

## ROLE OF NANOTECHNOLOGY IN DRUG DELIVERY

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### ABSTRACT

Nanotechnology is an emerging field, comprising the development of materials with 5-200 nanometers in size. Like many other fields advances in nanotechnology is utilized in medicine also specially for therapeutic drug delivery and treatment for a variety of diseases and disorders. The drug is dissolved and entrapped into biodegradable nanoparticles which are specially designed to absorb drug and protecting it against chemical and enzymatic degradation. Nanotechnology is helping the delivery of pharmacologically active molecules for site-specific action with accurate dose. The most promising aspect of utilizing nanotechnology in drug delivery system is lowering of side effects by depositing the active agent in the morbid region only with accurate dose. Nanoparticles for drug delivery are prepared by a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection of material depends on many factors such as the size of nanoparticles, inherent properties of the drug, surface characteristics such as charge and permeability, degree of biodegradability and most important the route of drug delivery. Gold nanoparticles are widely utilized for cancer therapy. Solid lipid nanoparticles have showed appreciable results in anti-cancer and antiviral therapy. Nanofibers, Nanosuspensions etc. are also in use. The use of nanotechnology has facilitated the delivery of many drugs in an appropriate amount and in a targeted manner.

**Keywords:** Drug delivery, Liposomes, Gold nanoparticles, Drug targeting, Biodegradability, dendrimers. Solid lipid nanoparticles, SPIO nanoparticles, carbon nanotubes, silica nanoparticles, magnetic nanoparticles, Liposomes.

### 1. Introduction

Nanotechnology is the engineering of functional systems at the molecular scale. It is a promising approach for efficient delivery of drugs inside the body. The nanotechnology as a drug delivery tool has many advantages over conventional drug delivery methods. It basically deals with development of nanostructures of 5-200nm in size. In this technology drug is dissolved and immobilized into biodegradable nanoparticles which actually helps in adsorption of drugs and protect them against physical and chemical degradation. The major aim of technology is to release the active and efficient molecules of drug for site specific action with accurate dose. Currently several biodegradable nanostructures are being developed for this purpose. Nanotechnology has provided the possibility of delivering drugs to specific cells using nanoparticles.

The overall drug consumption and side-effects

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may be lowered significantly by depositing the active agent in the morbid region only and in no higher dose than needed. Targeted drug delivery is intended to reduce the side effects of drugs with concomitant decreases in consumption and treatment expenses. Drug delivery mainly gives emphasis on increasing the biological availability both at particular places in the body and over a span of bit.

Another important dimension of relationship between biology and nanotech arises from observatory of Eric Drexler in 1981. "Nanopropellers are artificial nanostructures having biological molecular appliance which are prepared by carlomontemagno in 2000. These are wide range of products which are recognized as first generation nanomedicines like Abraxan (approved by FDA)- (an anticancer drug), cimzia ( a protein molecule) in 2005 attached to synthetic polymer molecule. In this way many more nonscientists opened the possibility of developing novel nano medicines and using them against different disease.

Drugs can be attached to individual carriers to achieve cell-specific targeting. Recent developments in nanotechnology have shown the great potential of nanoparticles as drug carriers.

Nanoparticulate drug carriers include a class of particles composed of polymers and lipids. Due to their small sizes, the nanostructures show unique physicochemical and biological properties that make them a favorable tool for biomedical applications and permits systemic and local treatment.

For a targeted therapy, way of conjugating the drug to the carrier and the strategy of its targeting is of immense importance. Nanocarriers surfaces either adsorb or covalently attach to the drug. The advantage of covalent linking over other ways of attaching the drug to the carrier is that it enables to control the number of drug molecules connected to the nanocarrier. An ideal nanoparticle drug carrier must be acceptable for use in human therapy, being biodegradable, biocompatible and non toxic. Active or passive mechanisms can be used up to accomplish cell- specific targeting with nanocarriers . The active strategy relies on the attraction of a drug – the nanocarriers conjugate to the affected site by using recognition ligands, or low molecular ligands, e.g. fatty acids, peptides, etc. Through manipulation of physical conditions (e.g., temperature, pH), active strategy can be achieved, whereas enhanced vascular permeability and retention (EPR) results from passive targeting, a feature of leaky tissues of tumors (Nevozhay D. *et.al.*, 2007 ). There is a release of therapeutic conjugated carriers as the drug-nanocarrier conjugates reaches the diseased tissues. A controlled release of drugs from nanocarriers can result into changes in physiological conditions such as temperature, pH, osmolality & magnetism etc. All these considerations have made the Nanomedicine an interesting and hopeful technique for the treatment of wide variety of diseases.

### 1.1 What makes a Nanoparticle special?

#### Size and Surface Characteristics

Nanoparticles must have the ability to remain in the bloodstream for a specific time without being eliminated in order to effectively deliver drug to the targeted diseased tissue. Conventional nanoparticles are usually caught in the circulation by the reticuloendothelial system, such as the liver and the spleen, depending on their size and surface characteristics (Moghimi S.M.*et.al.*,2001). The action and result of injected nanoparticles can be controlled by adjusting their size and surface characteristics.

**Size:** The major advantages of nanoparticles are that

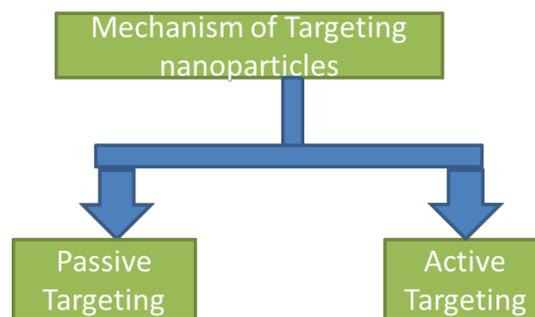
their size is tunable. The size of nanoparticles used in a drug delivery system should be small enough to escape capture by fixed macrophages and large enough to prevent their rapid leakage into blood capillaries. Consequently, the size of nanoparticles should be up to 100 nm to reach diseased tissues

**Surface characteristics:** In addition to their size, the surface characteristics of nanoparticles are also an important factor determining their action on tumor tissues. Nanoparticles should have a hydrophilic surface to escape macrophage capture (Moghimi S.M. *et.al.*, 2003). This can be achieved in two different ways: coating the surface of nanoparticles with a hydrophilic polymer, such as PEG (Polyethylene Glycol)( Adams M.L.*et.al.*,2003andHarris J.M.*et.al.*, 2001).

Nanoparticles are of great interest because of its unique size and surface properties, which are making it a suitable technique for loading of the drugs. They are acting as vectors as well as protectors of drug from degradation and for their controlled and sustainable release.

### 1.2 Mechanisms of targeting Nanoparticles:

There are two mechanisms by which nanoparticles attached on to the surface of drugs and load it onto the diseased tissue of body.



#### Passive Targeting:

**Increased permeability and retention time:** Nanoparticles that satisfy the above said characteristics requirements i.e. ability to circulate for longer times in the bloodstream and a greater chance of reaching the targeted tumor tissues. The unique characteristics of tumor cells enable nanoparticles to accumulate in tumor tissues (Maeda H.2001)). Fast-growing cancer cells need new vessels in order to get supply of oxygen and

nutrients (Carmeliet P.*et.al.*, 2000). This makes the tumor vessels dilated with numerous pores showing gap junctions between endothelial cells and lymphatic tissues (Carmeliet P.*et.al.*, 2000). These features are called the increased permeability and retention effect, which prepares an important mechanism by nanoparticles, can selectively accumulate in the tumor vessels and going to help in well targeting of drugs onto diseased tissues.

**Microenvironment of Tumor vessels.** Another characteristic of passive targeting is the unique environment surrounding tumor cells, which is different from that of normal cells. Fast-growing, cancer cells show a high metabolic rate, and the supply of oxygen and nutrients is usually not sufficient for them to maintain this. So, tumor cells use glycolysis to obtain extra energy, resulting in an acidic environment (Pelicano H.*et.al.*, 2006). Microenvironment of cancerous cells also impart an effect on nanoparticles.

Additionally, cancer cells release unique enzymes like matrix metalloproteinases, which are implicated in their survival mechanisms (Deryugina E.I.*et.al.*, 2006). An albumin-bound form of doxorubicin incorporating a matrix metalloproteinase-2-specific octapeptide sequence between the drug and the carrier was observed to be specifically cleaved by matrix metalloproteinase-2 in an in vitro study (Mansour A.M.*et.al.*, 2003).

### **Active Targeting by Nanoparticles**

Passive targeting mechanisms face intrinsic limitations of its specificity. In order to overcome these limitations is the inclusion of a targeting ligand in polymer-drug conjugates (Allen T.M.2002). Direct conjugation of an antibody to a drug was attempted earlier. However, in clinical study, such early antibody-drug conjugates have failed to show the expected results in using it as an effective tool for the treatment of cancer (Tolcher A.W.*et.al.*,1999). One of the reasons for this is that the number of drug molecules that can be loaded on the antibody is limited. The recent development and introduction of a wide variety of liposomes and polymers, nanotubes, metals as drug delivery carriers increases the potential number of drugs that can be conjugated to targeted nanoparticles without compromising their targeting affinity. When preparing ternary structure nanoparticles, some factors must be considered in order to create more efficient delivery systems.

**Antigen expression.** Ideally, cell-surface antigens and receptors should have several properties that render them particularly suitable tumor-specific targets (Allen T.M.2002). First, they should be expressed exclusively on tumor cells and not expressed on normal cells. Second, they should be expressed homogeneously on all targeted tumor cells. Last, cell-surface antigens and receptors should not be shed into the blood circulation.

**Internalization of targeted conjugates.** Whether targeted conjugates can be internalized after binding to target cells is an important criterion in the selection of proper targeting ligands.

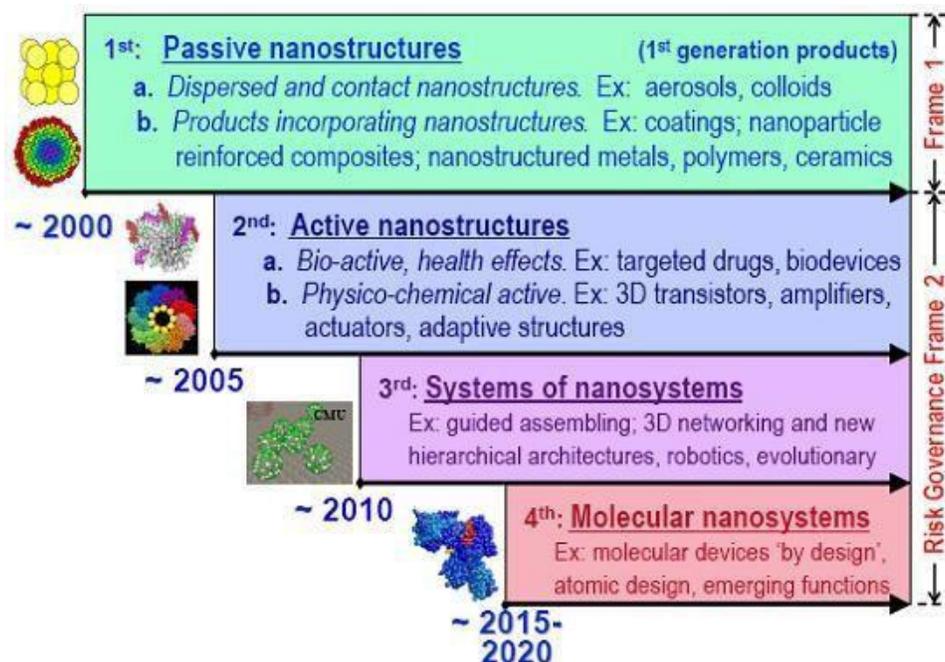
Internalization usually occurs via receptor-mediated endocytosis Using the example of the folate receptor, when a folate-targeted conjugate binds with folate receptor on the cell surface, the invaginating plasma membrane envelopes the complex of the receptor and ligand to form an endosome. Newly formed endosomes are transferred to target organelles. As the pH value in the interior of the endosome becomes acidic and lysozymes are activated, the drug is released from the conjugate and enters the cytoplasm, provided the drug has the proper physico-chemical properties to cross the endosomal membrane. Released drugs are then trafficked by their target organelle depending on the drug. Meanwhile, the folate receptor released from the conjugate returns to the cell membrane to start a second round of transport by binding with new folate- targeted conjugates( Leamon C.P.*et.al.*,2004).

This is how the limitations of passive targeting can be easily overcome by active targeting by proper antigen expression as well internalization of targeted conjugates. Basically because of these mechanisms nanoparticles have gained a special interest in the field of nanomedicine.

### **1.3 Four Generations of Nanotechnology**

Four different progenators of nanotechnology developments are mentioned by Mihail (Mike)

These four generations explain the developments in the field of nanomedicine from past decades to recent time. As it can be explained from above picture first generation was related to nanoparticles like aerosols colloids, polymers, ceramics etc. Second generation nanoparticles are related to targeted drugs and bio devices as well as physiochemical active nanostructures like amplifiers, adaptors etc. Third generation of nanosystems



relates to new robotics and revolutionary architectures. The Fourth generation is related to molecular nanostructures produced at molecular level. So these are the developments from past decades to till now.

#### 1.4 A Jump from Conventional drugs to Nanotechnology

Conventional drugs are administered in body via oral or injection routes which circulate throughout the body and can cause harmful effects in other organs as well. Protein and peptide drugs are poorly absorbed in oral administration. In treatment purposes, Conventional drugs need high doses in order to cure them. (Zhang *et al.*, 2008; Jain *et al.*, 2010) However in nanoparticles drug is confined to a cavity surrounded by a polymer membrane.

The advantages of nanoparticles as a drug delivery tool:

1. Increased drug remedial efficacy and lowering in side effects by proper emancipation of the drug during the transportation and at the place of treatment of tissue, changing the drug dispensation and clearance of the drug inside the body
2. The important thing in using nanotechnology as a drug delivery tool is that it can be assimilated inside the body without any side and chemical reaction.
3. The regulated delivery and drug mortification

features can be quickly harmonized.

4. The increased biological availability of drug at particular site in the for long cycle of time and very low wastage of drug make it a perfect tool for drug delivery
5. It can also enhance the half life of a drug in the circulation system as well as dissolving power of poorly water soluble drugs
6. Nanotechnology has that much of caliber that it can give contentment as well as consent, to the patient and improves the action and delivery of the drug over conventional drugs
7. In comparison to other conventional drugs nanotechnology is far economical

#### 2. Nanoparticles and drug delivery

Nanostructures can be made from wide variety of materials example-Proteins, polysaccharides, Polymers and liposomes etc. Using nanoparticles for drug delivery is the main interest of today's scientists as it gives many advantages over conventional drug delivery methods or tools. The primary goals for research of nano-bio-technologies in drug delivery include:

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

**Factors Included in Selection of Materials for**

### preparation of nanoparticles.

- ☐ Size of nanoparticle to be prepared
- ☐ Type of drug to be delivered

### 2.1 Types of Nanoparticles-

A range of nanoparticles are available for using them as a drug delivery tool. Mainly four types of nanoparticles are discussed below.

- Metallic nanoparticles like silver Gold ,Cadmium,Seleniumetc
- Lipid nanoparticles like Liposome
- Polymeric nanoparticles like Dendrimer, poly micelles
- Biological nanoparticles-BSA(Bovine serum Albumin)

### 2.2 Polymeric nanoparticles:

They are solid particles with size range of 10-100nm .They can be prepared from biodegradable and non-biodegradable polymers or materials (Arias JL *et.al.*, 2006 ). Due to their small size. They can be easily taken up by the cells and increases the accumulation of drugs at target site (Singh *et.al.*, 2006) .A wide spectrum of hydrophobic and hydrophilic drugs can be loaded in these nanoparticles. The surrounding of these polymeric materials consist of functional groups that can be modified with the help of targeting ligands (Ahmed *et.al.*,2006and Pandey *et.al.*,2006) Different methods for immobilization of drug in nanoparticles can be used. The polymer PCL (Poly (E-caprolectone) and PLGA (PolyLactone-co-glycoside) are compared, They are efficiently taken up by immune cells due to their hydrophobicity. (Singh J *et.al.*,2006) .These nanoparticles are also explored for asthma(Seong *et.al.*,2006 ).tuberculosis ( Pandey *et.al.*,2006) and hypertension (Kimura *et.al.*,2009) besides cancer.(Azarmi *et.al.*,2006). some other applications of polymeric nanoparticles also include oral delivery of insulin( Damage C.*et al.*,2007) ,targeted drug delivery for Alzheimer 's disease (Hartig W. *et.al.*,2003 )In order to target the drug at specific site,the drug is conjugated to a cell specific ligand that can reach the organs. Drugs are incorporated into nanoparticles by dissolution, adsorption or entrapment so that nanoparticles can provide efficient release of drug at targeted site. Literature review on polymeric nanoparticles proves that these are quite efficient and suitable for using them in drug delivery.

### 2.3 Liposomes

The word liposome originated from two Greek words namely lipo and soma which means fat and body that's why it is named so it is composed of phospholipids mainly. Liposomes were the first compounds investigated as drug carriers. They are colloidal carriers, usually with size range of 80–300 nm. Liposomes are mainly composed of phospholipid like phosphatidylglycerol ,Phosphatidic choline as discussed by Moussaoui *et.al.*, 2002 and Banerjee R. in 2001 . The characteristics and features of liposomes mainly rely on the choice of lipid, size, constitution and method by which its preparation is done.. Lipids are considered to be suitable chemicals to formulate solid lipid nanoparticles (SLNs) and nanocapsules. Liposomes have been reported to show a strong potential for effective drug delivery to the site of action by increasing the solubility of drugs and improving their pharmacokinetic properties, such as the therapeutic index of chemotherapeutic agents, rapid metabolism and a significant reduction of harmful side effects. Modified liposomes are an interesting type of such lipid structures. Drugs which act selectively on a particular tissue can be designed by the use of multifunctional liposomes, containing the specific proteins, antigens, or other biological substances. In the past few years, many drugs with liposomal delivery systems have been approved and some are in clinical trials. In the market, a range of liposomal drugs are available for many diseases. Anticancer liposomal drugs are also being studied by many scientists and commercialized till date; a few examples of them are mentioned below.

One another property of liposomes make them unique from others is that drugs with different lipophilicity can be encapsulated in liposomes which are stated below :

- 1- phospholipid layer,
- 2-in the entrapped substance
- 3-volume or mass at the bilayer surface

#### **Mechanism:**

A Liposome has a hydrophobic membrane i.e. they do not have ability to form hydrogen bonds with water (Water hating) as well as a core in them. These hydrophobic membranes are linked with lipid bilayer. So liposome can be used either with hydrophobic or with hydrophilic molecules .the contents of a liposome can be easily delivered to

the particular site i.e. diseased tissue in the body by linking the lipid bilayer with the cell membrane in which the delivery is to be done. The whole mechanism is very quick and easy as discussed by Cevc, G; Richardsen, H in 1993. They can be delivered by mixing or preparing in solution of DNA.<sup>1</sup>(Barenholz Y G, 000).Liposomes pH is constructed according to the drug with which it has to be used or with a substance it has to be coated or linked .At neutralization, The drug's as well as the liposome's inside pH will be neutralized, which makes its movement easier and quick through the membrane i.e. without any hindrance of pH or interference by other membranes. The mechanism with which drugs can be delivered with the help of liposomes is diffusion that is movement of a substance or a compound down a concentration gradient. Very different techniques can be used to deliver the drugs with empty liposomes having a transmembrane pH gradient and in such methods in order to reduce toxic effects the vesicles of liposomes acts as the scavengers. (Bertrand *et.al.*, 2010)

Liposomes are used as drug carrier due to their ability of preventing degradation of drugs and reduce side effects. Liposome has many disadvantages include low encapsulation efficiency, Leakage of drug, poor stability. To overcome all these limitations surface polymers like polyethylene glycol can be used to improve liposome's stability. Other vesicular structures like ethosomes,niosomes can be used for transdermal delivery .Liposomes has many applications like drug delivery to enhance skin permeation of drugs ,drug delivery to lungs by nabulisation and also in treatment of parasitic infections.

**List of clinically approved liposomal drugs**

- Liposomal amphotericin B
- Liposomal doxorubicin
- Liposomal IRIV vaccine
- Liposomal verteporfin

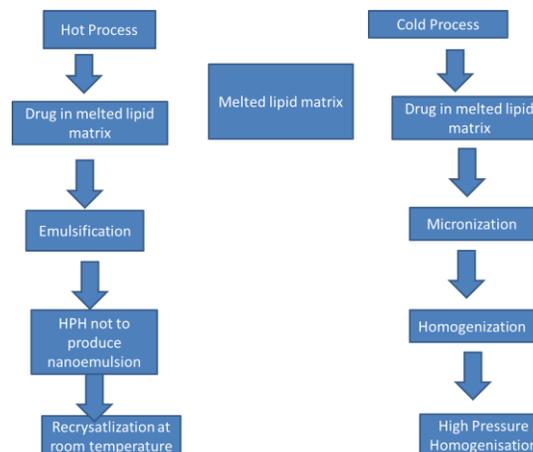
**Manufacturing**

There are different factors on which preparation methods of lipids depends are as discussed by Gomezzens *et.al.*, in 2006 and Mozafari *et.al.*, in 2008 mentioned below

- ☐ The physical and chemical characteristics of the material which is to be encapsulated into the medium

- ☐ The actual concentration of the entrapped material
- The size range , dispersion level as well as shelf-life of the vesicles
- The possibility of large-scale production of safe ,improved and effective liposomal products

**Methods of Fabrication for liposomes**



- ☐ In this way, many other nanoparticles are produced like dendrimers are produced by solvent, microemulsions and solvent diffusion.
- ☐ Method of preparing polymeric micelles includes dialysis, solution casting, direct dissolution.

**Applications of liposomes as a drug delivery tool:**

- Liposome snare very important as we know many Hydrophobic drugs like cyclosporin and paclitaxel are dissolved in surfactants and co-solvents for their administration inside body of humans and these surfactants and solvents are toxic in particular dose of drug. In comparison to that liposomes are made from lipids which are non-toxic, user friendly and compatible as well as biodegradable which provide more effective and safe drug delivery.
- Liposomal drug delivery is more systematic, controlled as well as cost effective than hydrophobic and any other conventional drugs.

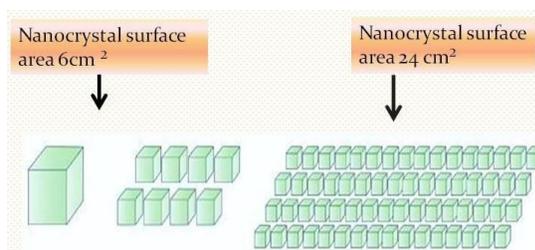
**2.4 Nanocrystals:**

Nanocrystals are aggregates of molecules that can be combined into a crystal form. They have wide applications in chemical and Biological engineering (W.C.Chan *et.al.*, 2016 and. Dabbousii *et.al.*, 1997), but less in nanomedicine for drug

delivery .It includes coating of hydrophilic layer on hydrophobic compound. The reaction of nanocrystals depends on hydrophilic coating on them. These all factors combine in order to prove nanocrystals as an efficient tool for drug delivery system.

**Properties of Nanocrystals:** The main two properties of nanocrystals have made them very unique from others are mentioned below.

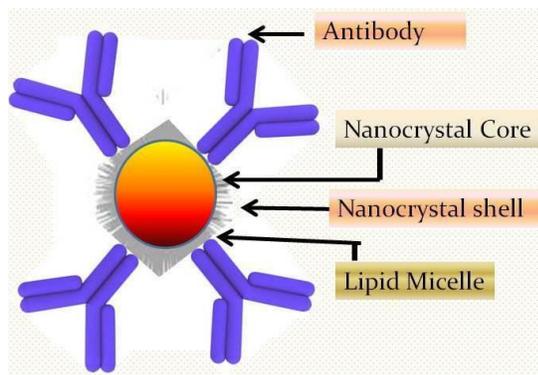
- Increase of dissolution velocity by surface area enlargement
- Increase in saturation solubility as discussed in figure-1



**Method of preparation:** There are many methods for the preparing nanocrystals like milling method, anti-solvent precipitation method which are discussed below:

### Milling methods

The method used for the preparation of crystals is bead or a pearl mill. First of all media, its stabilizer as well as drug are put into the milling chamber. Many forces are generated during its movement which led to reduction of particle size. Instead of other techniques like high pressure homogenization, it is a low energy consuming technique which is always economical and easier for the manufacturer. Different size of beads as well as pearls can use as medium for milling method. These beads or



pearls are made up of glass, stainless steel, highly cross linked polystyrene resins. These beads and pearls are needed to be coated in order to reduce impurities which are caused by various shear forces among media, its stabilizer as well as drug. And sometimes product also adheres to surface of mill which also causes problem during encapsulation or attachment of drug to nanoparticles. as shown in **figure 2**

**Anti-solvent precipitation method :**As we know nanocrystals have a potential to deliver the drugs with great efficiency and at minimal cost, the Anti-solvent precipitation method can also be used to produce these nanocrystals .By using this method stable nanocrystals are prepared with mainly three compounds that is glyburide, ibuprofen, and artemisinin having very complex and diverse structures(Shahzeb Khan *et.al.*, 2013). According to the drug with which nanocrystals has to be coated the growth inhibitors or enhancers of crystal are used .The effect of various physiological factors like temperature, pressure infusion to anti-solvent was generalized in order to answer the question how these variables effect the anti-solvent precipitation. The solubility of nanocrystals in aqueous solution was more rapid than other media. So the main difficulty in whole of this process was the choice of crystal growth inhibitors or enhancers.

**Clinically proved Products :** There are some clinically proved nanocrystals for commercialization, discussed below:

- **Rapamunen:** As the active drug, this is derived from *Streptomyces hygroscopicus* (actinomycetes) molecular weight of 914.2. Rapamune was the first product marketed by company named Wyeth Pharmaceuticals (Madison, NJ) in 2000. It is marketed in two formulations, as a tablet and .oral suspensions. The tablet has the advantage of over oral suspension for being more user and manufacture friendly.
- **Emend:** The second product on the market was Emend introduced in 2001 by Merck (Winehouse Station, NJ)
- **Tricor:** Tricor is being marketed by Abbott Laboratories and the active ingredient is fenofibrate, being available in 48 mg and 145 mg tablets
- **MegaceES:** InMegace ES(ES stands for Enhanced Stability) (megestrol acetate)

introduced by Par Pharmaceutical Companies, Inc. (Spring Valley, NY)

## 2.5 Carbon nanoparticles:

Carbon nanocarriers used in DDS are differentiated into nanotubes (CNTs) and nanohorns (CNH). Nanotubes are self-assembly sheets of atoms. Carbon nanotubes are cylindrical nanostructures having length to diameter ratio of 132000,000:1. Their highest strength to weight ratio helps in crating spacer crafts. They can easily penetrate in cell walls and membranes so helpful in cancer treatment. Nanotubes have several unique chemical, size, optical, electrical and structural properties that make them attractive as drug delivery

They are of two types:

- ☐ Single walled carbon nanotube with a single cylindrical carbon wall
- ☐ Multiwall carbon nanotube in which multiple cylinders are nested within cylinders.
- ☐ They are promising approach for drug delivery for cancer therapy as they have unique, thermal and structural characteristics. They have potential in targeting specific cancer cells with low dosage than other conventional methods.

**Properties:** The chemical, dimensional, structural as well as electrical properties of carbon nanotubes has made them unique as well as useful for drug delivery. Some of them are discussed below:

### Chemical

Nanotubes have enhanced dissolving power for poorly dissolving drugs when functioning with lipids which help them to penetrate and accumulate in human body more easier. Carbon nanotubes has strong optical properties

### Electrical and Structural

Carbon nanotubes can be of two types, one is semiconducting and other is metallic (On the basis of its structure). As we know carbon nanotubes consist of grapheme that is a form of carbon having one atom and shape of honeycomb, its having a unique structure. For a given (n,m) nanotube, if  $n = m$ , the nanotube is metallic; if  $n - m$  is a multiple of 3, then the nanotube is semiconducting (P.J.F. Harris 2009). So all nanotubes can be metallic and can be semiconducting

### Dimensional

Due to their nanoscale dimensions, electron transport in carbon nanotubes will take place through quantum effects and will only propagate along the axis of the tube. The Nanotubes are small which makes them perfect for delivery of small amount of drug at specific diseased site in the body with features of reduced side effects as well as improved drug targeting efficacy (P.J.F. Harris 2009). Drug immobilization in carbon nanocarriers can be achieved in three different ways, which are: encapsulation of a drug in the carbon nanotube (Arsawang U.*et.al.*,2011 and Tripisciano C.*et.al.*,2010), chemical adsorption on the surface or in the spaces between the nanotubes (by electrostatic, hydrophobic, p-p interactions and hydrogen bonds) (Chen Z.*et.al.*,

2011 and Zhang D.*et.al.*,2011), and attachment of active agents to functionalized carbon nanotubes (f-CNTs). Encapsulation is advantageous over the two remaining methods as it protects the drug from degradation during its transport to the cells and is released only in specific conditions (Perry J.L.*et.al.*,2011). The examples of drugs that were attached to CNTs are listed in Table 2. Drug release from carbon nanotubes can be controlled electrically or chemically controlled. The open ends of CNTs were sealed with polypyrrole (PPy) films in order to prevent the unwanted release of the drug (Luo X.*et.al.*, 2011). Attachment of homing devices, i.e., folic acid (Dhar S.*et.al.*,2008) and epidermal growth factor (Bhirde A.A.*et.al.*,2009) was accomplished to improve selectivity of such drug delivery systems.

Nanohorns – a type of horn shaped single-walled tubules with conical tip– exhibit similar properties to nanotubes (Shiba K.*et.al.*, 2006). They can be easily prepared with very low cost as their formation process does not require a metal catalyst, and these are of high purity (Shiba K.*et.al.*, 2006). The immobilization of drugs may rely on adsorption on nanohorns walls (Murakami T.*et.al.*, 2008) or nanoprecipitation of drugs with nanohorns (Ajima K.*et.al.*, 2008). Nanoprecipitation is much more effective (almost 3-fold increase in the number of molecules entrapped in nanohorns) than adsorption as revealed by a comparison of these two paths of cisplatin incorporation into nanohorns (Ajima K.*et.al.*, 2008). Their unique well-defined geometric structures are responsible to some extent for the toxicity of carbon nanomaterials (Jia G.*et.al.*, 2005).

The high length to diameter ratio and the toxicity of the sole material, which is graphite results in toxic potential of carbon nanotubes.

**Applications:** There is wide range of usefulness of these carbon nanotubes in many diseases. But destruction of cancer cells is very important which is discussed below:

### Cancer cell destruction

Carbon nanotubes are specially and particularly observed for the agent for cancer cell destruction and also can be used as biological carrier as discussed by Shi Kam, N. W. in 2005. Many scientists in their work with single walled carbon nanotubes (SWNTs) to have declared that they have a strong optical absorbance near 700-1100 nm infrared light, which make these molecules suitable for cancer cell destruction by stimulation of nanoparticles inside the living cells, if we combine this property of single walled carbon nanotubes with transporting capability, it can become a novel class or a novel material as a drug delivery tool for cancer therapy. (Shi Kam, N. W. 2005 and Liu *et.al.*, 2006)

### 2.6 Dendrimers:

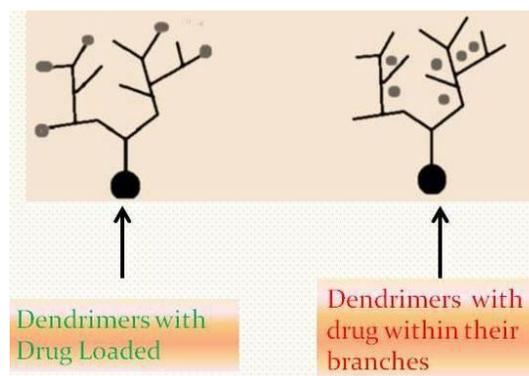
Dendrimers are unique polymers with well-defined size and structure. Dendritic architecture is one of the most popular structures observed throughout all biological systems. Dendrimers are the structures produced from polyamidoamine (PAMAM), polyacrylether. Its size ranges from 1-100nm. First dendrimer was synthesized by Tomalia and co-workers. Dendrimers are branched macromolecules having a central core unit having high degree of molecular uniformity, specific size and shape as well as narrow molecular weight. They have many advantages over other nanoparticles due to their small size, they can be easily uptake by the cells. They can be used for oral, transdermal and ocular delivery. (Patri *et.al.*, 2004 and Sugiski *et.al.*, 2008). Water soluble dendrimers can bind and solubilize small molecules and can be used as coating agents to protect drugs from physiochemical degradation. The property of dendrimers is determined by the variety of monomers and functional groups used in the preparation. In the field of biomedical dendrimers play an important role in drug delivery and diagnosis. The cytotoxicity also called polyvalence, the number of active group present in the surface of dendrimers,

depends on the material used for the core and surface preparation. For instance, amine surface group changed into hydroxyl ones may reduce the cytotoxicity level. Receptor present on the surface of dendrimers shows interaction with target site which may be specific ligands including folic acid (Singh.P.*et.al.*, 2008) antibodies (Wangler C.*et.al.*, 2008) cyclic targeting peptides – arginine-glycine-aspartic acid (RGD) (Waite, C.L.*et.al.*, 1908) selective A3 adenosine receptor (Tosh, D.K.*et.al.*, 2010) silver salts complexes antimicrobial agents (Balogh, L. *et.al.*, 2008) or poly(ethylene glycol) (PEG) (Lope, A.L.*et.al.*, 2009). The surface attached on the surface on dendrimers increase biological and physical activity.

### Structure of dendrimers :

1. Core
2. Layers of branched repeat units
3. Functional end groups on outer layer.

They are unique based on their series of branches, they show multivalences as shown in figure 3. Poly (amido amide) (PAMAM) is a dendrimer which is frequently used in biomedical applications. PAMAM is a common dendrimer that carries anticancerous drug carrier, spherical in shape; they are highly soluble and active due to the presence of number of functional end groups. PAMAM dendrimers are considered as nanoparticles for drug delivery, related to their multiple properties like 3D structure, versatility, biocompatibility. The drug can be linked to the dendrimers by covalent bonds or electrostatic



interactions etc.

### Dendrimers preparation method

There are many methods for the preparation of dendrimers. This method mainly deals with the

preparation of PAMAM dendrimers which were first dissolved in solvents like methanol, deionized water etc. and Ni(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O was used as the metal source.

### Formation of Nickel –Dendrimer

An appropriate ratio of Ni(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O was added to PAMAM dendrimer solution with continuous stirring. Subsequently, the dendrimer and metal complexes were prepared. After the time span of ten minutes with continuous stirring the color change was observed from colorless to golden which indicates the formation of nickel metal. And the whole procedure is needed to be done under nitrogen gas environment in order to prevent the oxidation of metal.

### Techniques for Characterization

A wide range of techniques can be used in order to analyze the physiochemical properties of Nickel nanocrystals. Examples of techniques used for this purpose are UV-Visible Spectroscopy, X-ray diffraction as well as transmission electron microscopy.

**The application of dendrimers:** (Macejewski M.1982 and Herrmann A *et.al.*, 2003)

1. Reduced toxicity and side effects
2. Active targeting
3. Drug shelf life enhancement
4. Improve efficiency of drug delivery
5. Improved drug solubility
6. Slow drug metabolism

### Drug delivered through dendrimers

Drug	Half life of unmodified drug	Half life of Dendrimer
Doxorubicin	0.5 hours	34 hours
Methotrexate	0.5 hours	≥ 50 hours

## 2.7 Solid Lipid Nanocarriers:

SLN (solid lipid nanoparticles), NLC (nanostructured lipid carriers) and LDC (lipid drug conjugates) are types of carrier systems based on solid lipid matrix. Solid Lipid Nanocarriers are nanostructures made from solid lipids such as stearic triglyceride, glycerol tripalmitate with a size range of 50-100nm (Muller R.H.*et.al.*,2000 and Wissing SA *et.al.*,2004). The use of SLN as a nanoparticle

emerges due to its scalability potential as well as its large scale production is cost effective. Till date, SLN has been studied for parenteral, dermal, ocular, oral and pulmonary routes of drug administration (Jones MC.*et.al.*,1999). It is proved to be inefficient for drug loading. In order to overcome the limitation of SLN nanostructure lipid carriers (NLC) were introduced, it was composed of solid lipids as well as liquid lipids with improved drug loading and increased stability on storage (Wissing SA *et.al.*, 2004 and Cavalli R *et.al.*, 2002). With NLC, another nanostructure was also introduced called lipid drug conjugate (LDC). Its main advantage is that it enables the incorporation of both hydrophilic and hydrophobic drugs. SLN need small amount of surfactant in order to get more stability.

Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could hold great promise for attaining the bioavailability enhancement along with controlled and site specific drug delivery.

Solid lipid nanoparticles have recently gain as a novel approach to oral and parenteral drug delivery systems. SLNs combine the advantages of both lipid emulsion and polymeric nanoparticle systems (Mehnert *et.al.*, 2001). It has been proposed that SLNs combine numerous advantages over the other colloidal carriers i.e. incorporation of lipophilic and hydrophilic drugs feasible, avoidance of organic solvents, possibility of controlled drug release and drug targeting, increased drug stability. A recent study has demonstrated the use of solid lipid nanoparticles as a platform for oral delivery of the nutrient mineral iron, by incorporating the hydrophilic molecule ferrous sulphate (FeSO<sub>4</sub>) in a lipid matrix composed of stearic acid. There are some modifications of solid lipid nanoparticles like NLC (Nanoparticle lipid conjugate) and LDC (Lipid drug conjugate) which are basically produced to overcome the disadvantages of conventional solid lipid nanoparticles as well as for efficient drug delivery. There are many methods both for the production of NLC and LDC like high-pressure homogenization. Special point about the production of these modified nanoparticles is their production without using any organic solvent. In high pressure homogenization the scale up of these nanoparticle's production process can be done easily. Nanoparticle lipid conjugate (NLC) are prepared at industrial scale

by combining solid lipids with liquid lipids. This feature of combination of lipids method is mainly used for the prevention of drug expulsion. Three types of NLC have been introduced: multiple type NLC (In this type of nanoparticles drugs are mainly dissolved in oils) imperfect type NLC (this type of nanoparticles allow free spaces for guest molecules for their settlement), and amorphous type NLC (Main focus is on the prevention of drug expulsion from the nanoparticle) (Uner, M. *et.al.*,2007) Lipid drug conjugate (LDC) are nanoparticles production make this technique more favorable as it increases the extent of release of drug ,only specific and particular diseased tissue is targeted without effecting others as well as it is cost effective technique than other which are mentioned above.

SLN has many advantages as a drug carrier:

- ☐ Drug release can be controlled
- ☐ They are biocompatible and non toxic to human body
- ☐ SLN formulations protect the sensitive drug from chemical and oxidative degradation.

## 2.8 Polymeric nanoparticles

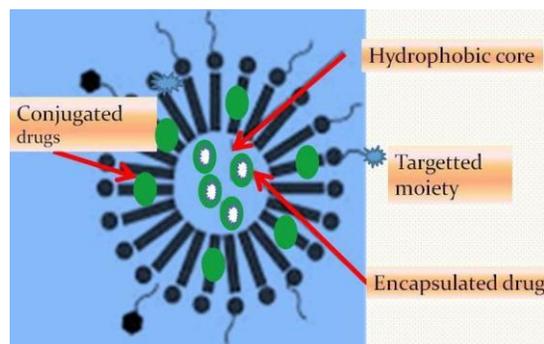
(PNPs) are particulate or solid particles structures of diameter ranges from the size 10 to 100nm. The PNP can be classified into Biodegradable and Non- Biodegradable. As they are less toxic and have better encapsulation and control release property make it most promising in the drug delivery system. For example, PLGA (poly-D, L-lactin-co-glycolide) used in the development of nanomedicine, it produces biodegradable monomer of metabolite includes lactic and glycolic acid which has very less toxicity in the body. So it can be used for the drug delivery in the body.(Avnesh K.*et.al.*,2010) The non- biodegradable PNPs are used for the control drug delivery and can also be used in diagnosis imaging, for example polymethylmethacrylate (PMP) used for drug delivery and particles derived from polystyrene taken as diagnostic agent (A.P.Ayre *et.al.*, 2014).The PNP can be obtained from synthetic such as polyacrylamide (Bai, J. *et.al.*,2007) caprolactone (Bilensoy, E. *et.al.*, 2009) and polyacrylate (Turos, E. *et.al.*, 2007) and natural sources natural polymers, such as DNA (Mao, H.Q.*et.al.*,2001) albumin (Martinem, A.*et.al.*, 2011) chitosan (Mao, H.Q.*et.al.*,2001 and Rejinold,N.S..*et.al.*,2011), gelatin (Saraog, G.K.*et.al.*,2010).In order to reduce immunological interaction ,which includes

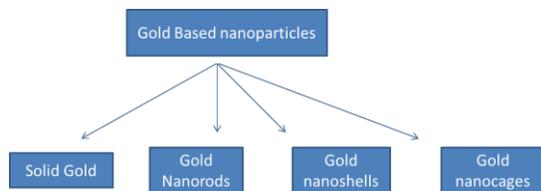
opsonization or presentation PNPs to CD8 T-lymphocytes, the non –biodegradable PNPs are coated with nonionic surfactants. After polymerization reaction the drug can be immobilized on the surface of the PNPs (Luo, G *et.al.*, 2010) or polymerized to encapsulate on PNPs structure (Mora-Huertas CE.*et.al.*,2010). Drug can be released to the target sit by diffusion, desorption or nanoparticle erosion (Torchilin V.2008) Table-1 represents drug delivery system of drug- polymeric nanocarrier conjugates.

In the development of biodegradable system for the nanomedicine has great advancement in term of drug delivery. Biodegradable polymers are used as nanocarriers hydrolyzed in the body to produce monomeric unit which least toxicity and can be eliminated from the body. A study done by Kumari *et.al.*, in 2010 showed least systemic toxicity by using PLGA for drug delivery. The material showing least toxicity shows promising property of using nanoparticles with cells and tissues [116]. In blood the biodegradable polymers conjugated with drugs are stable in blood, non-thrombogenic and nontoxic.

## 2.9 Polymeric micelles:

Are formed when amphiphilic surfactant associate in aqueous medium to form vesicles .Polymeric micelles are formed from amphiphilic block co-polymers and are more stable than surfactant micelles. They are efficient for drug delivery in tumor cells and reduced side effects, but have low drug loading ability .For this, lipid moieties can also be used to impart stability. PMs are self-assembled core-shell nanostructures formed in an aqueous solution consisting of amphiphilic block copolymers (G. Riess 2003 and M.-C. Jones *et.al.*, 1999), Formation of micelles in aqueous solution occurs when the concentration of the block copolymer increases above a certain





concentration named the critical aggregation concentration (CAC) or critical micelle concentration (CMC). At the CAC or CMC, hydrophobic segments of block copolymers start to associate to minimize the contact with water molecules, leading to the formation of a vesicular or core-shell micellar structure. As discussed in Figure-4

### 2.10 Nanocapsules:

Nanocapsules are spherical hollow structures in which drug is confined in the cavity and is surrounded by a polymer membrane (Tirak F.*et.al.*, 2001). NanoCapsules are known to improve the oral bioavailability of protein. Due to their high solubility and low permeability power, drugs are not easily and efficiently loaded onto target site., to improve this physiological changes are made

### 2.11 Ceramic nano particle:

Are the particles fabricated from inorganic compounds with porous characteristics like silica, alumina etc. (Orive G *et.al.*, 2005 and Medina C *et.al.*,2007 and Rawari M *et.al.*, 2006). Size of them is 100nm. These nanoparticles are also used in wide range of therapeutics. These nanoparticles give protection of pH and temperature to drug. But they are not biodegradable so can cause harmful effects. Nanoparticles are formed form wide variety of materials as discussed in table-1.

### 2.12 Gold Nanoparticles: -

Chemical and physical properties of gold make it suitable for novel biomedical applications. The major goal to produce gold Nanoparticles is to produce them with high stability, bio compatible and environment friendly. Gold particles have high affinity for alkynes than transition metals. Due to the unique optical and electronic properties of gold nanoparticles they have been widely used in the color indicating probes in the development of analytical techniques which are used for the sensing of various analytes (Murawala P *et.al.*,2014),

#### Solid Gold:-

**Table-1 Variety of Materials used for preparation of nanoparticles.**

Drug delivery technology	Materials	Nanostructure forms
Biologic	Lipid	Nanoparticles
	Nucleic acid Peptide	Vesicles
	Polysaccharide	
Polymeric	Poly(caprolactone)	Vesicles
	Poly(glycolic acid)	Spheres
	Poly(lactic acid)	
Silicon based	Silicon dioxide	Porous nanoparticles
Carbon based	Carbon	Nanotubes
Metallic	Gold	Nanoshells
	Silver	
	Platinum	

M.Faraday begins the syntheses of solid gold particles. He showed that gold chloride can be reduced heat or by heat or by reaction with phosphorous and tartaric acid. Zsigmondy prepares the colloidal gold by using formaldehyde as reduce. Many scientists initiated the work with solid gold nanoparticles. Recently Turkevick method was revised to control particle size, size distribution, shape and stability.

#### Gold nanoparicles:-

The absorption profile of gold includes two absorption bands. These are useful material for sensing, photo thermal therapy and imaging application. They can be produced with the help of three methods.

1. Template method.
2. Electro Chemical
3. Seeded grown method
  1. **Template:** - Includes the deposition of gold within the pores of nanoparticles alumina template
  2. **Electrochemical:-**Produced in electrochemical cathode is platinum plate, Both electrodes are immerse in on electrolyte solution containing. CTAB. The anions are migrated to cathode and reduction occurs.
  3. **Seeded growth:-** This method is based on non disperse colloids.

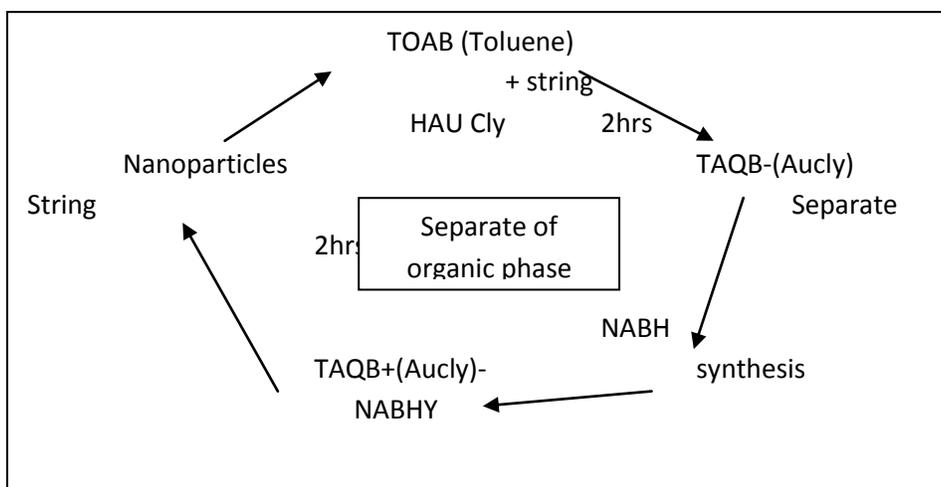
Gold nanoshells are spherical gold nanostructures and are composed of a dielectric core and coated by thin Gold shell. Its novel chemical and physical properties make them faultier candidate for applications in drug delivery.

**Gold NanoCages :-**

It possess hollow interiors and porous walls. The pore size is determined by molar ratio of chloroauric acid to silver. Silver nanostructures can also be produced like Gold particle. Gold nanocages are very useful in cancer diagnoses.

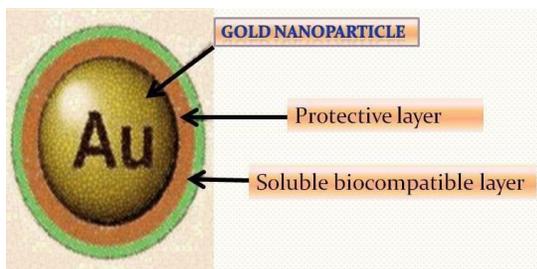
**Method of Preparation:**

Mechanism of gold Particles as drug delivery tool is described in Figure 5



**Advantages of Gold Nanoparticles:**

- Gold nanoparticles has high surface area which provides dense drug loading
- Unique optical chemical and physical properties making it suitable for drug delivery tool
- Biocompatible
- Small size so that they can reach targeted site easily.
- Non cytotoxic for normal cells.



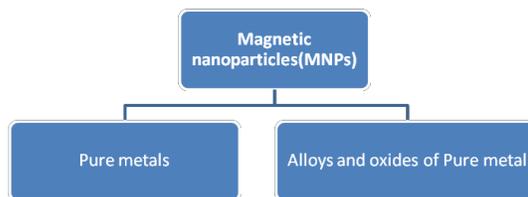
**2.13 Magnetic nanoparticles:**

The property of magnetic nanoparticles shows potential for the drug delivery. With the help of external magnetic field they can be used to deliver drug at particular site. Also they can be visualized by taking advantage of magnetic property of the nanoparticles. Magnetic nanoparticles are constructed having core of magnetite coated by polymers and polysaccharides. Magnetic nanoparticles(MNPs) can be divided as follows on the basis of their magnetic properties pure metals e.g. nickel (Kale S.N.*et.al.*,2012) cobalt (Meng X *et. al.*,2011) manganese(Sayed FN *.et.al.*,2011) and alloys and oxides of pure metals.

Theses MNPs may be negative effect in the

body also which restrict the use of MNPs in the human body. Which result in narrowing the application of MNPs in the medicine?

Only the MNPs of Iron oxide are approved by Food and Drug Administration for the clinical use. The iron oxide MNPs shows properties of chemical stability in physiological conditions (Asmatulu R.*et.al.*,2005) chemical modification of coating the iron oxide core with different shells for example, silane (Chang J.H.*et.al.*,2008) polymeric (Chomoucka J.*et.al.*,2010) or dendrimeric (Pan B.F.*et.al.*,2005), golden (Tamer U.*et.al.*,2010)

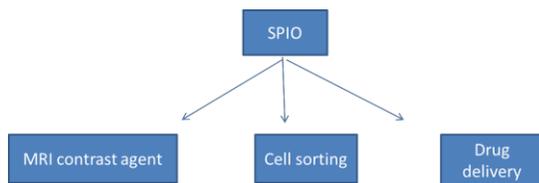


The super magnetic iron oxide particles are used

in MRI for improving imaging sensitivity and use particle toxicity. These oxides are used probes in MRI to study the outcome of transplanted cells. Electrostatic interactions, covalent binding (Figuerola A.*et.al.*, 2010) encapsulation process (Wu W.*et.al.*,2010) adsorption (Yallapu M.M.*et.al.*,2011) can be done to connect the drug with MNPs. Depending on the dimension and surface chemistry of MNPs conjugated drug can be targeted to diseases tissue can be carried out either passive or active mechanism,

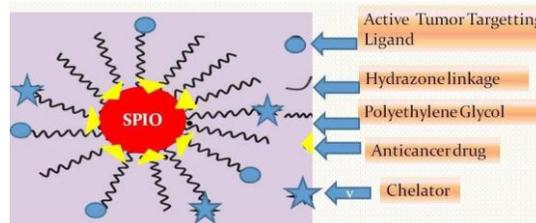
Passive targeting involves the uptake of MNPs by the cells which can be done by increasing permeability of MNPs through the cell membrane. The active strategy lies on the fundamental of attraction between the ligands attached on the surface of MNPs and the receptor of cell and by using external magnetic field (Figuerola A.*et.al.*,2010) Therapeutic activity of diverse drugs incorporated into iron oxide nanocarriers have been tested and reported (Tab. 3). MNPs are used in diagnosis as biosensors and also as drug carrier. Cancer therapy can be make effective by simultaneous use of magnetic resonance or magneto fluorescent imaging along with targeted therapy (Chomoucka J.*et.al.*, 2010)

MNPS are also used in treatment of in-stent thrombosis in which the tissue plasminogen activator (blood clotting dissolving protein) covalently linked to silanized (Kempe H.*et.al.*, 2010) and chitosan-modified (Chen J.P.*et.al.*,2010) nanoparticles. This strategy gets better clinical aspects of thrombolytic therapy. The nanoparticles can be engulfed by the macrophages which after inhalation can be accumulate in the brain and shows the potential to cross blood brain barrier. This property of distribution is majorly depends upon the surface chemistry of the MNP. The surface area bounded by the ligand which allow them to get opsonized and can be reached to the target site by movement reticuloendothelial system (Shubayev V.I.*et.al.*,2009) These MNPs can be traced by the external magnetic field and to move to the target site. In liver and spleen the overall uptake of nanoparticle are mostly observed (Wang J.*et.al.*,



2010).These all developments in the field of magnetic nanoparticles proves that they are efficient and suitable tool for drug delivery.

Mechanism of SPIO as drug delivery tool is described in Figure-6



### 2.14 Quantum Dot:

They are luminescent crystals having unique optical properties with size range of 2-10 nm and composed of 10-15 atoms. They are offering a wide range of advantages over commercial ones due to their photo stability and long term cell labeling. They are 10-20 times brighter than fluorescent proteins.(Gao.*et.al.*,2004) They have potential for better treatment over various diseases. Their high surface to volume ratio makes them a smart platform for nanomedicine. Quantum dots are semiconductor nanocrystals, and their size-tunable fluorescence spans all the way from the ultraviolet (UV) to the near infrared (NIR) regions of the electromagnetic spectrum. Generally, QDs with a large diameter will fluoresce in red within the visible light spectrum, while QDs with a smaller diameter will fluoresce in blue.

A Summated summary of all types of nanoparticles is as shown in table-2

### 2.15 Silica nanoparticles:

Silica nanoparticles are used in targeted drug delivery. They can be classified into three types namely xerogels (Czarnobaj K.*et.al.*,2008).Mesoporous silica nanoparticles (MSN) and Santa Barbara University mesoporous silica material (SBA-15) (Wei L,*et.al.*, 2010)..This technique has many benefits like easy drug loading, biologically compatible, targeted delivery (Amato G.at.al., 2010).These nanoparticles are more favorable for biological applications, among all inorganic nanoparticles (Slowing I. et.al., 2007)). Amongst all types of silica nanoparticles , xerogels are more favorable because of their larger surface area and high porosity inside. The porosity

mainly depends on parameters of synthesis (Echeverría J.C.*et.al.*,2009).There are many different techniques for the synthesis of xerogels but Sol-gel is often used. We can even alter the properties of xerogels by changing the reaction conditions like concentration, pressure, temperature etc. [Czarnobaj K.*et.al.*,2008 and Quintanar-Guerrero D.*et.al.*,2009). Sol-gel technique is used to load the drugs with the help of these xerogel nanoparticles. These are nanoparticles mainly used for the drugs like cisplatin Czarnobaj K.*et.al.*, 2007) doxorubicin (Prokopowicz M.2010), Phenytoin(Fidalgo A.2009)and heparin (Aholá MS.*et.al.*,2001)etc. In comparison with SBA having well-arranged hexagonal system of pores, the Mesoporous silica nanoparticles have hexagonal arrangement of mesopores (Wei L,*et.al.*, 2010).In comparison with xerogels the Mesoporous silica nanotechnology have more homogenous ,larger

surface area for diagnostic agents adsorption (Di Pasqua AJ.*et.al.*, 2009). Drugs can be loaded onto mesoporous silica nanoparticles by two different methods namely physical and chemical methods (Di Pasqua AJ.*et.al.*, 2009).The wide variety of drugs can be loaded with the help of mesoporous silica material like heart disease drugs (Popovici RF.*et.al.*,2011), antibiotics (as well as anticancer drugs((Di Pasqua AJ.*et.al.*, 2009 and He Q.*et.al.*,2011). As we know a controlled drug release is provided with these mesoporous silica nanoparticles which can be controlled by diffusion method (Li Z.*et.al.*, 2010).These all characteristics of mesoporous silica nanoparticles makes them suitable for their application in biomedical and pharmaceutical field. We can easily incorporate different sized molecules like small (Di Pasqua AJ.*et.al.*, 2009) and large (Kim TW.*et.al.*, 2011) with the help of mesoporous silica nanoparticles. They

**Table 2-Summary of Nanosystems with their characteristics and functions.**

**Types of NPs**

	<b>Characteristics</b>	<b>Functions</b>
1. Liposomes	Composed of liquid bilayer with hollow core.	Many used for drug delivery in case of tumors.
2. Polymeric	Polymers like PCL, PLGA are used which can be taken up by immune cells.	Efficient in drug delivery due to their hydrophobicity.
3. Nanotubes	Water Insoluble	Used for targeting special cancer cells with low dosage.
4. Nanocrystals	Establish Nanosuspension which are highly stable.	Mainly used for HIV based drug delivery.
5. Dendrimers	Composed of core & layers of branched repeated units & functional end groups on outer. Layer multivalency.	It works both for hydrophobic & phyllic drugs. Used as coating agent drugs for their protection.
6. SLN	Composed of solid layers like tripalmitate.	Efficient drug delivery routes like pulmonary rectal, oral & ocular of administrator.
7. Polymeric micelles	Composed of amphiphilic surfactants.	Effective drug delivery in tumor cells with reduced side effects.
8. Nanocapsuls	Spherical structures with a dielectric core.	Cancer treatment. Biomedical imaging.
9. Ceramic nanoparticles	Fabricated from inorganic cps with porous character alumina etc.	Non biodegradable . So harmful. Poor drug loads.
10. Gold Particle	Composed of both hydrophobic & hydrophilic ----- into vesicles covered with Gold layer.	Bio compatible. Stable & eco-friendly.

can be used in combination therapy as well (He Q.*et.al.*, 2011). With all these benefits of using MSN, there are some limitations which are associated with toxicity especially in the in vitro studies. Due to all these advantages silica nanoparticles are of great interest in drug delivery tool for some diseases.

### 3 Applications

- **Nanotech and cancer:** - Many nanoscientists used ethylene glycol mol. 1.0 deliver therapeutic drug to cancer cello-ethylene glycol stop WBCs from recognizing NPs as foreign maternal and allow them to circulate in blood stream and attach to cancer cells. Researchers at IBM demonstrated drug delivery by Hydrogels. So research is going on to enhance the ability of drug carrying nanoparticles to enter tumors.
- **Anti-inflammatory:-** Indomethacin is used as an agent. Nanoparticles have great role as on anti-inflammatory agent.
- **Regenerative Medicine:** - Its main aim is to strengthen the self-healing process of human body. Three main approaches of Regenerative Medicine includes
  1. Cell band
  2. Biomaterials based
  3. Combined tissue engineering strategies. Stem cells have ability of self-renewal.
- Bioactive materials are used for hard tissue regeneration
- **Bone regeneration:** - bone tissue is made from collagenous fibers and calcium phosphate in the form of hydroxyl apatite with embedded osteoclasts. So, nanoscaffolds are provided for bone tissue generations. Nano scaffolds promote biomineralitala
- Carbon nanotubes which are discussed earlier are also used for selective differentiation into osteoblast like cells
- **Nanotech in heart disease:** - protein nanoparticles are applied to damaged portion of artery .Super Iron Oxide (SPIO) particles are also used for this propose
- It treats the defective heart valve.
- Detect and treat arterial plague if heart valves have wrong level of collagen, it will make valve floppy and stiff. so gold nanoparticles with

collagen changes the properties of valves and repair the defective heart valve without surgery ( University of South Caroline)

- **Nanotech -in Ageing:-** Nanoparticles are also of great choice as an anti-ageing agent. Drug molecules are attached with nanodiamond embedded in contact lenses and are in contact with tears, Provide more consistent dosing than eye drops
- Nanotubes:-Capsules are used for releasing insulin when glucose level rise in order to control blood sugar level
- Nanoparticles also have role in tacking autoimmune diseases by delivery autism for particular disease in blood stream.

#### 3.1 Importance of nanoparticles as a nano medicine:

Instead of free durg particles When drugs molecules are attached with nanoparticles through encapsulation, adsorption or I conjugation, the characteristics as well as mechanism of action of the drugs against the particular disease can be enhanced. Many advantages of nanoparticle-based drug delivery have been observed by different scientists which includes improved solubility of poorly soluble drug, reduced side effects, cost effective technique, prolonged half-life in body circulation system, releasing drugs in proper sustainable manner at proper site of action.(Zhang *et. al.*, 2008; Davis *et al.*, 2008). Nanostructures band nanoparticles have different, unique and specific physical as well as chemical properties like their small size which enable them to use in a small amounts, larger surface area to mass ratio, simple structure and high efficiency. These nanostructures and nanoparticles are not encountered in the way of larger-sized particles easily (Rao *et. al.*, 2010).All these advantages or benefits of nanoparticles make them best suitable for Nanomedicine. The Nanomedicine has become a field which is well studied for large & controlled production of drugs for various diseases. And now a day's scope of nanoparticles is also emerging in other fields as well, bringing a new hope for better treatment of diseases like cancer, which were even unthinkable in past decades.

#### Overview of Application

1. Biodetection of Pathogen

2. Probing of DNA stream
3. Tissue engineering
4. Detection of protein
5. Tumor destrachas via heart
6. MRI Contrast enhancement gold nanoparticles prepared by Brost

An Overview of applications of nanoparticles in other areas is discussed in table-3

**Table-3 Overview of nanoparticles & their applications in life science. Particle class**

Particle class	Materials	Application
Natural materials or derivatives	Chitosan Dextrane Gelatine Alginates Liposomes Starch	Drug/Gene delivery
Dendrimers	Branched polymers	Drug delivery
Fullerenes	Carbon based carriers	Photo dynamics Drug delivery
Polymer carriers	Poly(lactic acid) Poly(cyano)acrylates Polyethyleinimine Block copolymers Polycaprolactone	Drug/gene delivery
Ferrofluids	SPIONS USPIONS	Imaging (MRI)
Quantum dots	Cd/Zn-selenides	Imaging In vitro
Various	Silica-nanoparticles Mixtures of above	Gene delivery

### 3.2 Cancer a special issue as a challenge for nanotechnology

Cancer as we know is the proliferation of unlimited cells inside our body. Till now many therapies and treatments are discovered in VXVC order to get rid of this disease which is now a days comes under the title of most threaten disease of the world. Many scientists are working in collaboration in order to get some positive results or remedy for the cancer. Synergistic approach is also quite successful for the treatment of certain kind of drugs which means combining the different therapies for its treatment. It is helpful as more efficient tool as its main focus is on reducing the toxic effects of drugs. Nanotechnology also acting as a promising strategy for efficient and successful delivery of anticancer drugs (Priyambada P.*et.al.*,

2012)

Due to the problems like drug resistance, availability of drugs, toxic and side effects of drugs ,the conventional methods did not proved so efficient for cancer treatment, many developments in scientific approaches have increased the basic information or biology of cancer treatment (Ma W.W.*et.al.*, 2009)

But as far as nanomedicine is concerned, it is showing a great progress in the field of cancer treatment. Nanomedicine has used many different nanoparticles for its treatment ranging from Gold nanoparticles to polymeric nanoparticles (Rani D.*et.al.*, 2012)

The main points which has to be included in chemotherapy is reducing the toxic and adverse effects, making our technology more economical, producing potent drugs ,increased physical stability, proper controlled drug release (Scheinber D.A.*et.al.*, 2010). Nanoparticles which are prepared specially for chemotherapy are

1. **Nanoshells-** It is basically concerned with the targeting of only tumor cells, healthy cells will remain intact (Neal.D.P.*et.al.*, 2004).
2. **Carbon nanotubes:** As described in nanoshells, in similar way carbon nanotubes are also working for the same that is mainly helping in carrying DNA into the cells. They are of great interest now days for using them in cancer treatment.
3. **Liposomes:** These particles are tremendously studied in chemotherapy. The first liposomal drug used as anticancer drug was doxorubicin which is mainly concerned with the ovarian cancer (Park J.W.*et.al.*, 2004). Many other liposomal drugs are also commercialized specially for tumor treatment
4. **Polymeric nanoparticles:** The main advantage of using polymeric nanoparticles as a chemotherapy agent is their reduced side effects as well as low toxicity. (Branon L.P.2004). Nanomedicine even has achieved the target of producing artificial white and red blood cells ( Somawanshi *et.al.*, 2013).
5. **Dendrimers:** Dendrimers for cancer therapy are very efficient as they help in over expression of folate receptors and targeting specific cancer cells (Majoros IJ.*et.al.*, 2006)).

6. **Quantum Dots:** Quantum dots are the trackers of activities of cells but they show more toxic effects on other organs. But they have controlled drug targeting at tumor cells ,this makes them suitable for cancer treatment.
7. **Supermagnetic nanoparticles:** They are mainly used in therapy of prostate cancer as well as MRI in clinical studies.

### Two Generations of Nanomedicine

**First Generation:** Many medicines till now approved by US Food and Drug Administration (FDA). Examples of trade names are Ontak, Doxil, Zevalin, Myoset, Abraxane etc. These all medicines are considered under first generation nanomedicine. The disadvantages or limitations of production of these drugs, loading as well attaching them to nanoparticles or we can say a modified form of these drugs are suppressed by second generation discussed below.

**Second Generation:** Second Generation was mainly concerned with the overcoming of limitations of first generation that is reduced toxicity, specific targeting as well as over expression of folate receptor (Visaria R K.*et.al.*, 2006). Many other findings of investigators also show the more applicability of second generation nanomedicine over first generation in chemotherapy.

scientists are working on anticancer drugs & loading them onto the diseased tumor cells with the help of nanoparticles. Recent developments in the field of nanotechnology have opened the discovery of wide variety of drugs chemotherapy. But only few of them are commercialized and marketed, as their production at large scale faces many problems which are already mentioned in the main course of this topic. So, Nanotechnology has yet more to be achieved in treatment of cancer, as well as in other diseases.

### 4 FUTURE PROSPECTIVE

Nanotech is an emerging field with potential to revolution drug delivery. Nanotechnology in the field of medicine is set to bring advances in the fight against many diseases. The manufacturing complexity of nanodrug delivery may be an obstacle for drug companies. Experts from different fields need to work together to translate a novel lab. Innovation into commercial viable products. The ultimate goal of nanodrug delivery system is to develop clinically useful formulation for treating wide range of diseases.

The availability of nanoparticles as a drug delivery tool in market is as mentioned below in Table-4

#### The future of Nanotech drug delivery

- Smart Insulin delivery

**Table-4 . Availability of Nano drug systems in market**

Type of nanostructures	Active ingredient	Company	Indication
Polymeric nanoparticles	Adenosine deaminase	Enzon Pharmaceuticals USA	Adenosine deaminase activity
Liposomes	Amphotercin B	Enzon Pharmaceuticals USA	Neutopenia
Polymeric micelles	Paciltaxel	Symyang pharmaceutical Korea	Cancer chemotherapy
Nanocrystal drugs	Sirolimus	Elan Corporation USA	immunosuppresseant
Lipid colloidal dispersion	Amphotericin B	InterMune USA	Fungal Infections

In this way we can conclude that Nanotechnology has given a range of nanoparticles to be used as a vector for anticancer drugs. Many

- Accurious from BIND Therapeutics
- HIV drug AZTTP into brain
- Cornell doto deliver cancer drugs

- Harnessing RNAi as a gene silencer
- Cloaked nanoparticles system

## CONCLUSION

So from above stated findings and advancements in the field of nanotechnology for drug delivery, it can be proved that nanoparticles are the best suitable carriers or vectors for drug delivery system in our body. As well as they provide the many advantages over the properties of conventional drug delivery methods. These nanocarriers are not only used as vectors for carrying the particular drug at specific site in the body, they also act as a coating over the drug in order to prevent their degradation that might be caused by the conditions inside the body. The nanoparticles have propounded the proper, sustainable and controlled release of drug inside the body. In comparison with the traditional and conventional methods they are more effective, less toxic as well as are cost effective. These are less toxic in the sense that adverse side effects can be minimized by targeting the drug only at particular site of diseased tissue. These nanoparticles can be operated at molecular and cellular level. As the name suggests nanoparticles, they are having a size of nanometer; due to this feature they can easily cross the blood-brain-barrier (BBB). All these properties of nanoparticles make them effective at even their low doses.

With all these positive characteristics of nanoparticles there are some limitations also which are now a days are the biggest challenge in front of nanomedicine that are their larger surface area and their small size due to which aggregates of these particles are formed which are very difficult to handle during the delivery of drug. Second limitation is the commercialization of these nanocarriers coated drugs, as we know many scientists are working on the production of new and effective nanoparticles for drug delivery but still there are only few nanoparticles which are commercially available in the market. The examples of which are mentioned the main course of this topic. Nanocarrier-drug conjugates can be sometimes easily phagocytosed by cells which can have toxic effects in non-diseased tissues or cells. The many other limitations of nanoparticles are also there like their poor drug loading ability as well as efficiency. The verification and validation of Quality of nanoinstruments and devices is also limited.

So all these limitations are an emerging challenges in front of scientists of this field, they have to work more on toxic effects as well as drug loading problems and its targeted release increasing its biocompatibility and making it more user as well as manufacture friendly. One major issue is their impact on natural environment is yet to be discussed properly in order to meet the specifications of regulatory bodies in the production of drugs coated with nanocarriers. Actually the cells which are to be treated with the help of this technology also have an effect on some properties of nanoparticles which acts as a limitation for nanoparticles. Nanoparticles of particular size sometime remain intact with the cells and can cause inflammatory responses inside the body which comes under the adverse side effect of drug coated with nanoparticles. Magnetic nanoparticles are trying to overcome all above mentioned problems as their property of being attracted by magnetic fields. Specifically inorganic magnetic nanoparticles which contain gadolinium as well as iron are proved to be more potent and enhanced agents as a drug delivery system. The inorganic magnetic nanoparticles are specifically proved as the contrast agent for MRI technique and it is approved by Food and Drug Administration (FDA) as discussed by Agnieszka Z and Wilczewska *et.al.*, in 2012. So a lot is yet to be achieved in the field of nanomedicine in order to overcome all of its limitations as well as improving the targeted and diagnosis therapy for its use in future for various diseases and specially for treatment of cancer and for those diseases which are untreated till now.

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