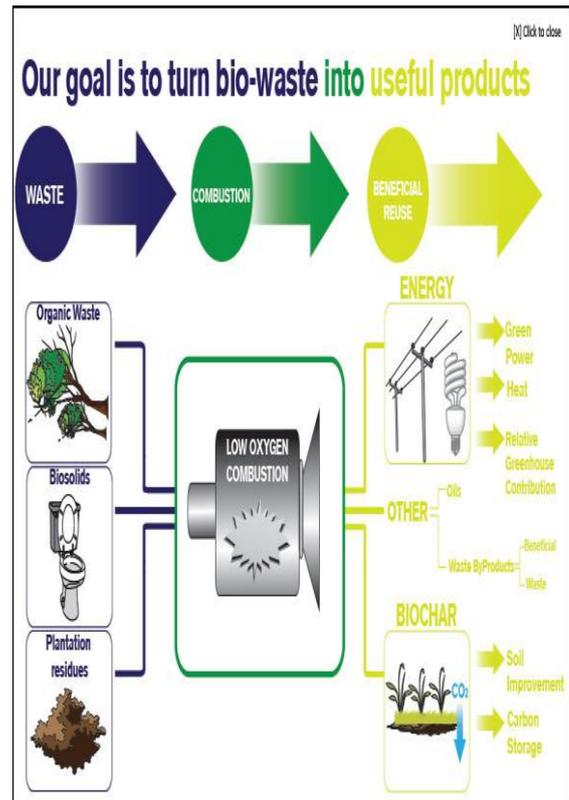


Figure 1 - Biochar and energy (biofuel) from organic waste

2.1 Biochar production

2.2 Pyrolysis:

The Biochar production process begins with biomass being fed into a pyrolysis kiln—a furnace that burns with little or no oxygen. The biomass could be crop residue, wood and wood waste, certain animal manure, or various other organic materials^[4]

At the end of this, two main products come out of the kiln. The first is

Biochar, usually representing about 50 per cent of the carbon content of the biomass. The other is biofuel. The biofuel is often syngas, which is a mixture of mainly hydrogen and carbon monoxide, with a little carbon dioxide. The proportions of the three gases vary according to the processes used to create the syngas. However, the important point is that syngas is combustible and so can be used as a fuel source. Depending on the process, the biofuel from the kiln could also be bio-oil, which can be used as a substitute for diesel in some engines. The pyrolysis occurs at temperatures below 700°C; but some parameters can be altered, such as the rate of pyrolysis. Generally, faster pyrolysis results in more oils and liquids, slower pyrolysis produces more syngas. Minimising the oxygen present during pyrolysis optimises the production of Biochar.

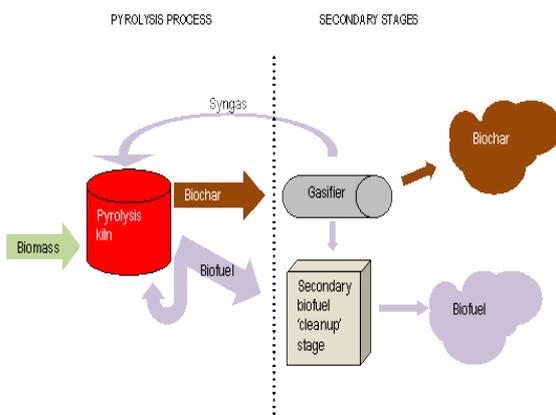


figure 2: Simplified pyrolysis process flow diagram

Gasification:

Pyrolysis can be followed by a second stage: gasification. Gasification liberates more energy-rich syn gases from the char (usually hydrogen-based). There may also be a 'gas cleanup' stage to remove some of the particulates, hydrocarbons and soluble matter from the gas.

The biofuel generated from the pyrolysis process can be used to create the electricity needed to power the kiln or secondary stages of the process. So it is possible for the system to run autonomous of external power sources. The pyrolysis process described is summarised in the diagram. (Refer Figure 2)

An important advantage of Biochar is that it can be produced either from small, simple mobile units or from larger, stationary ones. Small-scale systems for biomass inputs of 50 to 1000 kilograms per hour can be used on farms^[6], while large units of up to 8000 kilograms per hour can be operated by large industries. (Refer Figure 2)

Biochar applications

Biochar has been popularised by its potential role in climate change mitigation. Biochar is rich in carbon and, depending on its ultimate use, the Biochar may retain the carbon, thereby delaying or completely preventing the release of the carbon back into the atmosphere in the form of carbon dioxide gas. The benefits of Biochar go beyond this, extending to the agricultural sector and to various types of waste management. Furthermore, its production process co-generates biofuel, a sustainable renewable energy source. (Refer Figure 3)

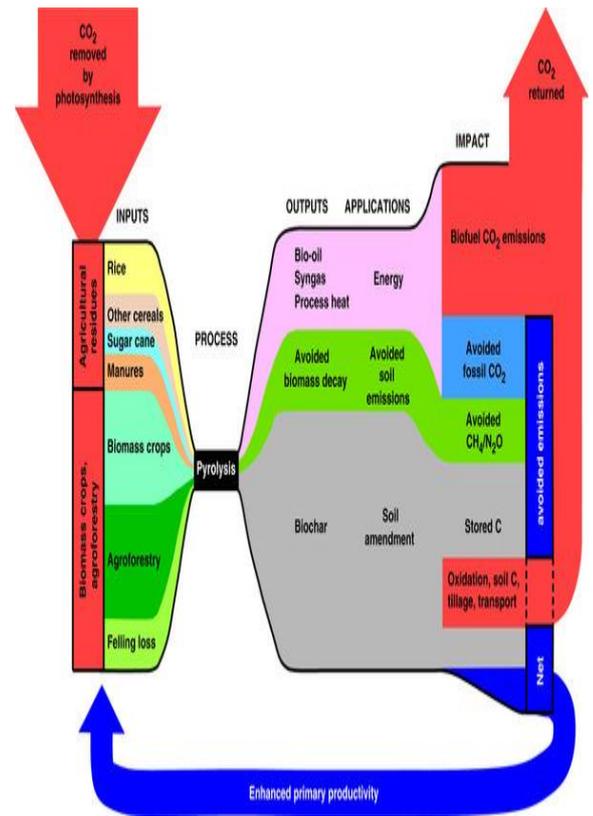


Figure 3 - Biochar: overall details

Fourth generation biofuel:

One definition of a fourth generation biofuel is crops that are genetically engineered to consume more CO₂ from the atmosphere than they'll produce during combustion later as a fuel. Another definition is genetically engineered crops similar to the ones just mentioned but combined with synthesized microbes that will convert the biofuels produced into even more efficient fuel. For example a plant could be grown then converted into a

fuel which is then exposed to a microbe that changes it directly into gasoline. Yet another definition is genetically modified or synthesized microbes that convert CO₂ in the atmosphere directly into usable fuels. Thus with all these definitions it can be seen that a fourth generation biofuel involves genetic modifications.

To look at things in perspective, First generation biofuels are the fuels currently in use such as biodiesel. Second generation biofuels are similar fuels but produced from non-food crops. Third generation biofuels are genetically modified crops that capture more CO₂ from the atmosphere resulting in a carbon neutral fuel. This third generation is why fourth generation has to be more than simply genetically modified crops. Therefore a fourth generation biofuel is that which results in a negative carbon impact when combusted.

Role in Climate change mitigation:

Biochar has been given a lot of attention recently as one means of addressing climate change. It has the capacity to do so in three ways: the storage of carbon over long periods;

the reduction of greenhouse gases such as methane (CH₄) and carbon dioxide (CO₂) that can be generated from waste disposal, waste processing or recycling; and the production of renewable energy^[1].

Through the production process, around 50 per cent of the feedstock's carbon content is retained in the Biochar. This compares to the 10 to 20 per cent that remains in biomass after 5 to 10 years of natural decay, and the less than 3 per cent that remains in ash after complete burning. If it proves practicable to replace traditional slash-and-burn practices with slash-and-char methods, Biochar may present a real quantifiable and verifiable option for storing carbon in the long term. (Refer Figure 4)

At the same time, it has the potential to reduce emissions from other activities that might need to take place in the absence of the Biochar option. These other activities are the waste disposal process described above and any recycling process. Both can be sources of greenhouse gas emissions, either as carbon dioxide from transport and processing, or methane from landfill sites.

Finally, the pyrolysis process also produces viable forms of renewable

energy. The syngas and bio-oils that result from the Biochar production process, and the generated heat, can be used either to produce electricity, or as fuel. Not only does this represent a renewable energy alternative but it also improves the energy efficiency of the pyrolysis process^[3]

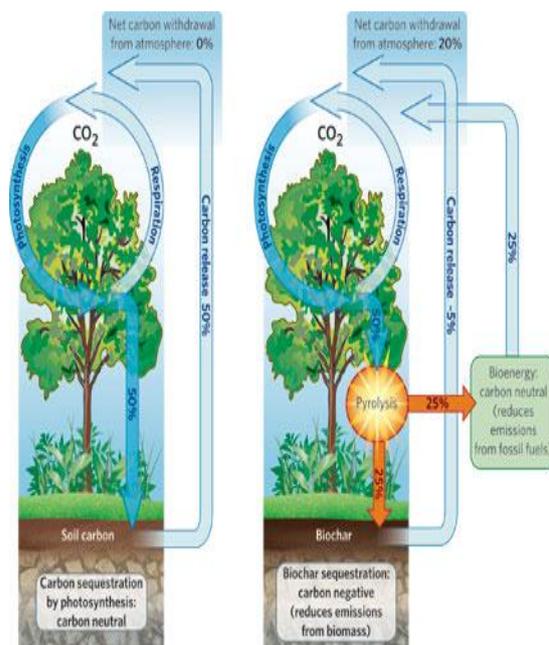


Figure 4 - Carbon negative energy through carbon capture

Conclusion

The overall concept of Biochar is now well understood. Take the farmyard scraps, feed them into a pyrolysis kiln, apply the material produced back to the land and in doing so, improve soil health, lock away carbon, and generate renewable energy. But not all Biochar is the same. Production process, applications, benefits and costs vary with the biomass, soil-types and

ultimate purpose^[9]. The scientific, financial and societal factors of Biochar have yet to be assessed on any significant scale^[5]. Biochar has a role to play in the capture of terrestrial carbon, but its capacity to mitigate climate change should not be overestimated. Rather, it should be seen as a complementary measure to attempts at reducing emissions.

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Relation between λ_{\max} and p-substituents in some mono-azo dyes

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Abstract

In this project, two series of azo dyes were synthesized by diazotization of para substituted anilines and coupling with 2-naphthol (series 1) and N,N-dimethylaniline (series 2). The wavelength of maximum absorption for the azo dyes of both the series was found with a UV-VIS spectrophotometer. For a particular series, the variation between the inverse of wavelength of maximum absorption with the Hammett coefficient of the para substituent of that particular azo dye was studied.

1. INTRODUCTION

1.1 Azo dyes^[1]:-

Azo compounds are compounds bearing the functional group $-N=N-$. IUPAC defines azo compounds as: "Derivatives of diazene (diimide), $HN=NH$, wherein both hydrogens are substituted by hydrocarbyl groups, e.g. $PhN=NPh$ azobenzene or diphenyldiazene." The more stable derivatives contain two aryl groups. The $N=N$ group is called an *azo group*. The name azo comes from *azote*, the French name for nitrogen that is derived from the Greek *a* (not) + *zoe* (to live).

As a consequence of π -delocalization, aryl azo compounds have vivid colors, especially reds, oranges, and yellows. Therefore, they are used as dyes, which are commonly known as azo dyes. Some azo compounds are used as acid-base indicators due to the different colors of their acid and salt forms. The development of azo dyes was an important step in the development of the chemical industry.

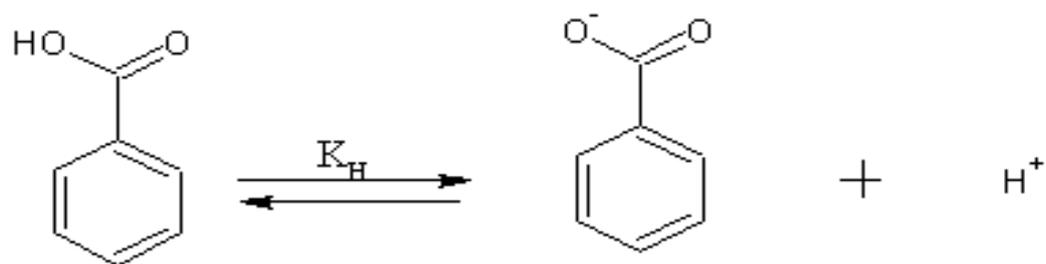
1.2 Hammett equation:-

The Hammett equation in organic chemistry describes a linear free-energy relationship relating reaction rates and equilibrium constants for many reactions of meta- and para-substituted benzene

derivatives with just two parameters: a substituent constant and a reaction constant ^[2]. This equation was developed by Louis Plack Hammett in 1937^[3] as a follow up to qualitative observations made earlier^[4].

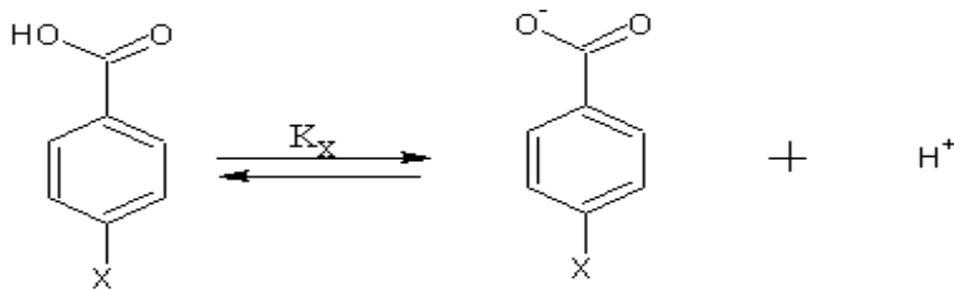
in the type of substituent, the change in free energy of activation is proportional to the change in Gibbs free energy ^[5]. This notion does not follow from elemental thermochemistry or chemical kinetics and was introduced by Hammett intuitively.

The basic idea is that for any two reactions with two aromatic reactants only differing



Reaction 1 (Reference [5])

(K_H is the equilibrium constant of the corresponding reaction)



Reaction 2 (Reference [5])

(Where X is a para substituent and K_X is the equilibrium constant of the corresponding reaction)

$$\log (K_X/K_H) = \sigma \quad (\text{Hammett coefficient}) \dots \dots \dots (1)$$

$\sigma =$ positive, if X is electron withdrawing group

$=$ negative, if X is electron donating group

From Arrhenius equation,

$$k = Ae^{-E_a/RT}$$

$$\therefore \ln k = \ln A - E_a/RT$$

$$\therefore \ln k \propto \Delta E_a \text{ (energy)}$$

Now, $\ln k \propto$ Hammett coefficient $\dots \dots \dots$ from (1)

$$\therefore \Delta E_a \propto \text{Hammett coefficient } (\sigma)$$

Hence, there is a direct relationship between an energy term of p-substituted aromatic compounds with the

corresponding Hammett coefficient. In case of azo dyes, there exists an energy term which determines the λ_{\max} , and which can be expressed as,

$$\Delta E \propto (1/\lambda_{\max})$$

Literature survey was done regarding this topic and the related articles were sourced from Chemical Abstracts.

Since $\Delta E_a \propto \sigma$, $1/\lambda_{\max}$ is expected to be proportional to σ .

Such a relationship was first described^[6] by Russian workers in 1964, wherein they studied solvatochromism in a series of substituted nitro benzenes and Hammett constants. The linear co-relation between Hammett constant σ with the shift of the electronic absorption spectra of some nitro compounds in different solvents was analyzed. Solvatochromism $\Delta\nu$, the difference in ν (max) in n-heptane and ethyl alcohol of nitro derivatives of benzene decreased linearly as σ increased.

They also studied ^[7] solvatochromy of some substituted p-amino benzene and Hammett constants. The solvatochromic effect was studied for the meta and para substituted derivatives of diazo compounds in ethyl alcohol. The linear relationship was given by

$$\Delta\nu = 1640 - 800\sigma$$

To the best of our knowledge no further work in this direction was reported after 1964.

Therefore, in this project the relationship between the wavelength of maximum absorption and the corresponding Hammett coefficient of the para substituted azo dyes was studied.

2. EXPERIMENTAL

2.1 AIM: Preparation of azo dyes.

Two series of azo dyes with 2-naphthol and N,N-dimethylaniline as the coupling components and para substituted anilines was prepared. The following aniline derivatives were used:

Aniline, 4-nitroaniline, 4-anisidine, 4-chloroaniline, 4-aminophenol, 4-toluidine, 4-aminobenzonitrile.

A generalized procedure as reported in Ref. 8 was followed for preparing these azo dyes.

2.2 PROCEDURE ^[8]:

Diazotization:

1. 5 g of the corresponding aniline was dissolved in the required amount of conc. hydrochloric acid and water.
2. The resulting solution was cooled with the help of ice and salt (freezing mixture) and with constant shaking or stirring.
3. A solution of sodium nitrite (equivalent to the amount of aromatic amine used) was added to the above cooled solution at 0°-2°C.

The mixture was stirred at 0°-5°C and completion of reaction was checked by starch iodide paper.

Coupling:

For series 1: β -Naphthol as the coupler:

1. The required amount of β -naphthol was dissolved in adequate amount of water containing an equivalent amount of NaOH.
2. It was stirred in an ice bath such that a temperature of 0°-2°C was obtained.

3. The diazotized amine was added to this coupler solution slowly as a thin stream at 0°-5°C.
4. The precipitated dyestuff was filtered and washed with adequate amount of water.
5. The resulting wet cake was dried in an oven at 60°-65°C.

For series 2: N,N-Dimethylaniline as the coupler:

1. The required amount of N,N-dimethylaniline was dissolved in adequate amount of glacial acetic acid.
2. The above solution was added slowly to the diazotized amine with constant stirring at 0°-5°C.
3. A 2.5N solution of soda ash was added to the above solution very slowly till the reaction mass exhibited a pH of 4-5 (pH paper).
4. The mixture was stirred for half an hour, filtered and the wet cake was washed with adequate amount of water.
5. After adequate washing the wet cake of the dye is dried in oven.

Tables 1 and 2 give the actual amounts of all the reaction materials used.

Note: Since N,N-dimethylaniline is not as reactive as sodium-β-naphtholate towards

electrophilic substitution and also the diazonium salts obtained from 4-anisidine and 4-aminophenol are weak electrophiles; the coupling reaction did not take place in these cases at various acidic pH. Thus, no dye is obtained in these cases.

Table 1: β -Naphthol as the coupler (series 1)

Dye No.	Compound (5g)	Moles (mole)	Conc. HCl (ml)	Sodium nitrite (g)	Water (during diazotization) (ml)	NaOH (g)	Soda ash (g)	Water (during coupling) (ml)	β -Naphthol (g)
1	Aniline	0.054	75 ml (2N)	3.73	60	2.16	5	75	5.3
2	4-Nitroaniline	0.036	11 ml+ (11 ml water)	2.5	40	6.7	10	85	5.2
3	4-Anisidine	0.041	50 ml+ (187.5 ml Water)	2.82	20	7.61	11.5	97	5.85
4	4-Chloroaniline	0.039	12 ml+ (40 ml Water)	2.71	19.5	7.31	11	91	5.62
5	4-Aminophenol	0.047	57 ml+ (211 ml Water)	3.18	24	8.63	12	110	6.63
6	4-Toluidine	0.047	70 ml	3.3	53	8.8	12	109	6.8

			(2N)						
7	4-Aminobenzonitrile	0.042	15 ml+ (15 ml Water)	2.95	30	7.9	11	100	6.1

Reference [8]

Table 2: N,N-Dimethylaniline (N,N-DMA) as the coupler (series 2)

Dye No.	Compound (5g)	Moles (mole)	Conc. HCl (ml)	Sodium nitrite (g)	Water (ml)	N,N-Dimethylaniline (ml)	Acetic acid (ml)
8	Aniline	0.054	75 ml (2N)	3.73	60	6.84	3.1
9	4-Nitroaniline	0.036	11 ml+ (11 ml water)	2.5	30	4.56	2.1
-	4-Anisidine (coupling reaction was not observed)	0.041	50 ml+ (187.5 ml Water)	2.82	20.15	5.18	2.4
10	4-Chloroaniline	0.039	12 ml+ (40 ml Water)	2.71	19.36	4.96	2.4
-	4-Aminophenol (coupling reaction was not observed)	0.047	57 ml+ (211 ml Water)	3.18	24	5.80	2.75
11	4-Toluidine	0.047	70 ml (2N)	3.3	53	6.00	2.80

12	4-Aminobenzonitrile	0.042	15 ml+ (15 ml Water)	2.95	30	5.31	2.52
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Reference [8]

Purity of the dyes obtained was checked by thin layer chromatography (TLC) (90:10 hexane: ethyl acetate). In all cases a single spot was obtained. In some cases the melting point of the dye was determined and compared with literature values.

Table 3:

Dye no.	Melting point (reported) °C	Melting point (obtained) °C
1	132 ^[9]	132-134
2	250 ^[10]	248-251

References [9], [10]

3. RESULTS AND DISCUSSION

Tables 4 and 5 give λ_{\max} values (10 ppm in ethyl acetate) of all the dyes prepared along with the corresponding σ values (Hammett coefficient).

Table 4: β -Naphthol as coupler (series 1)

Dye no.	p-substituent	Maximum wavelength λ_{\max} (nm)	Absorbance at maximum wavelength	$1/\lambda_{\max}$ (nm^{-1})	Hammett coefficient (σ)
1	-H	470	0.274	0.002128	0
2	-NO ₂	482	0.104	0.002075	0.78
3	-OCH ₃	416	0.317	0.002404	-0.27
4	-Cl	473	0.299	0.002114	0.23
5	-OH	416	0.105	0.002404	-0.37
6	-CH ₃	416	0.339	0.002404	-0.17
7	-CN	476	0.49	0.002101	0.66

Reference [3]

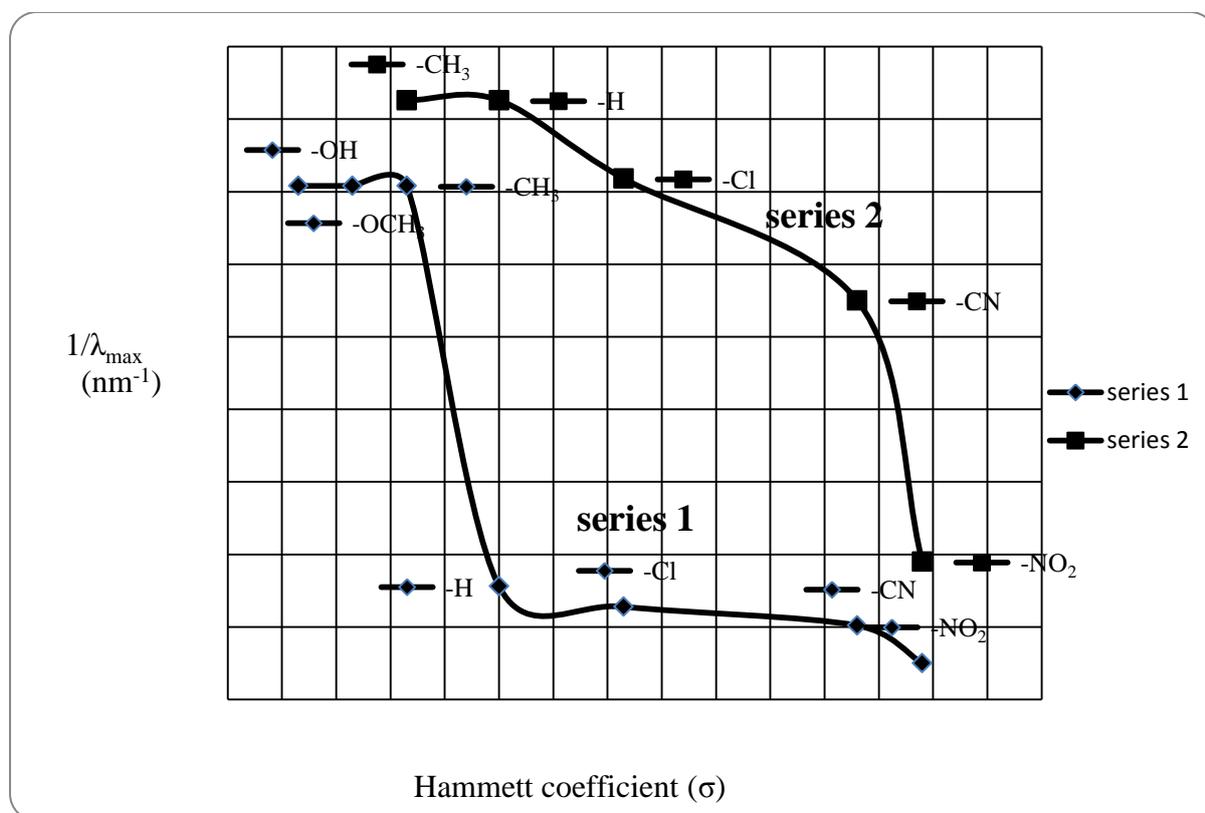
Table 5: N,N-Dimethylaniline as the coupler (series 2)

Dye no.	p-substituent	Maximum wavelength λ_{\max} (nm)	Absorbance at maximum wavelength	$1/\lambda_{\max}$ (nm^{-1})	Hammett coefficient (σ)
8	-H	406	3.155	0.002463	0
9	-NO ₂	466	0.900	0.002145	0.78
10	-Cl	415	2.223	0.002409	0.23
11	-CH ₃	406	3.654	0.002463	-0.17
12	-CN	430	1.810	0.002325	0.66

Reference [3]

Figure3: $1/\lambda_{\max}$ vs Hammett coefficient plot

The following graph gives the plot of $1/\lambda_{\max}$ vs Hammett coefficient of the corresponding p-substituent for β -Naphthol as coupler (series 1) and N,N-Dimethylaniline as coupler (series 2).



1. From the graph, the slope for series 2 is steeper than that of series 1.

As we compare both the series 1 and 2, the N,N-Dimethylamino (series 2) is a stronger electron donating group compared to the hydroxyl group (series 1) and also the number of double bonds involved in conjugation between the donor and the acceptor is more in series 2 (5 double bonds) than in series 1 (4 double bonds). Therefore, the effect of para substituent is more pronounced in series 2 than in series 1 and hence, the slope for series 2 is steeper.

2. There is a distance between the plots of the two series. For example, aniline when coupled with β -naphthol has λ_{\max} at 470nm but when coupled with N,N-dimethylaniline has λ_{\max} at 406nm. Hence, there is a red shift when β -naphthol is used as a coupler. This shows that the conjugation is more in case of β -naphthol as it has one more aromatic ring than N,N-dimethylaniline. Therefore, as the conjugation increases, the delocalization of electrons increases and hence, the excited state of the compound becomes more stable and we get a red shift, that is, λ_{\max} increases. The same phenomenon is observed in the case of all the derivatives of aniline.

3. The graph for both series 1 and series 2 shows similar behaviour in the 1st quadrant ($\sigma \geq 0$). In this region, we can observe that the plots of dyes formed from diazotization and coupling of aniline, 4-chloroaniline and 4-aminobenzonitrile lie in a straight line, but a sharp fall is observed in the plot of the dye formed from 4-nitroaniline. This shows that the nitro group has a stronger bathochromic effect with respect to its Hammett coefficient as compared with other azo dyes whose plots fall in the 1st quadrant of the graph.

4. In the 2nd quadrant ($\sigma < 0$) of the graph, the inverse of the wavelength of maximum absorption ($1/\lambda_{\max}$) remains constant with the variation in Hammett coefficient. Hence, we conclude that for the electron donating para substituents in series 1, the variation of Hammett coefficients with $1/\lambda_{\max}$ for the azo dyes is not prominent and the wavelength of maximum absorption remains constant on changing the para substituent from $-\text{CH}_3$ to $-\text{OH}$ to $-\text{OCH}_3$.

5. Another observation is that, as the para substituent is changed from $-\text{H}$ to $-\text{CH}_3$; in series 1 the λ_{\max} for the corresponding dye is decreased from 470nm to 416nm. But no such change in λ_{\max} is observed for series 2 which is surprising and

we could not arrive at any suitable explanation.

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Ionic liquid as a Green Catalyst and Solvent Media for Friedel-Craft Acylation Reaction

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Abstract:

Ionic liquids, being composed entirely of ions, their lack of measurable vapor pressure characterizes them as green solvents, and that a wide range of chemical reactions can be performed in them. Friedel–Crafts acylation reactions are of great importance in both laboratory work and industry processes to synthesize aromatic ketones. AlCl_3 , H_2SO_4 , HF or other Lewis acid can be used as catalyst in Friedel–Crafts reactions. However, these catalysts can cause a serious environmental problem during purification, and are very difficult to reuse. Therefore, it is important to replace these highly corrosive and hazardous acid catalysts with environmentally friendly catalysts which are active under mild conditions and can be easily regenerated after reaction. In recent years, ionic liquids have shown great promise as an attractive alternative to conventional catalysts and solvents for synthesizing organic chemicals. The Friedel–Crafts acylation using ionic liquids have been reviewed in this article.

Key-Words: Ionic Liquids, $[\text{bmim}]\text{Cl}/\text{AlCl}_3$, $[\text{bmIm}][\text{dca}]$, $[\text{emIm}][\text{dca}]$, $([\text{bmim}][\text{BF}_4])^-$, $([\text{bmim}][\text{PF}_6])^-$, Friedel–Crafts Acylation.

1. INTRODUCTION:

From the viewpoint of today's environmental consciousness, there is a growing need for greener and more sustainable processes in the chemical industry. Replacement or elimination of some toxic reagents or volatile organic solvents in chemical processes is one of the main goals of green chemistry.

It is well known that, Friedel-Crafts acylation of aromatic compounds has been an important reaction in the production of aryl ketones, which are important intermediates in the production of pharmaceuticals and fine chemicals. Friedel-Crafts acylation of aromatics is usually conducted in volatile organic solvents with acyl halide and acid anhydride being used as acylating agents. The conventional catalysts are Lewis acids (AlCl_3 , FeCl_3 , TiCl_4 , and BF_3) and Bronsted acids (HF , H_2SO_4 , and HCl). Until now, AlCl_3 or HF was still used as catalysts in many of the industrial processes, producing a high amount of contaminated waste. Moreover, the FC acylation using these Lewis acids are associated with ecological and economic problems including toxicity, corrosion, generation of large amounts of waste, and difficulty in the purification of the final product. Consequently, there remains a

strong need for developing a green, moisture-insensitive, simple and cost-effective catalytic system for Friedel-Crafts acylation¹.

Ionic liquid is actually just a liquid salts consisting of ions and ion pairs². Ionic liquids (ILs) have attracted growing academic and industrial interest because of their special properties including excellent thermal and chemical stability, no measurable vapor pressure, non-explosive, good tuneable solubility and it provides the reusability of 'green' solvent and catalyst for chemical reactions. In F. C. acylation reaction, ionic liquids have been applied successfully as a way of avoiding corrosive and polluting catalyst system such as HF or AlCl_3 in chloroform or benzene³.

Ionic liquids offer numerous advantages over conventional organic solvents for carrying out organic reactions. Such as, easy product recovery, catalyst can be reused, favourable thermodynamic and kinetic behaviour, enhanced rate of reaction and high selectivity. Ionic liquids usually show the properties summarised in Table No.1.

A salt	Cation and/or anion quite large
Freezing point	Preferably below 100°C

Liquidus range	Often > 200°C
Thermal stability	Usually high
Viscosity	Normally < 100 cP, workable
Dielectric constant	Implied < 30
Polarity	Moderate
Specific conductivity	Usually < 10 mScm ⁻¹ , "Good"
Molar conductivity	< 10 Scm ² mol ⁻¹
Electrochemical window	> 2V, even 4.5 V, except for Bronsted acidic systems
Solvent and/or catalyst	Excellent for many organic reactions
Vapour pressure	Usually negligible

Table 1: Properties of ionic liquids⁴-

Source: - Ref. 4

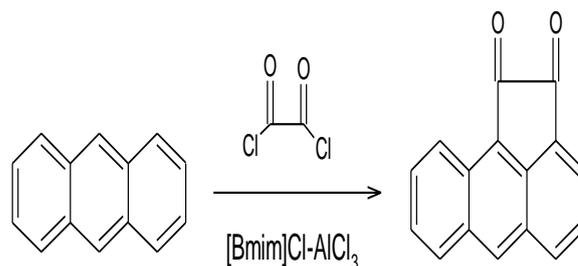
2. APPLICATIONS:

Boon et al., firstly reported the acylation of benzene with the ionic liquid of [emim]Cl/AlCl₃ ([emim]⁺ = 1-methyl-3-ethylimidazolium cation) to produce acetophenone. There is only mono-substitution, when benzene and acetyl chloride were reacted in acidic

[emim]Cl/AlCl₃ ionic liquid. Ionic liquid provided an excellent medium for Friedel–Crafts reaction⁵.

2.1.1 The acylation reaction of anthracene with oxalyl chloride⁶:

Xin-hua et al., reported an efficient preparation method of 1,2-aceanthrylenedione through acylation of anthracene with oxalyl chloride in the presence of [bmim]Cl/AlCl₃ ([bmim]⁺ = 1-butyl-3-methylimidazolium cation) ionic liquid, which was demonstrated to be efficient and reusable catalyst and can be used as solvent for the acylation (See Scheme 1).



Scheme 1: Acylation of anthracene with oxalyl chloride.

Source: - Ref. 6

The acylation carried out as, anthracene and oxalyl chloride were put into a 100-mL three-neck flask equipped with a stirrer, a reflux condenser with drying pipe and a thermometer, then certain amount of [bmim]Cl/AlCl₃ was added to the flask in 10 min with continuous stirring. The acylation reaction was conducted for

certain time with continuous stirring under atmospheric pressure at 45⁰ C. Then the reaction mixture was cooled to room temperature, and induced into two liquid phases (organic phase and ionic liquid phase) by extracting with chloroform. Ionic liquid could be reused after the organic phase was extracted out with trichloromethane. Quantitative analysis was conducted according to the GC spectrum of organic phase accompanying with a correction factor. The organic phase was rinsed with acetonitrile and toluene after vacuum distillation, then red acicular 1,2-aceanthrylenedione was obtained after recrystallizing with ethanol. The maximum yield 88.2% and selectivity 98.2% of 1,2-aceanthrylenedione was obtained.

2.1.2 Comparison of [bmim]Cl/AlCl₃ ionic liquid with AlCl₃:

Friedel–Crafts acylation can be catalyzed by some other inorganic lewis acidic catalysts, of which AlCl₃ has the highest catalytic activity. In order to compare, the acylation of anthracene with oxalyl chloride was also carried out with equivalent AlCl₃ as catalyst, and CS₂ was used as solvent. The results show that [bmim]Cl/AlCl₃ is an environmentally friendly catalyst, and the catalytic efficiency of [bmim]Cl/AlCl₃ is better than that of AlCl₃. The yields of 1,2-aceanthrylenedione when using

[bmim]Cl/AlCl₃ and AlCl₃ were 88.2% and 83.8%, respectively, and the selectivity of 1,2-aceanthrylenedione were 98.2% and 92.3%, respectively. Furthermore, in the presence of [bmim]Cl/AlCl₃ ionic liquid, the isolation and purification for the target products was more easy and the acylation is free of any volatile organic solvent since the ionic liquid plays dual roles of Lewis acid catalyst and solvent. However, for AlCl₃ catalyst system, some problems were caused, such as heavy environmental pollution, troublesome recovery and purification of product, and difficult recovering of catalyst.

2.1.3 Recycle of Ionic Liquid:

The reusing performance of [bmim]/AlCl₃ was investigated with the recycle experiments. After extracting the reaction mixture with chloroform, the reaction mixture became two liquid phases, organic phase (unreaction reactants and products phase) and [bmim]Cl/AlCl₃ ionic liquid phase. [Bmim]Cl/AlCl₃ was reused as catalyst after extracting out the organic phase with ether and vacuum drying at 80–100⁰C for 30 min. The acylation results which catalyzed by the recycled [bmim]/AlCl₃ are summarized in Table 2.

Reusing times	Yield (%)	Selectivity (%)
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1	88.2	98.2
2	88.0	98.2
3	88.1	97.5
4	87.9	96.4
5	87.3	96.1

Table 2: Reusing performance of [bmim]/AlCl₃ in the acylation reaction

Source: Ref. 6

Thus the pure 1,2-aceanthryenedione was successfully prepared by acylation reaction of anthracene with oxalyl chloride in the presence of [bmim]Cl/AlCl₃ ionic liquid and Xin-hua et al., showed that [bmim]Cl/AlCl₃ can be used as a novel environmentally friendly catalyst and solvent for anthracene acylation reaction.

2.2 O-acetylation of alcohols and carbohydrates⁷:

Forsyth et al., reported that dicyanamide based ionic liquids are not only effective solvents for alcohols and saccharides but also active base catalysts for their O-acetylation. The ionic liquids investigated were butylmethylimidazolium dicyanamide [bmIm][dca] and ethylmethylimidazolium dicyanamide [emIm][dca] (See Figure 1).

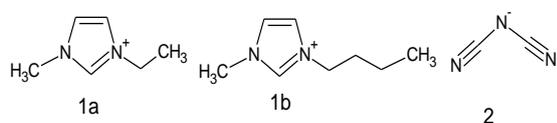


Figure 1: (1a or 1b) Imidazolium cation and (2) dicyanamide anion.

Source: - Ref.7

Glucose is soluble in these liquids to greater than 10 weight percent at room temperature. The solubility of disaccharides (e.g. sucrose) and trisaccharides (e.g. raffinose) is less than glucose, although solubility of all saccharides increases with rising temperature. The dicyanamide ionic liquids appear to be unique, thus far, among families of ionic liquids in presenting high solubility to saccharides.

The acetylation reaction for range of alcohols and saccharides (such α -D-Glucose, β -Me-Glucose, Raffinose, 2-Naphthol, *t*-BuOH, and Cyclohexanol) by using dicyanamide ionic liquid and acetic anhydride and no added catalyst is carried out. In a typical reaction procedure, acetic anhydride (1.42 g, 13.9 mmol) was added to α -D-glucose (0.5 g, 2.78 mmol) and [bmIm][dca] ionic liquid (1.14 g, 5.56 mmol). The mixture was stirred at room temperature until completion of reaction. Water was added to precipitate penta-O-acetyl-D-glucopyranose (isolated yield 89%), whereas the reaction at 50^oC gives the 98% isolated yield. The extent of acetylation and the anomeric ratio were determined using ¹H NMR for samples of

crude reaction mixture and isolated product. The acylation reactions of all the substrate using the dicyanamide ionic liquid yielded the completely acetylated product with more than 85% yield.

Forsyth et al., observe that the reactions proceed just as rapidly, in the absence of catalyst, whereas the catalysed reaction indicates that the ionic liquid has a more crucial role than simply as an inert solvent. This suggests that the ionic liquid is acting as a regenerating catalyst. The mechanism of this catalysis is currently under investigation, but it is most likely related to the basicity of the dicyanamide anion. The absence of any reaction in the case of the butylmethylimidazolium bis(trifluoromethanesulfonyl) amide [bmIm][tfsa] ionic liquid further supports this proposition. The recovered [emIm][dca] was re-used in an acetylation reaction and a similar reaction time was required for complete acetylation.

2.3 Gadolinium triflate immobilized in imidazolium based ionic liquids; recyclable catalyst and green solvent ⁸:

Room temperature ionic liquids (RTILs) that are air and moisture stable have recently been found to be excellent environmentally benign solvents for a variety of reactions. Alletti et al., have explored the recyclability of Gd(OTf)₃ catalyst in RTILs, 1-butyl-3-

methylimidazolium tetrafluoroborate ([bmim][BF₄]⁻) **3**, and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF₆]⁻) **4**, (See Figure 2).

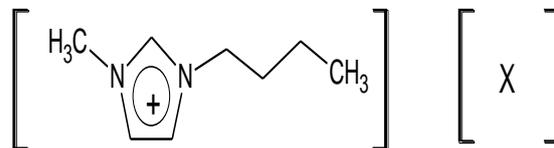


Figure 2: Room temperature ionic liquids.

3; X = BF₄⁻

4; X = PF₆⁻

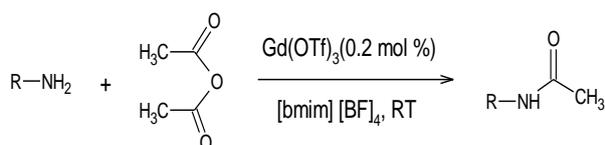
Source: - Ref. 8

Gd(OTf)₃ is relatively more water tolerant than other lanthanide based metal triflates. Thus strictly anhydrous reaction conditions that have been used with other Lewis acid catalysts can be avoided in the case of this catalyst. In addition, it is a relatively inexpensive reagent. Alletti et al., have recently used this catalyst for efficient and convenient acetylations of alcohols and amines using acetic anhydride as the reagent in conventional organic solvents. A variety of primary, secondary and tertiary alcohols as well as phenols and amines can be acylated readily using this water-tolerant Lewis acid.

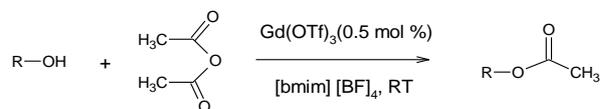
To examine the catalytic activity of Gd(OTf)₃ in RTILs, acetylation of benzyl alcohol with acetic anhydride was chosen initially as a model reaction. Benzyl

alcohol reacted with acetic anhydride at room temperature in [bmim][BF₄] and [bmim][PF₆] in the presence of 0.5 mol percent of the catalyst. In [bmim][BF₄] the yields are good to excellent (92% 1st run), whereas in [bmim][PF₆] relatively lower yields (76% 1st run). When the solvent-catalyst system is recycled and reused, the catalytic activity was slightly decreased in the case of [bmim][BF₄] (72%, 3rd run), whereas a drastic decrease of yield (40% 3rd run) was observed in the case of [bmim][PF₆].

After having optimized the reaction conditions for benzyl alcohol, acetylations of various alcohols with acetic anhydride have been carried out in [bmim][BF₄] in the presence of 0.5 mol% of Gd(OTf)₃ as a catalyst at room temperature (See Scheme 2). The reactions of a variety of alcohols, Excellent yields of acylated products obtained for various substrates are as shown in Table 3 (Entry 10-13).



phenols, diols as well as allylic alcohols proceeded in excellent yields as shown in Table 3 (Entry 1-9).



Scheme 2: Gd(OTf)₃-[bmim][BF₄] catalyzed acetylation of alcohols.

Source: - Ref. 8

Alleti et al., have also investigated the acetylation of amines using Gd(OTf)₃ as the catalyst in [bmim][BF₄]. Using as low as 0.2 mol% of the catalyst, high yields of N-acetylated products have been obtained (Scheme 3). Gd(OTf)₃ catalyzed acetylation of amines proceeded in relatively shorter times as compared to acetylation alcohols as was also observed in case of CH₃CN as the solvent.

Scheme 3: Gd(OTf)₃ catalyzed acetylation of amines in [bmim][BF₄].

Source: - Ref. 8

Entry	Substrate	Product	Yield (%)
1	phenol	phenyl acetate	88
2	naphthalen-1-ol	naphthalen-1-yl acetate	92
3	naphthalen-2-ol	naphthalen-2-yl acetate	90
4	4-nitrophenol	(4-nitrophenyl) acetate	76
5	benzene-1,4-diol	(4-acetyloxyphenyl) acetate	99
6	benzene-1,3-diol	(3-acetyloxyphenyl) acetate	93
7	benzene-1,2-diol	(2-acetyloxyphenyl) acetate	95
8	cyclohexanol	cyclohexyl acetate	92
9	3,7-dimethylocta-2,6-dien-1-ol	3,7-dimethylocta-2,6-dienyl acetate	86
10	phenylmethanamine	N-benzylacetamide	90
11	aniline	N-phenylacetamide	96
12	N-methylaniline	N-methyl-N-phenylacetamide	86
13	2-methylaniline	N-(2-methylphenyl)acetamide	89

Table 3: Acetylation of alcohols using Gd(OTf)₃-[bmim][BF₄] (Entry 1-9), and Acetylation of amines using Gd(OTf)₃ catalyst in [bmim][BF₄] (Entry 10-13)

Source: - Ref. 8

For selected compounds of alcohol and amines, Alletti et al. have demonstrated recyclability and reuse of the Gd(OTf)₃-[bmim][BF₄] catalyst system (See Table 4). Moderate to high yields of the products were obtained in second and third runs.

Sr. No.	Substrate	Product	Yield (%)
1.	naphthalen-1-ol	naphthalen-1-yl acetate	92 (1st run)
			83 (2nd run)
			46 (3rd run)
2.	cyclohexanol	cyclohexyl acetate	92 (1st run)
			87 (2nd run)
			82 (3rd run)
3.	N-methyl aniline	N-methyl-N-phenylacetamide	86 (1st run)
			78 (2nd run)
			72 (3rd run)

Table 4: Reuse of $\text{Gd}(\text{OTf})_3$ -[bmim][BF_4] for representative acetylation reactions.

Source: - Ref. 8

In order to gain insight into the mechanism of these acetylation reactions, Alletti et al. have recorded a broad-band ^1H decoupled ^{13}C NMR spectrum for a solution of $\text{Gd}(\text{OTf})_3$, Ac_2O and [bmim][BF_4] (1:30:7 mol ratio). A weak absorption at $\delta^{13}\text{C}$ 183.9 was (CD_2Cl_2 solvent) was observed indicating the formation of AcOTf as the reactive acylating agent. Based on this observation, a schematic representation of the proposed mechanism is shown in Figure 3.

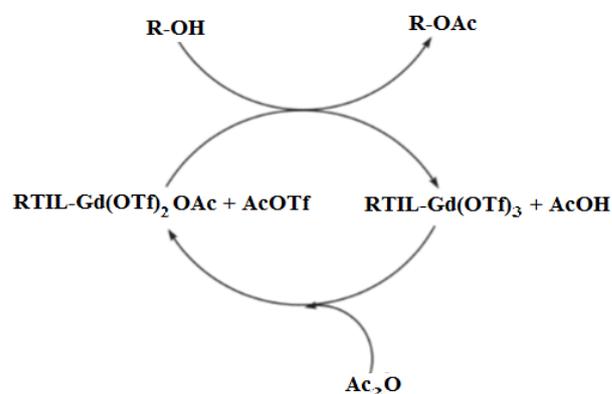


Figure 3: Schematic representation of the catalytic cycle for RTIL- $\text{Gd}(\text{OTf})_3$ catalyzed acetylation mechanism.

Source: - Ref. 8

Thus, $\text{Gd}(\text{OTf})_3$ immobilized in RTILs is an efficient recyclable catalyst system for acetylation of aliphatic and aromatic alcohols and amines. A variety of alcohols, phenols, diols as well as allylic alcohols and amines have been acetylated using 0.2 mol percent of the catalyst in these environmentally benign solvents.

3. CONCLUSION:

The application of ionic liquids in Friedel-Crafts acylation reactions is reviewed in present paper. Ionic liquids can be used as catalyst and solvents giving high reaction rate, conversion and selectivity, and catalyze both activated and deactivated aromatic compounds. The 88.2% yield and 98.2% selectivity of 1,2-Aceanthrylenedione was obtained by acylation of anthracene using [bmim]Cl/AlCl₃ and oxalyl chloride with 5 times reuse of the IL catalyst gives about similar results, and it was found to be better method than the Lewis acid catalyst. Similarly, the acylation of alcohols, carbohydrates and amines has been discussed and excellent results were obtained using ionic liquids. By choosing the correct ionic liquid, high product yields can be obtained and a reduced amount of waste can be produced in a given reaction. This method offers a good catalyst system in the context of “green” chemistry.

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Sketches & Paintings



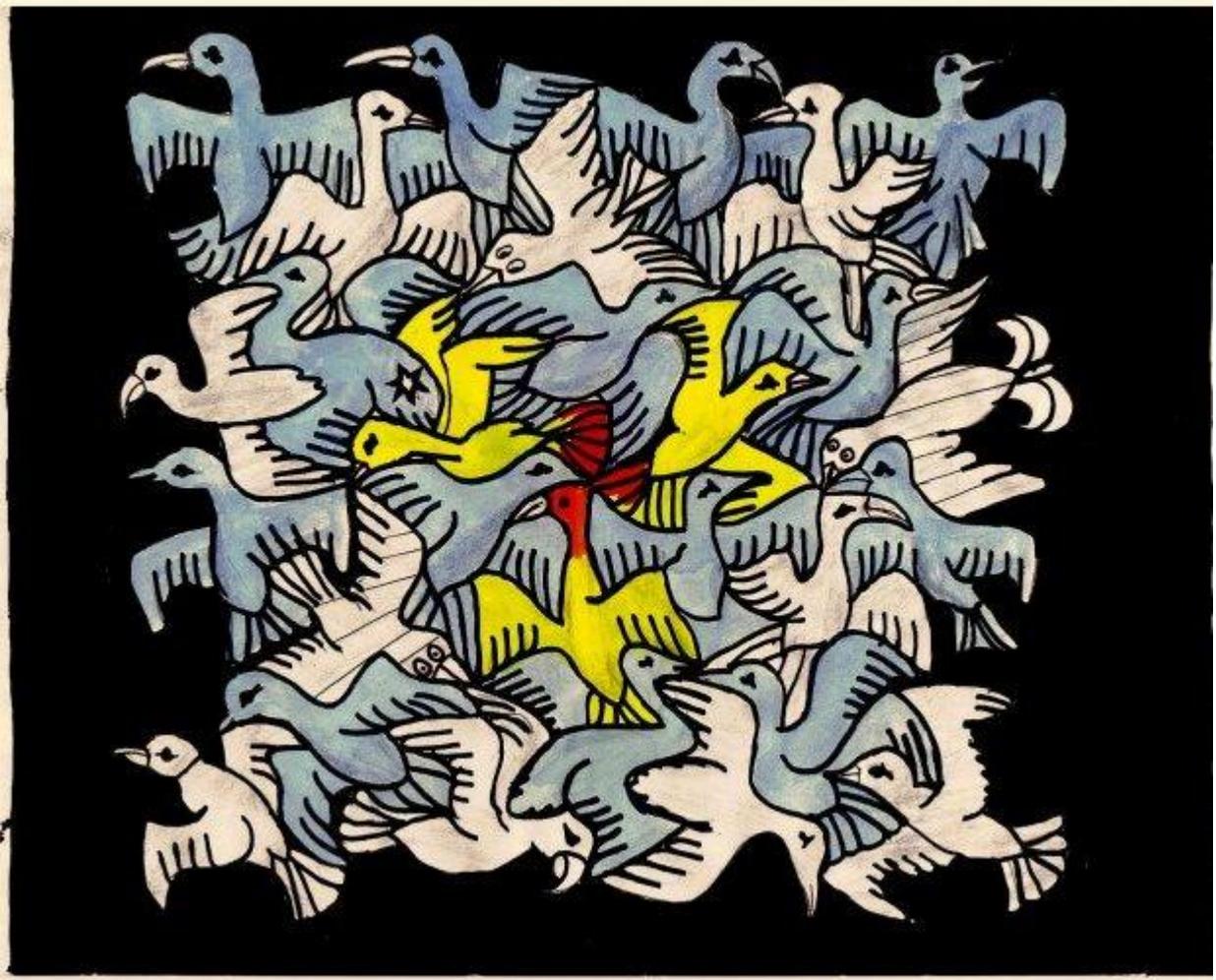
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Poems

लादेनला शोधणार्या.....

लादेनला शोधणार्या तथाकथित जगाच्या ठेकेदारांनो

जगदगुरु तुकारामांचे पार्थिव शोधुन काढा

धर्माधता कोणतीही असु दे

तिला तिथल्या तिथे गाडा

असे कसे जातील संत तुकाराम

सदेह वैकुंठास

ज्यांना ठरले अडचणीचे

त्या नराधमांनीच धुळवडीला केले खलास

काय म्हणताय

खून झाल्याचा पुरावा काय?

मग वैकुंठास सदेह गेले

हयाचा तरी दाखला कुठाय?

दोन्ही गोष्टींना पुरावा नाही

तर आता तर्क लावलाच पाहीजे

संत तुकारामांचे अभंग वाचू

त्यांचा खूनी घावलाच पाहीजे

जे म्हणतात संत तुकाराम सदेह वैकुंठास गेले

त्यांनी आजच्या युगात जावून दाखवावं

नाहीतर आपल्याच बापजाद्यांनी खून केलाय

हे बर्‍या बोलान स्विकारावं

.....प्रशांत गंगावणे

- Prashant Gangawane, Ph.D.(Tech) Research Scholar, Department of Fibers and Textile Processing Technology

पुणे बॉम्बस्फोट ...

बॉम्बस्फोटाची मालिका पुन्हा सुरु झाली

जपुन रहा लोकहो, आपल्या प्राणाला भीती जी आली .

अतिरेक्यांच आवडत स्थान नेहमी मुंबईच असे

पण का कुणास ठाऊक, आता त्यांना पुणे कसे दिसे?

आधी नरीमन हाउस तर आता जर्मन बेकरी उडविली

आणि बिचा-या ज्यू धर्मीयांची जीवन यात्राच संपविली.

८ ठार तर ४० जण जखमी अशी बातमी कानावर येते

आणि आमचे जीव अधिकच टांगणीवर टांगले जाते.

सरकारहो काय करत आहात तुम्ही ?

आणि या बिकट परिस्थितीत जगायचे तरी कसे आम्ही ?

तुमचे सर्व लक्ष My name is khan कडे

पण का नाही थोडेसे लक्ष देत आमच्याकडे ?

Celebrities च्या सुरक्षिततेसाठी तुम्ही आहात तत्पर

मग आम्हा सामान्य लोकांच्या वेळीच का करता अशी काटकसर ?

सरकारहो , आम्हाला भरपूर जगायचे आहे अजून

थोडीशी सुरक्षा द्या आम्हाला तशी,

काहीतरी करून,काहीतरी करून ...

- रामेश्वर ज-हाड

- Rameshwar Jarhad, T.Y.B.Pharm, Department of Pharmaceutical Sci. & Technology

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- Sunanda B Phadtare, Ph. D. Research Fellow (GSS Research Group), Department of Dyestuff Technology



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