

Nanoparticles-Based Novel Drug Delivery System: A Review

Margi H. Patel¹, Dr. (Mrs.) Farida P. Minocheherhomji²

¹Research Scholar, ²Associate Professor
Microbiology Department, B. P. Baria Science Institute, Navsari-396445, India.

ABSTRACT: For the past few years, there has been a considerable research on the basis of Novel drug delivery system, using particulate vesicle systems as drug carriers for small and large molecules. Nanoparticles, Liposomes, Microspheres, Niosomes, Pronisomes, Ethosomes, Proliposomes have been used as drug carrier in vesicle drug delivery system. Various polymers have been used in the formation of Nanoparticles. Nanoparticles have been improving the therapeutic effect of drugs and minimizing the side effects. Basically, nanoparticles have been prepared by using various physical, chemical, mechanical and biological techniques. Nano-medicines have been particularly used for cell repair, antimicrobial techniques, anticancer therapy, gene delivery system, vector cell repair, nano-robot for chromosome repair therapy etc. Sometimes, nanoparticles are likely to be unsafe for the biological system. Nanoparticles have been evaluated by using parameters of drug entrapment efficiency, particle shape, drug release study.

KEYWORDS: Nanoparticles, Drug delivery system, Nano-medicines, Nano-robot.

INTRODUCTION:

'Nano' word has its origin from Latin language, which means dwarf. The term 'Nanotechnology' was defined by Tokyo Science University Professor Norio Taniguchi in a 1974 paper as follows: 'Nanotechnology mainly consists of the processing, separation, consolidation, and deformation of materials by one atom or by one molecule' [1]. This is a term that has entered into the general and scientific vocabulary only recently but has been used at least as early as 1974 by Taniguchi. The beginning of this twenty first century has been a witness to a tremendous rush of scientific activity in the field of 'Nanoscience' and 'Nanotechnology', whose seeds were sowed in the last century. Scientists, technocrats and even governments of many countries all over the world are convinced that nanotechnology based on Nanoscience is the technology of twenty first century. In recent years nanotechnology has become one of the most important and exciting forefront fields in Physics, Chemistry, Engineering and Biology. It shows great promise for providing us with many breakthroughs that will change the direction of technological advances in a wide range of applications in near future. Nanotechnology is the technology of materials dealing with very small dimension of materials usually in the range of 1 to 100 nm. At this length scale, Nano materials have very large surface to volume ratio. When at least one of the dimensions of any type of material is reduced below ~ 100 nm, it's mechanical, thermal, optical, magnetic and other properties change at some size characteristic of that material. As a result, nano materials are found to possess unique or enhanced properties compared with their bulk material and more and more devices continue to be fabricated to utilize these properties. Nano science and nanotechnology is a highly multidisciplinary field of applied science and technology covering a broad range of topics. The potential benefits of nanotechnology are so compelling that over 30 countries are now initiating national research and development initiatives.

Preparation of Nanoparticles:

Nano crystalline materials can be synthesized either by consolidating atoms / molecules / clusters, or breaking down the bulk material into smaller and smaller dimensions. The former is known as the 'Bottom up' approach whereas the later is referred to as the 'Top down' method. Many techniques including both Top-down and Bottom-up approaches have been developed and applied for the synthesis of the nanoparticles.

In the Top-down approach a block of a bulk material is whittled or sculptured to get the nanosized particle (**Figure 1**). The Top-down approaches include milling or attrition, lithography etc. The main disadvantage of the Top-down approach is the imperfection of the surface structure. Nanoparticles produced by the attrition have a relatively broad size distribution and various particle shape or geometry. In addition they may contain significant amount of impurities.

In the Bottom-up approach, the individual atoms and molecules are placed or self-assembled precisely where they are needed. Here the molecule or atomic building blocks fit together to produce nanoparticles. Bottom-up approaches are more favorable and popular in the synthesis of nanoparticles and many preparation techniques of Bottom-up approach have been developed.

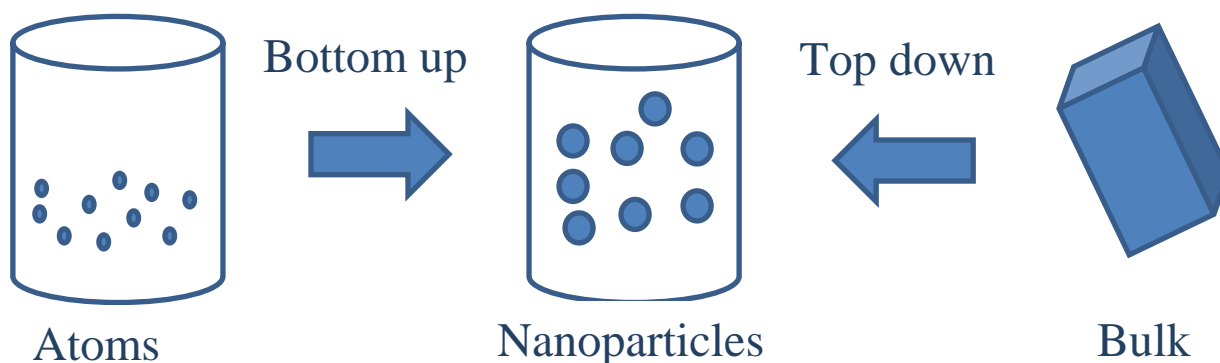


Figure-1 Schematic representation of Bottom-up and Top-down technique

Nano-structured materials have been synthesized by different methods such as physical, chemical and biological routes.

Physical methods:

Inert gas condensation and laser ablation are the most important physical approaches. The absence of solvent contamination in the prepared thin films and the uniformity of NPs distribution are the advantages of physical synthesis methods in comparison with chemical processes. Moreover, a typical tube furnace requires power consumption of more than several kilowatts and a preheating time of several tens of minutes to reach a stable operating temperature.

1. **Inert gas condensation** is a bottom-up approach to synthesize nanostructured materials, which involves two basic steps. The first step is the evaporation of the material and the second step involves a rapid controlled condensation to produce the required particle size [2].
2. **Laser ablation (LA)** is a process in which a laser beam is focused on a sample surface to remove material from the irradiated zone. Laser ablation has been considered and used for many technical applications, including: the production of nano materials, deposition of thin metallic and dielectric films, fabrication of superconducting materials, routine welding and bonding of metal parts.

Chemical methods:

1. Chemical Precipitation and Co-precipitation:

A chemical precipitation process consists of three main steps: chemical reaction, nucleation and crystal growth. To obtain nanoparticles with a narrow size distribution, the necessary requirements are (i) a high degree of super saturation, (ii) a uniform spatial concentration distribution inside a reactor and (iii) a uniform growth time for all particles or crystals. The other commonly used solution method for the synthesis of multi component oxide ceramics is the co-precipitation method, which produces a 'mixed' precipitate comprising two or more insoluble species that are simultaneously removed from solution. The precursors used in this method are mostly inorganic salts (nitrate, chloride, sulphate, etc.) that are dissolved in water or any other suitable medium to form a homogeneous solution with clusters of ions. The advantages of co-precipitation reactions are:

- (i) The homogeneity of component distribution,
- (ii) Relatively low reaction temperature,
- (iii) The fine and uniform particle size with weakly agglomerated particles,
- (iv) Low cost.

2. Sol-gel Synthesis:

Sol-gel processing is also a promising method for the preparation of nano dimensional materials. It is a wet chemical technique used for the fabrication of metal oxides from a chemical solution which acts as a precursor for integrated network (gel) of discrete particles or polymers. The precursor sol can be either deposited on the substrate to form a film, cast into a suitable container with desired shape or used to synthesize powders.

3. Sonochemical Synthesis:

Currently, ultrasound irradiation has become an important tool in chemistry. Ultrasound irradiation also offers a very attractive method for the preparation of various nanosized metal particles. They vary in size, shape, structure and in their solid phase (amorphous or crystalline), but they are always of nanometre size.

4. Photochemical Synthesis:

Absorption of photo energy can change the structure of molecules and induce a variety of photochemical reactions. During recent years, a photochemical technique has emerged as an effective synthetic technique for the preparation of nanosized metal particles with various morphologies. This method has the advantages of mild reaction conditions and convenient operations and the equipments involved are simple and cheap. Generally, a low-pressure mercury pillar lamp and a high-pressure column-like indium lamp are most commonly used as the ultraviolet irradiation and visible photo irradiation source, respectively.

5. γ -Irradiation Method:

γ -Irradiation is one of the new and effective methods employed for synthesis of nano-meter materials. It has been extensively used in the preparation of nanocrystalline metals, alloys, oxides and polymer/metal nano-composites [3].

6. Microwave Synthesis:

Microwave irradiation as a heating method has found a number of applications in chemistry. Microwave assisted synthesis for the production of inorganic compounds has been studied since 1986. Microwave irradiation has been used in the synthesis of inorganic nanoparticles. Microwave assisted heating method has the advantages of short reaction time, high energy efficiency and the ability to induce the formation of particles with small size, narrow size distribution and high purity. In the past few years, microwave assisted heating has been applied in the soft chemical synthesis of various nanocrystalline metal particles and presents a promising trend in its future development.

Biological methods:

Physical and Chemical processes are costly as well as harmful to the environment. So there is a need for biosynthesis of nanoparticles using green chemistry route, which is cheaper and eco-friendly. Biosynthesis of nanoparticles is a kind of bottom-up approach where the main reaction occurring is either reduction or oxidation. Many bacteria, fungi and plants have shown the ability to synthesize metallic nanoparticles and all have their own advantages and disadvantages [4, 5, 6]. Intracellular or extracellular synthesis, growth temperature, synthesis time, ease of extraction and percentage synthesized versus percentage removed from sample ratio, all play an important role in biological nanoparticle production.

1. Synthesis of Nanoparticles by Bacteria:

Many researchers have focused mainly on prokaryotes as a precursor for synthesizing metallic nanoparticles. Due to their abundance in the environment and their ability to adapt to extreme conditions, bacteria are a good choice for study. They are also fast growing, inexpensive to cultivate and easy to manipulate. Growth conditions such as temperature, oxygenation and incubation time can be easily controlled.

2. Nanoparticle Synthesis by Fungi:

The use of fungi in producing metallic nanoparticles has gained significant interest as they offer certain advantages over the use of bacteria for the synthesis of nanoparticles. The ease of scaling up and downstream processing, the economic feasibility and the presence of mycelia offering an increased surface area, are important advantages to consider [7]. Mukherjee et al. also suggested that because fungi secrete significantly higher amounts of proteins than bacteria, this would amplify the nanoparticle synthesis productivity.

3. Nanoparticle Synthesis by Plants:

Bacteria and fungi have been studied extensively in the past few decades for their ability to synthesize metallic nanoparticles; however there has been less of a focus on plants in this matter. In the past decade, an increasing amount of research has been conducted on the green synthesis of metallic nanoparticles using plants or plant extracts. This area is yet relatively underexplored and offers promising results for the field. A very important aspect of using plants instead of bacteria or fungi for NP production is the lack of pathogenicity.

Characterization of Nanoparticles:

Characterization of nanoparticles is based on the size, surface morphology, shape and surface charge, using advanced microscopic techniques like Atomic Force Microscopy (AFM), Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). Properties such as the size distribution, average particle diameter and charge, affects the physical stability and the in vivo distribution of the nanoparticles.

Applications of Nanoparticles:

Nanomaterials possess unique mechanical, optical, magnetic, electrical and biochemical properties with their vast range of applications ranging from basic material science to personal care applications. Some recently developed applications of nanotechnology are in sectors like energy storage production and conversion, agriculture productivity enhancement, water treatment and remediation, disease diagnosis and screening, drug delivery systems, food processing and storage, air pollution and remediation, constructions, health monitoring using nanotubes and NPs, space science material production, chemical industry, information technology, textile industry, electronic consumer production, vector and pest detection and control, automobile industries.

1. Nanotechnology in Medicine:

Nanotechnology is used in field of medicine for drug delivery, Gene therapy, cancer therapy, imaging, diagnostic and monitoring techniques, bio sensors, antimicrobial techniques and cell repair [8] (Figure-2). National Institute of Health in USA, has defined nano-medicine as 'highly specific medical intervention at the molecular scale for diagnosis, prevention and treatment of disease' [9].

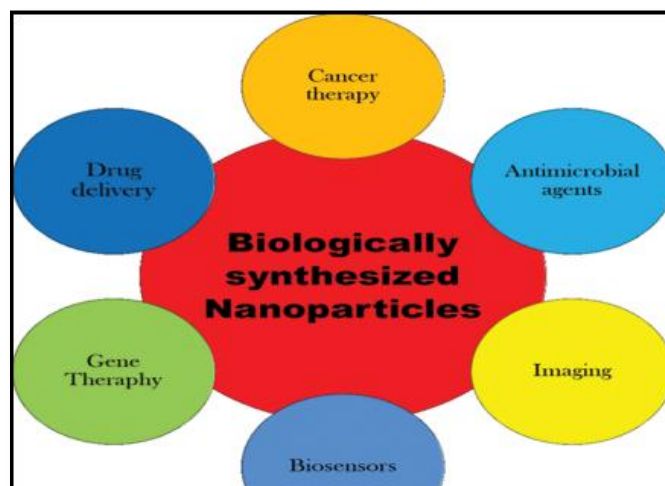


Figure 2: Application of Nanotechnology in Medicine.

Endoscopy, in next generation will extend its capability from imaging to diagnostics and therapy using nano-fiber technology. Some nano drugs used in medical application are described in **Table 1** with company codes [10]

Table 1: Nanotechnology in Medicine: Company Directory

Sr. #	Company	Product
1	Bio-Delivery Sciences	Oral drug delivery of drugs encapsulated in a nanocrystalline structure called a cochleate
2	CytImmune	Gold nanoparticles for targeted delivery of drugs to tumors
3	Invitrogen	Q-dots for medical imaging
4	Smith and Nephew	Antimicrobial wound dressings using silver Nano crystals
5	Luna Inovations	Bucky balls to block inflammation by trapping free radicals
6	NanoBio	Nano emulsions for nasal delivery to fight viruses (such as the flu and colds) or through the skin to fight bacteria
7	NanoBioMagnetics	Magnetically responsive nanoparticles for targeted drug delivery and other applications

Nanotechnology in Drug Delivery System:

More than 150 years ago, Michael Faraday prepared gold particles in nanometer scale. These colloidal gold particles were conjugated with antibodies for target specific staining known as immune-gold staining. This application of gold particle considered as a precursor of recent application of gold particles in nanotechnology. In 1960s, Liposomes and polymer micelles were first prepared, however it was never referred as nano-particles until 2000. In 1970s, NPs and dendrimers were first prepared without the knowledge of nanotechnological application. In 1980s, the period reported to be the successful development of micelles as drug delivery system. And in 1990s, Block co-polymers of polyethylene glycol (PEG), PEG-Polylysine have been invented by Kataoka [11]. Prior to nanotechnology revolution, in past liposomes, polymeric micelles, nanoparticles, dendrimers, and nano-crystals used for drug delivery, but in the era nanotechnology, the terms were unknown.

Current immature nanotechnology use microchips, carbon nanomaterials, micro needles based transdermal therapeutic systems, layer by layer assembled system and various microparticles produced by inject technology as well as previous nano-carriers were developed using co-polymers such as polyethylene glycol(PEG) and ligands [11].

Nanoparticles for Drug Delivery System:

Drug delivery system (DDS) is defined by national institute of health in USA as 'Formulation of a device that enables the introduction of therapeutic substances in to the body and improves efficiency and safety by controlling the rate, time and place of release of drug in the body.' The process of drug delivery can be mainly divided into the following three parts:

1. The administration of the drug or therapeutic product can be divided as non-invasive and invasive administration. Non-invasive administration is by oral, topical (skin), nasal, and inhalation routes. Invasive administration is injection or nano-needle array.
2. The release of the active part of the drug by the product.
3. Transport active ingredients across the biological membrane to the target site to perform action.

DDS interface, between the patient and the drug and it may be formulation of the drug or device used to the deliver the drugs to the particular site [12, 13]. The usual drug delivery systems are not up to the satisfactory level. There were many drawbacks include poor bioavailability, generation of side effects, low drug loading capacity, poor ability to control the size range, plasma fluctuation of the drug levels, low therapeutic effectiveness, low in- vivo stability, low solubility, no control over the time,

location and lack of target delivery to the site of action as well as some drugs are only active in a narrow range. If concentration is above the threshold level it becomes toxic, if it is low lack of therapeutic effect. These drawbacks put pressure on scientists to investigate more about new DDS and its control and determine the rate and location of drug release [14]. New DDS has the ability to deliver drugs to specific target cells in various areas of the body without degradation in the gastrointestinal track. It includes delivery and targeting of pharmaceutical, therapeutic and diagnostic agents by the help of NPs to the cells such as cancer cells. The ultimate goal of NP drug delivery is to improve the proper treatment diagnostics and prevention of disease [15, 16].

The NP used in DDS contains encapsulated, absorbed, dispersed or conjugated drugs and this were able to, provide lower toxic side effects, provide multi functionality targeting, delivery and reporting ability, have high saturation solubility, drug particles resistance to settling, provide improved therapeutically index, high efficiency of drug delivery, rapid dissolution, reduces plasma fluctuation level, reduces the drug dosage, The drug directly releases to site and it is in nanosize, ultimately cut down the cost of drugs [17].

Mechanism of drug delivery using nanoparticles:

The drug bullets are attached to NP and it contains ability to cure the diseases. The nanotechnology based DDS is only to provide proper delivery of drug to target sites without any changes occurring in parental therapeutic particle. The drugs requires special pH conditions, it should be poorly water soluble or required high concentration of drugs in order to become therapeutically effective [13]. Drug Polymer attachments are by encapsulation, non-covalent complexation and conjugation to polymeric carriers via liable linkers. Size of polymer-drug conjugate plays a major role and it should be controlled by adjusting the molecular weight of polymer. Drug-polymer attachment changes the drug solubility, hydrophobicity and permeability [11].

The NP's has drug loading capacity and it depends on matrix density. The drug loading capacity can increase by minimizing solubility, increase ionic interactions between drug and matrix and by maximizing the absorption of drug load. Drug and polymer covalently attach via linkers and they are pH or enzyme sensitive [18, 19]. The drug attached NP can be recognized by the immune cells and it can destroy them. To overcome this problem the particle surface is decorated with biodegradable, hydrophilic copolymers to allow particles to circulate for long period. The degradability could be controlled by sustained release of the drug. Poly-glycolic acid (PGA), poly-lactic acid (PLA) and their co-polymers are widely used for decorating the surface. PEG-copolymers are of greater interest due to their ability to condense nucleic acid into nano-sized polyplex with protective and biocompatible PEG shell. Moreover PEG can resist serum protein adsorption, prolonging the systemic circulation of particles and reducing toxicity [13]. Ligands also attached to the NP surface to get higher specificity drug delivery to the target site. Antibodies, protein, peptides, carbohydrates, lipoproteins, charged molecules and Nucleic acid ligands (DNA, si-RNA, m-RNA) are known as aptamers and have high affinity and specificity for target [20].

Oral, intravenous, arterially, dermal, transdermal and inhalation are methods used for the entry of NP into the body. The Drug-NP conjugate is injected into the circulation system and it can take up by the cells/tissues. Drug is delivered through blood by dissolving, dispersing and finally reaching the target site. Traditional DDS circulate drug in to all the cells in body while nanotechnology based DDS provide drug to target site by their ligand attraction process. The drug-NP conjugate should be able to deliver drug to target site without degradation in gastrointestinal track, without reducing drug activity and volume. Secondly it should attack to target cells without harm to other cells and reduces side effects [11, 21].

The drug delivery to the cells can be of two types:

1) **Passive targeting:-** The drugs are diffused to the extra cellular matrix and diffused into the cell. It can enhance permeability and cellular retention effect of NP. Tumor vesicles are highly disorganized and presence of pores enlarges the gap between endothelial cells. These pores of tumor site allow NP to enter easily into tumor cells than normal cells. Passive targeting is not applicable to all tumors and normal cells, because some tumor cells lack pores. Diffusion of drugs out of NP decreases with decreasing concentration of reservoir [22, 23].

2) **Active Targeting:-** Affinity ligands, antibodies, aptamers bind to the specific receptor on the cell surface. Nano-carriers bind to the target cell through ligand-receptor interaction by the expression of receptors or epitopes on cell surface. These receptors are highly expressed on tumor cells than other cells [24, 25].

The NP surface is decorated by ligands and these ligands can attach with the specific receptors in the surface of targeted cell by biorecognition. The NP's enter into the target cells by receptor mediated endocytosis. In this endocytotic vesicle is generated when segment of plasma membrane invaginate, enclosing it with NPs. Thousands of NP's easily enter the cell by this method. Inside the cell NPs are developed in to endosomes. Then endosomes merge with each other to form large endosomes or lysosomes. Finally therapeutic drugs can release in response to enzymes or acidic pH with controllable manner by degradation of polymeric NP shell [15].

Controllable drug release at particular sites can be controlled by different ways,

1) Polymers are biodegradable and if degraded in controllable manner can release drug to site

2) Pores within the polymer can be altered in the preparation method. So drug diffusion occurs more readily or slowly.

3) The distance of fusion and surface area of the NP can alter by changing size.

The size of NP also plays a major role, smaller size means larger surface area. Drug releasing and drug dissolving is faster and this can control engineering by changing size of NP. The drugs are released by diffusion, swelling, erosion or degradation. Constant drug releasing can be achieved by tuning the properties of nano-fluidic devices [23].

Uses of Nanotechnology in Various Treatments

Cancer treatment: The usual drug delivery to the tumor cells develop side effects in normal tissues such as nephrotoxicity, neurotoxicity, cardio toxicity and multiple drug resistance (MDR) which reduces drug concentration at target location. Poor accumulation of MDR is mostly due to the increase efflux pumps in cell membrane such as P-glycoprotein. Paclitaxel loaded NP can pass drugs without being disturbed by MDR [26]. To overcome these problems NP based drug delivery system is used. The tumor sites forms new blood vessels to supply nutrients and oxygen rapidly. These newly formed vesicles are defective and have leaky vasculature allowing NP to diffuse. The energy requirement increases and glycolysis occur, which results into acidic environment and is ultimately advantageous in drug release system [13, 27].

Nano X-ray nano-particle therapy: 1) In standard radiotherapy X-rays are able to hydrolysis water molecules to produce free radicals. It can ultimately damage DNA and other molecular structures in both tumor cells and healthy cells. Nano X-ray NP has self-protecting layer to minimize unwanted interactions and is suspended in water. It is injected into cancer patients and it gets attached only with tumor cells by specific recognition. Nano x-ray NP attracts X-ray more readily than water. Finally it can damage both double stranded and single stranded DNA in Tumor cells to kill only tumors without harming healthy cells.

2) The NPs are attached with highly toxic cancer drugs like Doxorubin and NP surface is decorated with PEG and target ligands to deliver drug to target site without harming healthy cells [28].

3) Photo-thermal therapy-Au NP has optical properties and that allow absorption of light near ultraviolet radiation. Due to the increase temperature of cell above 42°C the viability of cells are lost. Following the irradiation of the body, under magnetic field, the NP gets heated up and that leads to the irradiation of tumor cells. In Angiogenesis process metal particles can inhibit phosphorylation of protein involved in the process by binding to the cysteine residues in heparin binding growth factor [29].

4) Cetureimab, fluorouracils are drugs attached with liposomes, hydrogels, crystals to treat oral cancers and overcome low solubility, permeability and poor bio-availability [30].

5) Researchers try to a) Improve blood circulation period of NP by coating their surface with red cell membrane instead of PEG. b) Reduce side effects by using gold NP's for platinum cancer therapy. c) Design different NP's with different shapes, ligands and drug particles to treat tumors. d) Using photosensitive agents that accumulate in tumor and cause blood vesicles more porous to penetrate NPs more easily. e) Attach RNA to treat skin cancers (<http://www.understandingnano.com/nanotechnology-drug-delivery.html>). f) Spherical NP Coated with si.RNA to treat lung cancers [31]. g) Monoclonal antibodies and vaccines are directed against tumor [32, 33].

Heart Diseases: NP protein produced by translation and used to attach damaged regions of arteries as well as to break blood clots. NPs under magnetic field are directly used to deliver proteins to the right place in arteries.

In Diabetics: Developed NP contains Insulin attached to matrix. The enzymes are attached to NP, when blood glucose level increases enzymes stimulate insulin releasing and ultimately it can regulate blood glucose level for several days.

Ophthalmic diseases: a) Polymeric NP, nano-gels, liposomes, micelles, dendrimers, chitosan and protein NP's are investigated to treat several ophthalmic applications for back of the eye diseases like diabetic retinopathy, retinoblastoma, retinitis pigmentosa. The drug and gene deliver to the target tissue used for the treatment of posterior segment disorders like choroid and retina which improving diagnosis and retain prosthesis .b). Nano-diamonds with drug (timolol maleate) embedded in contact lenses are used to treat Glaucoma [34, 35].

In Tuberculosis (TB): Treatment of TB requires continuous and frequent drug supply to the cells. The NP attached with drugs such as rifampin (RMP), Inosiazid (INH)/Pyrazinamide (PZA) are covered with PEG to provide drugs in a sustainable manner to TB cells. Researchers try to improve bioavailability, reducing dosage frequency and drug administration methods in TB treatment [36].

Bone diseases: The calcium-phosphate based NPs are used in drug delivery to treat bone diseases without any toxicity to bone tissues. Arthritis, osteoarthritis, osteosarcoma and metabolic bone cancer can be treated using drugs such as bisphosphonates. Silica and magnetic NP found success in bone regeneration [37].

Central nerve system diseases: NP can cross blood brain barrier (BBB) so it can be used to deliver drugs to brain tumors, Alzheimer's disease, inborn metabolic errors like lysosomal storage disease, infectious diseases and aging etc. Most therapeutic particles are unable to pass through BBB, blood cerebrospinal fluid barrier, or other specialized central nervous system barriers. Only a small class of drugs or molecules with high lipid solubility and low molecular mass can pass through BBB. NP has high affinity and able to specifically transport drug through BBB. Some transport molecules like growth factors, insulin and transferrin can increase efficiency and kinetics of drug across the range of tissues [38, 39].

Importance of Nanotechnology in Drug delivery system: Nanotechnology increases oral bioavailability of drugs as a result of their special uptake mechanisms such as absorptive endocytosis. The NPs are also able to remain in the blood for long period and release the drugs in controllable manner to the target tissue. The self-controlling system of drug releasing helps to reduce the plasma fluctuation and minimize the side effects. The drug is incorporated in to the NP which is in nano scale which is easily diffused through biological membranes. Cells take up these particles for the efficient drug delivery to site of action [11]. Nanotechnology improves performance, effectiveness, safety, patient adherence as well as reduces the cost compared to

traditional DDS. The nanotechnology is successfully used in drug delivery in the treatment of cancer, asthma, and hypertension as well as diabetics. There are hundreds of various ongoing researches in this field to improve efficiency of DDS [24]. Nanotechnology is capable of producing biodegradable, biocompatible, targeting and stimulating responsive carriers such as liposomes, nanofabricated materials, metals and polymers. The nanoparticles can assume different shapes such as spherical, rods, wires, discs, hemispherical and ellipsoidal [23]. NPs are known as successful drug delivery material because it contains several properties such as, high drug carrying capacity, higher stability for the drugs inside blood stream and can travel without sedimentation. The drug conjugated NP can enter into the body using various methods such as non-invasive and invasive administration. The drug releasing from the NP matrix can be controlled. NPs can be easily penetrated into the tissues such as cancer cells. NPs can be taken up by cell naturally or via endocytosis. These properties of NP attached drug delivery methods, leads to improve duration of drug circulation, bio-availability of the drug and control drug releasing at a particular site.

Other ongoing researches: 1) NASA developed bio-capsules to protect astronauts from effect of radiation. 2) Try to deliver antigens to the body to enhance immune system. 3). Improve dental implant by adding nanotubes to surface of implant matrix. 4) Try to attach RNA to NP surface to improve time of circulation [40].

Future opportunities: In future nanotechnology based DDS can improve treatment of antitumor therapy, gene therapy, radiotherapy, delivery of proteins, antibiotics, vaccines, vesicles. Multi-functional NPs might be developed that are capable of detecting malignant cell, deliver different drugs at same time, visualize the location by imaging agents, killing cancer cells with minimum side effects and they monitor and treat at the same time [17, 22, 37, 41]. There is an ability to improve this particle to cure diseases like HIV, cancer and same nanoparticles can develop as robots for cardio vascular operations. The nanoparticles can combine with computer programming system to automatically regulate homeostasis in humans such as blood glucose level, Ca^{+2} -level. NPs can be improved as powerful protectors in body towards foreign particles in future.

DISCUSSION AND CONCLUSION

Nanotechnology as drug delivery systems is designed to improve the pharmacological and therapeutic properties of conventional drugs. Specific drugs are transported to the target site without accumulating at any place by using nanoparticles. The nanotechnology improves bioavailability of drugs, efficiency and reduces the side-effects and toxicity. Reduction of plasma fluctuation and higher solubility also play a vital role in drug delivery. Various nanoparticles are used to deliver drug such as polymeric NPs, polymeric drug conjugates, dendrimers, nano crystals and lipid based nanoparticles like liposomes, solid lipids. Inorganic NPs like metal NPs (gold, silver, iron, platinum, quantum dots) and Silica NPs (mesoporous, xerogels).

The drugs bind to the nanoparticle with the help of different conjugations like encapsulation and conjugation to polymeric carrier via liable linkers. The drug conjugate NP enters to the cell by passive diffusion or active targeting by receptor mediated endocytosis. Finally nanoparticles can release drugs in a controllable manner in response to enzyme or pH changes. NP based drug delivery is still in its infant stage to cure diseases like cancers, diabetics, heart diseases and central nerve diseases. The nanoparticle based drug delivery can be further developed to cure most challengeable diseases like AIDS in future. Nanotechnology can be developed in future to treat all type of diseases in human at the same time by producing multifunctional nano-particles.

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