A REVIEW ON PHARMACEUTICAL NANOTECHNOLOGY

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ABSTRACT

Research interest and revolution in materials science has been creating considerable interest in the area of drug delivery systems using particulate systems as carrier for small and large molecules. In many cases, it is now possible to manipulate atoms and molecules within materials one at a time and therefore, to construct materials with nanometre-scale precision. This new capability in material science is called nanotechnology. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the motion of the drug within the tissue with respect to time (i.e. pharmacokinetics) and fruitful therapeutic effects of the drug on the body (i.e. pharmacodynamics) of various types of drug molecules. The potential intersection between nanotechnology and the biological sciences is vast. Biological function depends heavily on units that have nanoscale dimensions, such as viruses, ribosomes, molecular motors and components of the extra cellular matrix. In addition, engineered devices at the nanoscale are small enough to interact directly with sub-cellular compartments and to probe intracellular events. They have been used in vivo to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled rate and sustained manner to the desired site of action. Various polymers have been used in the formulation of nanoparticles aiming to increase the therapeutic benefit through drug delivery research, while minimizing side effects. The purpose of this review work is to give the brief idea about various aspects of nanoparticles with their history, formulation, characterization, effect of their characteristics and their applications in delivery of drug molecules.

Key words: *Nanoparticles; Polymeric; Biodegradable; Drug Delivery System.*

INTRODUCTION:

The term nanotechnology was first defined by Tokyo science university Professor Norio Taniguchi in 1974. The most common definition of nanotechnology is manipulation, observation and measurement at a scale of less than 100 nanometres. The nanotech components from the base for the drug delivery system (DDS) that will hopefully carry therapeutic and diagnostic agents to specific sites in the body allowing for highly targeted treatments that could minimize side effects. Drugs that exhibit toxicity when administered systemically may prove to be an ideal therapeutics when delivered in a direct manner by nanotechnology method.[1, 2] Drug particles in the nanometre size range have unique characteristics that can lead to enhanced performance in a variety of dosage forms. Formulated

correctly, particles in which size range are resistant to settling and can have higher saturation solubility, rapid dissolution and enhanced adhesion to biological surfaces thereby providing a rapid onset of therapeutic action and improved bioavailability. [3] Nanoparticulate drug delivery system may offer plenty of advantages over conventional dosage forms which include improved efficacy, reduced toxicity, enhanced bio distribution and improved patient compliance. Nanoparticles for a wide array of applications including oral, pulmonary and parenteral delivery. Controlled and targeted delivery is one of the most enviable requirements from a carrier, which involves multi-disciplinary site specific or targeted approach. Pharmaceutical nanoparticles are subnanosize structure, which contain drug or bioactive substances within them and are constituted of several tens or hundreds of atoms or molecules with a variety of sizes (size from 5 nm to 300 nm) and morphologies (amorphous, crystalline, spherical, needles, etc). It is necessary to use additives (surfactants, dispersants, and metals) to obtain uniform and stable particles. With further processing steps, nanostructure powders and dispersions can be used to fabricate coatings, and components or devices. These different types of nanoparticles are prepared according to prerequisite and straightforwardly reach to the desired site to deliver bioactive therapeutic and diagnostic agents.[4,5] Although opportunities to develop nanotechnology based efficient drug delivery systems extends into all therapeutic classes of Pharmaceuticals, many therapeutic agents have not been successful because of their limited ability to reach to the target tissue. Nanotechnology for drug delivery applications may not suitable for all drugs. Especially those drugs that are less potent because the higher the dose of the drug that would make the drug delivery system much larger, which would be difficult to administer.[6-8] The challenge of drug delivery is liberation of drug agents at the right time in a safe and reproducible manner, usually to a specific target site. Conventional dosage forms, such as orally administered pills and subcutaneous or intravenous injection, are the predominant routes for drug administration. But pills and injections offer limited control over the rate of drug release into the body; usually they are associated with an immediate release of the drug. Consequently, to achieve therapeutic levels that extend over time, the initial concentration of the drug in the body must be high, causing peaks (often adjusted to the stay just below known levels of toxicity for the drug) that gradually diminish over time to an ineffective level. In this mode of delivery, the duration of the therapeutic effect depends on the frequency of dose administration and the half- life of the drug. This peak and valley delivery is known to cause toxicity in certain cases, most famously with chemotherapy drugs for cancer. In recent years, the pharmaceutical and biotech industries have developed more sophisticated and potent drugs.[9-11] Interest in new types of drug agents has catalyzed innovation in controlled-release drug delivery systems. A number of mechanisms can provide controlled release of drugs including transdermal patches, implants, inhalation systems, bio adhesive systems and microencapsulation and now there are pioneering, commercially available products in all of these categories. One of the major advances in recent years has been further reduction in the size of these systems: it is now possible to make polymer delivery systems that are nanometre in scale, can be easily injected or inhaled and are much smaller than and capable of being internalized by many types of human cells. While there are many ways of achieving nanoscale delivery systems, including selfassembling systems based on liposome or micelles, the most stable and versatile systems are miniaturized versions of the synthetic materials that already have been used in drug delivery applications. This is usually accomplished with degradable polymers such as poly (lactide-co-glycolide). These particles can be injected for circulation or used to release drug locally. The encapsulated drugs can be complex, if appropriate methods of fabrication are used to assemble the nanoparticles. The major goals in designing nanoparticles as a delivery systems are to control particle size, surface properties of

pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. [12, 13].

Advantages: [14-16]

1. Applicable to broad category of drugs; Small molecules, proteins and polynucleotide.

2. Ability to lyophilize.

3. Reproducible and stable.

4. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.

5. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.

6. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.

7. The system can be used for various routes of administration.

Some of the main disadvantages of nanotechnology in the pharmaceutical field are high aggregation in biological system due to high surface energy, poor solubility and poor incompatibility in case of carbon nanotubes, quickly scavenged by RES system of body resulting in low biological half life, poor target and site specificity, high immunogenicity of foreignness, undefined and unpredictable safety issue and acute and chronic toxicity.

Two groups for Drug Delivery Systems are as follows: [17-20]

First generation systems: Include Microcapsules and microspheres for control of Chemo mobilisation and control release of proteins and peptides for drug delivery within the brain.

Second Generation Systems: These systems are also true carriers based on monoclonal antibodies (MAb), which characterizes with a capability of specific recognition. To this group belong MAb and liposomes, nanoparticles nanocapsules and nanospheres (called passive colloidal carriers), and certain active carriers which release their contents after a specific signal, such as temperature sensitive liposomes and magnetic nanospheres.) Piloted by MAb or their ligands.Nano-particles here are defined as being sub-micronic (<1nm) colloidal systems generally made of polymers. Nanoparticles generally vary in size from 10 to 1000nm. Depending upon the process used for the preparation of nanoparticles, nanospheres or nano-capsules can be obtained.The drug is discovered, entrapped, encapsulated or attached to a nanoparticle matrix. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices with the prospects of their applications in controlling drug release.

TYPES OF PHARMACEUTICAL NANOSYSTEMS:

Carbon nanotubes

These are hexagonal networks of carbon atoms. Length and diameter of these tubes are 1nm and 1-100nm in length. Nanotubes are of two type's single walled nanotubes (SWNTS) and multi walled nanotubes (MWNTS). These are small macro molecules have unique size, shape and remarkable physical properties (Sinha N et al., 2005).
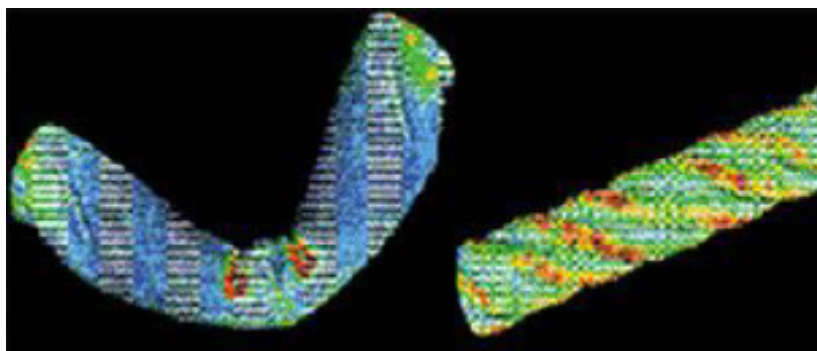

Figure.1 carbon nanotubes

Quantum Dots

These are semi conducting materials consisting of a semi conductor core coated by a shell to improve optical properties. Their properties originate from their physical size which ranges from $10\text{-}100A^0$ in radius. These have a large impact on imaging, in-vitro and in-vivo detection and analysis of biomolecules, immunoassay, and DNA hybridization and in non-viral vectors for gene therapy. It has main function in labeling of cells and therapeutic tools for cancer treatment (Bailey et al., 2004).
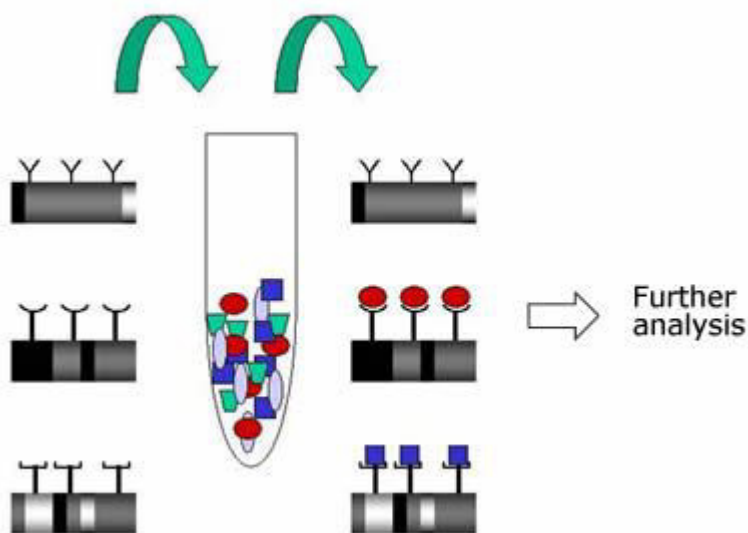

Figure.2 Quantum dots

Dendrimers

These are hyper branched, tree-like structures and have compartmentalized chemical polymer. It contains three different regions core, branches and surface. The core forms the central part and the branches radiates from it forming an internal cavity and a sphere of groups. The branches can be altered or modified according to requirements. The dendrimers can be made more biocompatible compounds with low cytotoxicity and high biopermeability according to the requirements. These can deliver bioactive s like drug, vaccines, materials and genes to desired sites.The space between the core and branches accommodates drugs or bioactive products (Kreuter and Speiser., 1976).
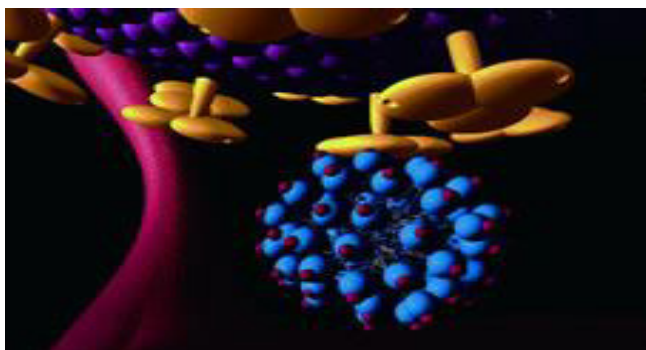

Figure.3 dendrimers

Polymeric nanoparticles

These are colloidal carrier, 10nm-1µm in size consistingof synthetic or natural polymers. These nanoparticles providealternative to above mentioned nanosystems due to inherentproperties like biocompatibility, non-immunogenicity, non-toxicityand biodegradability. Polymeric nanoparticles are classified andcomprised of nanocapsules and nanosphere. Nanocapsules aresystems in which drug is confined to a cavity surrounded by unique polymeric membrane, where as nanospheres are systems in which the drug is dispersed throughout the polymer matrix. Natural polymers used are gelatin, albumin and alginate in the preparation of nanoparticles synthetic polymers used for nanoparticles preparation of nanoparticles synthetic polymers used fornanoparticles of preparation may be in the form of preformed polymer. e.g.:- polyesters like polycarpolactone (Maincent P et al., 1992).
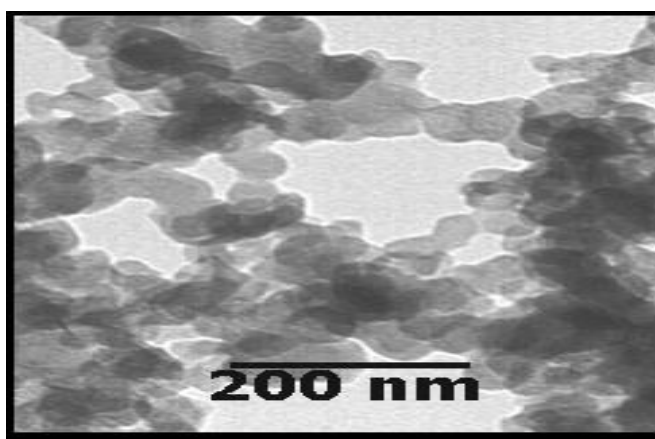

Figure.4 polymeric nano particles

Metallic nanoparticles

Metallic nanoparticles are more favor in the good delivery as carrier for drug and biosensor. Nanoparticles of various metals have been made yet silver and gold nanoparticles are of prime importance for biomedical use, a large number of ligands have been linked to nanoparticles such as sugar, peptides, proteins and DNA. These nanoparticles have surface Functionalization and are very easy to decorate ligands onto the surface. Due to this Functionalization ability, these are used for active delivery of bioactive, drug discovery, bioassays, detection, imaging and many more other applications.

Liposomes

These are the closed vesicles forms when dry phospholipids are hydrated. These are of 3 types based on size and number of bi-layers

a) Multilamellar vesicles

These consists of several lipid bi-layers separated from one another by aqueous spaces. These are heterogeneous in size, ranging from few hundreds to thousands of nm in diameter.

b) Small unilamellar vesicles (SUV'S) and large unilamellar vesicles (LUV'S)

These consist of a single bi-layer surrounding the entrapped aqueous space. SUV'S are less than 100nm and LUV'S are more than 100nm. Drug is either entrapped in the aqueous space or intercalated into lipid bi-layer of liposome's, depending on physicochemical characteristics of the drug. Liposome's can be prepared with great diversity in structure, composition, size,

flexibility and a variety of surface modification approaches for both active and passive delivery of bioactive. They are used in cancer therapy, carrier for antigens, pulmonary delivery, leishmaniasis, ophthalmic drug delivery (Jain S et al., 2004).

Polymeric micelles

Amphiphillic block copolymers assemble into nanoscopicsupra molecular core shell structure known as 'polymeric micelles'. These are usually of less than 100nm and their hydrophilic surface protects their nonspecific uptake by reticuloendothelial system. Micelles formed in solutions as aggregates in which the component molecules are arranged in a spherical structure with hydrophobic core shield from water by a mantle of hydrophilic groups. These are used for systemic delivery of water insoluble drugs. And drugs are trapped physically within the hydrophobic cores or can be linked covalently to component molecules of the micelles. These have high loading capacity, stability in physiological conditions, slower rate of dissolution, high accumulation of drug at target site and possibility of Functionalization of end group for conjugation of targeting ligands (Ferrari, M., 2005).

Polymer drug conjugate

The conjugation of low molecular weight drugs with polymer causes drastic change in pharmacokinetic disposition of drug in whole body and at cellular level. So, these are designed to increase the overall molecular weight, which facilitates their retention in cancer cells through EPR effect using passive delivery approach (Ferrari M., 2005).

Polyplexes or lipopolyplexes

These form spontaneously between nucleic acids and polycations or cationic conjugated to targeting ligands or hydrophilic polymers and are used in transfection protocols. The

shape, size distribution and transfection capability of these complexes depends on their composition and charge ratio of nucleic acid to that of cationic lipid or polymer.

E.g.:- poly-l-lysine, linear and branched poly ethylene amine, poly amidoamine, poly-amino esters and cationic cyclodextrin (Ferrari M., 2005).

Methods of Preparation of Nanoparticles:

Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection of matrix materials is dependent on many factors including:

(a) Size of nanoparticles required

(b) Inherent properties of the drug e.g., aqueous solubility and stability

(c) Surface characteristics such as charge and permeability

(d) Degree of biodegradability, biocompatibility and toxicity

(e) Drug release profile desired

(f) Antigenicity of the final product. [34-37]

Most frequently three methods have been preferred for preparation of nanoparticles: (1) dispersion of preformed polymers (2) polymerization of monomers and (3) ionic gelation or coacervation of hydrophilic polymers. However, other methods such as supercritical fluid technology and particle replication in non-wetting templates (PRINT) have also been described in the literature for production of nanoparticles. The latter was claimed to have absolute control of particle size, shape and composition, which could set an example for the future mass production of nanoparticles in industry. Dispersion of preformed polymers is a common technique used to prepare biodegradable nanoparticles from poly (lactic acid) (PLA); poly (D,Lglycolide), PLG; poly (D, L-lactide-co-glycolide) (PLGA) and poly (cyanoacrylate) (PCA), 13-15. This technique can be used in various ways as described below[38-42]:

1) Solvent Evaporation Method

In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform or ethyl acetate, which is also used as the solvent for dissolving the hydrophobic drug. The mixture of polymer and drug solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent to form oil in water (o/w) emulsion. After the formation of stable emulsion, the organic solvent is evaporated either by reducing the pressure or by continuous stirring. Particle size was found to be influenced by the type and Concentrations of stabilizer, homogenizer speed and polymer concentration. In order to produce small particle size, often a high-speed homogenization or ultrasonication may be employed.

2) Spontaneous Emulsification or Solvent Diffusion Method

This is a modified version of solvent evaporation method 18. In this method, the water miscible solvent along with a small amount of the water immiscible organic solvent is used as an oil phase. Due to the spontaneous diffusion of solvents an interfacial turbulence is created between the two phases leading to the formation of small particles. As the concentration of water miscible solvent increases, a decrease in the size of particle can be achieved. Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. In the case of

hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase.

3) Polymerization Method

In this method, monomers are polymerized to form nanoparticles in an aqueous solution. Drug is incorporated either by being dissolved in the polymerization medium or by adsorption onto the nanoparticles after polymerization completed. The nanoparticles suspension is then purified to remove various stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate)nanoparticles. Nanocapsules formation and their particle size depend on the concentration of the surfactants and stabilizers used.

4) Coacervation or Ionic Gelation Method

 Much research has been focused on the preparation of nanoparticles using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate. Calvo and co-workers developed a method for preparing hydrophilic chitosan nanoparticles by ionic gelation. The method involves a mixture of two aqueous phases, of which one is the polymer chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEOPPO) and the other is a poly anion sodium tripolyphosphate. In this method, positively charged amino group of chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometer. Coacervates are formed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation involves the material undergoing transition from liquid to gel release. These practical problems have to be overcome before nanoparticles can be used clinically or made commercially available. The present review details the latest development of nanoparticulate drug delivery systems, surface modification issues, drug loading strategies, release control and potential applications of nanoparticles.

5) Production of Nanoparticles Using Supercritical Fluid Technology

Conventional methods such as solvent extraction-evaporation, solvent diffusion and organic phase separation methods require the use of organic solvents which are hazardous to the environment as well as to physiological systems. Therefore, the supercritical fluid technology has been investigated as an alternative to prepare biodegradable micro- and nanoparticles because supercritical fluids are environmentally safe. A supercritical fluid can be generally defined as a solvent at a temperature above its critical temperature, at which the fluid remains a single phase regardless of pressure. Supercritical CO_2 (SC CO_2) is the most widely used supercritical fluid because of its mild critical conditions (Tc = 31.1 C, Pc = 73.8 bars), nontoxicity, non-flammability, and low price. The most common processing techniques involving supercritical fluids are supercritical antisolvent (SAS) and rapid expansion of critical solution (RESS). The process of SAS employs a liquid solvent, e.g. methanol, which is completely miscible with the supercritical fluid (SC CO_2), to dissolve the solute to be micronized; at the process conditions, because the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting the formation of nanoparticles. Supercritical fluid technology technique, although

environmentally friendly and suitable for mass production, requires specially designed equipment and is more expensive.

Applications of Nanotechnology in pharmaceutical field [43-52]

A) Tumor Targeting Using Nanoparticulate Delivery Systems

The rationale of using nanoparticles for tumor targeting is based on following characteristics:

1) Nanoparticles will be able to deliver a concentrate dose of drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or active targeting by ligands on the surface of nanoparticles.

2) Nanoparticles will reduce the drug exposure of healthy tissues by limiting drug distribution to target organ. Studies show that the polymeric composition of nanoparticles such as type, hydrophobicity and biodegradation profile of the polymer along with the associated drugs molecular weight, its localization in the nanospheres and mode of incorporation technique, adsorption or incorporation, have a great influence on the drug distribution pattern in vivo. The exact underlying mechanism is not fully understood but the biodistribution of nanoparticles is rapid, within hour to 3 hours, and it likely involves mononuclear phagocytic system (MPS) and endocytosis/ phagocytosis process. Such propensity of MPS for endocytosis/phagocytosis of nanoparticles provides an opportunity to effectively deliver therapeutic agents to these cells. This biodistribution can be of benefit for the chemotherapeutic treatment of MPS-rich organs/tissues localized tumors like hepatocarcinoma, hepatic metastasis arising from digestive tract or gynaecological cancers, brochnopulmonary tumors, primitive tumors and metastasis, small cell tumors, myeloma and leukaemia.

B) Ligand based Nanoparticles

To be successful as a drug delivery system, nanoparticles must be able to target tumors, which are localized outside MPS-rich organs. In the past decade, a great deal of work has been devoted to developing so called stealth particles or PEGylated nanoparticles, which are invisible to macrophages or phagocytes. A major breakthrough in the field came when the use of hydrophilic polymers (such as polyethylene glycol, poloxamines, poloxamers, and polysaccharides) to efficiently coat conventional nanoparticle surface produced an opposing effect to the uptake by the MPS. These coatings provide a dynamic cloud ofnhydrophilic and neutral chains at the particle surface,which repel plasma proteins. As a result, those coated nanoparticles become invisible to MPS, therefore remained in the circulation for a longer period of time and hence called as long circulating nanoparticles. Hydrophilic polymers can be introduced at the surface in two ways, either by adsorption of surfactants or by use of block or branched copolymers for production ofnanoparticles. Studies show nanoparticles containing a coat of PEG not only have a prolonged half-life in the blood compartment but also be able to selectively extravasate in pathological sites such as tumors or inflamed regions with a leaky vasculature. As a result, such long-circulating nanoparticles have increased the potential to directly target tumors located outside MPSrich regions. The sizes of the colloidal carriers as well as their surface characteristics are the critical to the biological fate of nanoparticles. A size less than 100 nm and a hydrophilic surface are essential in achieving the reduction of opsonisation reactions and subsequent clearance by macrophages. Coating conventional

nanoparticles with surfactants or PEG to obtain a long circulating carrier has now been used as a standard strategy for drug targeting in vivo. Extensive efforts have been devoted to achieving active targeting of nanoparticles in order to deliver drugs to the right targets, based on molecular recognition processes such as ligand receptor or antigen-antibody interaction. Considering that fact that folate receptors are over expressed on the surface of some human malignant cells and the cell adhesion molecules such as selectins and integrins are involved in metastatic events, nanoparticles bearing specific ligands such as folate may be used to target ovarian carcinoma while specific peptides or carbohydrates may be used to target integrins and selectins[46]. Targeting with small ligands appears more likely to succeed since they are easier to handle and manufacture. Furthermore, it could be advantageous when the active targeting ligands are used in combination with the long-circulating nanoparticles to maximize the likelihood of the success in active targeting of nanoparticles.

C) Nanoparticles for Oral Delivery of Peptides and Proteins

Significant advances in biotechnology and biochemistry have led to the discovery of a large number of bioactive molecules and vaccines based on peptides and proteins. Development of suitable carriers remains a challenge due to the fact that bioavailability of these molecules is limited by the epithelial barriers of the gastrointestinal tract and their susceptibility to gastrointestinal degradation by digestive enzymes. Polymeric nanoparticles allow encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation. For instance, it has been found that insulin-loaded nanoparticles have preserved insulin activity and produced blood glucose reduction in diabetic rats for up to 14 days following the oral administration. The surface area of human mucosa extends to 200 times that of skin [48]. The gastrointestinal tract provides a variety of physiological and morphological barriers against protein or peptide delivery, e.g.,

(a) Proteolytic enzymes in the gut lumen like pepsin, trypsin and chymotrypsin;

(b) Proteolytic enzymes at the brush border membrane (endopeptidases);

(c) Bacterial gut flora;

(d) Mucus layer and epithelial cell lining itself. The histological architecture of the mucosa is designed to efficiently prevent uptake of particulate matter from the environment. One important strategy to overcome the gastrointestinal barrier is to deliver the drug in a colloidal carrier system, such as nanoparticles, which is capable of enhancing the interaction mechanisms of the drug delivery system and the epithelia cells in the GI tract.

D) Nanoparticles for Gene Delivery

Polynucleotide vaccines work by delivering genes encoding relevant antigens to host cells where they are expressed, producing the antigenic protein within the vicinity of professional antigen presenting cells to initiate immune response. Such vaccines produce both humoral and cell-mediated immunity because intracellular production of protein, as opposed to extracellular deposition, stimulates both arms of the immune system. The key ingredient of polynucleotide vaccines, DNA, can be produced cheaply and has much better storage and handling properties than the ingredients of the majority of protein-based vaccines. Hence, polynucleotide vaccines are set to supersede many

conventional vaccines particularly for immunotherapy. However, there are several issues related to the delivery of polynucleotides, which limit their application. These issues include efficient delivery of the polynucleotide to the target cell population and its localization to the nucleus of these cells, and ensuring that the integrity of the polynucleotide is maintained during delivery to the target site. Nanoparticles loaded with plasmid DNA could also serve as an efficient sustained release gene delivery system due to their rapid escape from the degradative endolysosomal compartment to the cytoplasmic compartment. Hedley et al. reported that following their intracellular uptake and endolysosomal escape, nanoparticles could release DNA at a sustained rate resulting in sustained gene expression. This gene delivery strategy could be applied to facilitate bone healing by using PLGA nanoparticles containing therapeutic genes such as bone morphogenic protein

E) Nanoparticles for Drug Delivery in to The Brain

The blood-brain barrier (BBB) is the most important factor limiting the development of new drugs for the central nervous system. The BBB is characterized by relatively impermeable endothelial cells with tight junctions, enzymatic activity and active efflux transport systems. It effectively prevents the passage of water soluble molecules from the blood circulation into the CNS, and can also reduce the brain concentration of lipid-soluble molecules by the function of enzymes or efflux pumps. Consequently, the BBB only permits selective transport of molecules that are essential for brain function. Strategies for nanoparticle targeting to the brain rely on the presence of and nanoparticle interaction with specific receptor-mediated transport systems in the BBB. For example polysorbate 80/LDL, transferring receptor binding antibody (such as OX26), lactoferrin, cell penetrating peptides and melanotransferrin.

F) Implantable delivery systems

Nanoparticles can act as the delivery systems by virtue of its size, controlled an approximately zero order kinetics, otherwise they may cause toxicity when compared to I.V. Carriers are liposome, ethosome and transferosome. These help in minimizing peak plasma levels and reduce risk of adverse reactions, allow for more predictable and extended duration of action, reduce the frequency of re-dosing and improve patient acceptance and compliance (Jain NK., 2002).

G) Drug discovery

Nanotech helps in identification and validation of target by identifying the protein present on the surface or target surface. Nanotech will enhance drug delivery process, through miniaturization, automation, speed and reliability of assays. Single walled nanotubes are successfully used to identify surface protein of pathogen. Quantum dots- track individual glycine receptors and to analyze their dynamics in the neuronal membrane of living cells,

for periods ranging from milliseconds to minutes. Gold nano particles, nanobodies (smallest, available, intact antigen-antibody fragments) produced by ablynx are some commonly used

nanomaterials in diagnosis. The pharmaceutical nanotechnology is used in the biodetection of pathogens in humans, separation and purification of molecules and cells and detoxifying agents. Future nanomachine (respirocyte) is the nano-on-board mini computer,that can be used for detection of disease causing marker or antigen, to view the diseased site and to deliver the therapeutic agent at the site.

H) Molecular diagnostics: (molecular imaging)

It is representing, characterizing and quantifying sub cellular biological processes include gene expression, proteinprotein interaction, signal transduction, cellular metabolism. Theyare used in magnetic resonance imaging, optical imaging, ultrasonic imaging and nuclear imaging. Other applications are specific labeling of cells and tissues,

useful for long-term imaging, multicolor multiplexing, dynamic imaging of sub cellular structures and fluorescence resonance energy transfer (FRET) and magnetic resonance imaging (MRI). MRI agents are replaced by nanomaterials like dendrimer, quantum dots, carbon nanotubes and magnetic nanoparticles. They are very efficient, stable, intense, clearer image due to high intensity, photostability, resolution, resistance (Gupta P.k et al., 1987).Quantum dots, iron oxide nanocrystal and metallic nanoparticles.

I) Biosensor and bio-labels

These tools are employed for determination of various pathological proteins and physiological-biochemical indicator associated with disease or disrupted metabolic conditions of body.

Biosensor is a measurement system that consists of a probe with a sensitive biological recognition element or bio-receptor, a physiochemical detector component and a transducer to amplify and transducer these signals into measurable form. A nanobiosensor or nanosensor is a biosensor that has dimensions on the nanometer size scale. Biosensors are used in target identification, validation, assay development, ADME, toxicity determination (Khopde AJ et al., 2001).

CONCLUSION:

Pharmaceutical nanotechnology has emerged as a discipline having enormous potential as a carrier for spatial and temporal delivery of bioactives and diagnostics and provides smartmaterials for tissue engineering. It offers new tools, opportunities and scope, which are expected to have a great impact on many areas in disease, diagnostics, prognostic and treatment of diseases through its nano-engineered tools.Pharmaceutical nanotechnology provides opportunities to improve materials, medical devices and help to develop new technologies where existing and more conventional technologies may be reaching their limits. It raises new hope to industries by providing new patentive technologies in view of revenue loss caused due to off-patent drugs. Pharmaceutical nanotechnology has a profound influence on disease prevention efforts because it offers innovative tools for understanding the cell as well as the difference between normal and abnormal cells. It could insights into molecular basis of disease.

Some of the advantages are:-
1. Identifying, defining and characterization of model nanomaterials.
2. Developing toxicity testing protocol.
3. Detecting and monitoring exposure level.
4. Assessing the impact of environment.
5. Developing the biocompatible hybrid system.

But still we lack the sufficient data and guidelines regarding safe use of these nanotechnology based devices and materials. There are several confounding unresolved issues, which warrant the application in its full boom.No doubt the next era of the drug development will be greatly influenced by Nanotechnology and the newer aspect of drug delivery will be reliable, effective and safe.

REFERENCES:

[1] Kammer F.W., Gudal U., Berger M., Exercise in Alberti Kggm, Zemmel P., De Fronzo Reads, International Textbook of Diabetes Mellitus, 2nd edition Chichester: John Holley and Sons 1977, 799-815.

[2] Ha TKK, Lean MEJ, *Eur J Clin Nutrition*, 1998, 52, 467-481.

[3] Jorl G. Hardman, Lee E. Limbird, Perry B. Molinoff, Raymond W. Ruddon, Alfred Goodman Gilman, The Pharmacological Basis of Therapeutics, 9th ed., published by McGraw Hill, International edition, USA, 1493-1500.

[4] http://en.wikipedia.org/wiki/Histroy_of _nanotechnology

[5] Soppimath, K.S.; Aminabhavi, T.M.; Kulkarni, A.R. and Rudzinski, W.E. *J. Controlled Release,* 2001, 70 (1-2), pp. 1-20.

[6] William O. Foye, Principle of medicinal chemistry, 3rd ed., Verghese publication group, Mumbai, India, 532.

[7] Whelan, *J Drug Discov. Today*, 2001, 6 (23), 1183-1184.

[8] Aboubakar, M.; Couvreur, P.; Pinto- Alphandary, H. ; Gouritin, B. *Drug Dev. Res*. 2000, 49,109-117.

[9] Damage, C. ; Vonderscher, J. ; Marbach, P. And Pinget, *M. Pharm Res*., 1997, 18, 949-954.

[10] Fernandez-Urrusuno, R.; Calvo, P.; Remunan-Lopez, C.; Vila-Jato, J.L., *Pharm. Res*., 1999,16, 1576-1581.

[11] Guteress, S.S.; Fessi, H.; Barratt, G. ; puisieux, F. *Pharm. Res*., 1995, 12, 1545-1547.

[12] Guteress, S.S.; Fessi, H.; Barratt, G. ; puisieux, F. *J. Biomater. Sci.-Polymer*, 2000, 11,1347-1355.

[13] Orive G., *Current Opinion in Biotechnology*. 2003, 14: 659-664.

[14] Davis S. S. and Illum L., *International Journal of Pharmacology*. 1998, 18, 76.

[15] Mohanraj V.J. and Chen Y., *Tropical Journal of Pharmaceutical Research*. 2006, 5 (1),561-573.

[16] Langer R., *Acc. Chem.Res*. 2003, 33, 94-101.

[17] Bhadra D., Bhadra S., Jain P, Jain NK., *Pharmazie*. 2002, 57, 5-29.

[18] Kommareddy S., Tiwari S.B., Amiji M.M., *Technol Cancer Res Treat*. 2005, 4, 615-625.

[19] Lee M., Kim S.W., *Pharm Res*. 2005, 22, 1-10.

[20] Vila A.; Sanchez A.; Tobio M.; Calvo P.; Alonso M.J., *J Control Release*. 2002, 78, 15-24.

[21] Mu L. and Feng S.S., *Int.J. PharmTech Res*.2009,1(4), 1026

[22] Nilesh M. Mahajan, *J Control Release*, 2003, 86, 33-48.

[23] Kreuter J., Nanoparticles. In Colloidal drug delivery systems. J. K. Ed. Marcel Dekker: New York. 1994, 219-342.

[24] Reverchon E. and Adami R., *The Journal of Supercritical Fluids*. 2006, 37, 1-22.

[25] Rolland J.P., Maynor B.W., Euliss L.E., Exner A.E.,Denison G.M. *J. Am.Chem. Soc*, 2005, 127:10096-10100.

[26] Kompella U.B., Bandi N., Ayalasomayajula S.P., *Drug Deliv. Technol*, 2001, 1, 1-7.

[27] Ravi M.N., Bakowsky U., Lehr C.M., Preparation and characterization of cationic PLGA nanospheres as DNA carriers. Biomaterials. 2001, 25, 1771-1777.

[28] Li Y.P., Pei Y.Y., Zhou Z.H.. *J Control Release*, 2001, 71, 287-296.

[29] Kwon H.Y., Lee J.Y., Choi S.W., Jang Y. *Eng. Aspects*, 2001, 182: 123-130.

[30] Zambaux M., Bonneaux F., Gref R., *J. Control. Release*, 1998, 50, 31-40.

[31] Niwa T., Takeuchi H., Hino T., *J.Control.Release*, 1993, 25, 89-98.

[32] Zhang Q., Shen Z., Nagai T. *Int. J. Pharm*. 2001, 218: 75-80.

[33] Boudad H., Legrand P., Lebas G., *Int J. Pharm*. 2001, 218: 113-124.

[34] Puglisi G., Fresta M., Giammona G., *Int. J. Pharm*, 1995, 125, 283-287.

[35] Calvo P., Remunan-Lopez C., Vila-Jato J.L., *J. Appl. Polymer Sci*, 1997, 63, 125-132.

[36] Calvo P., Remunan-Lopez C., Vila-Jato J.L. *Pharm Res*. 1997, 14, 1431-1436.

[37] Jung J., Perrut M., *J. Supercritical Fluids*. 2001, 20, 179-219.

[38] Thote A.J., Gupta R.B., *Biology Medicine*, 2005, 1, 85-90.

[39] Sun Y., Mezian M., Pathak P., *Chemistry*, 2005, 11, 1366-1373.

[40] Panyam J. and Labhasetwar V., *Adv Drug Deliv Rev*, 2003, 55, 329-347.

[41] Kroll R.A., Pagel M.A., Muldoon L.L., Roman-Goldstein S., Fiamengo S.A., *Neurosurgery*, 1998, 43: 879-886.

[42] Zauner W., Farrow N.A., Haines A.M., *J Control Release*, 2001, 71, 39-51.

[43] Redhead H.M., Davis S.S., Illum L., *J Control Release*, 2001, 70, 353-363.

[44] Dunne M., Corrigan O.I., Ramtoola Z..*Biomaterials*, 2000, 21, 1659-1668.

[45] Swarbrick J., Boylan J., Encyclopedia of pharmaceutical technology. 2nd ed.; Marcel Dekker:New York, 2002.

[46] Muller R.H., Wallis K.H., *Int. J.Pharm*, 1993, 89, 25-31.

[47] Grislain L., Couvreur P., Lenaerts V., Speiser P., *Int. J. Pharm*, 1983, 15: 335-345. Behera A.L *et al Der Pharmacia Sinica, 2010, 1 (1):20-28.*

[48] Couvreur P., Barratt G., Fattal E., Legrand P., Vauthier C., *Crit RevTher Drug Carrier Syst,* 2002, 19, 99-134.

[49]   Govender T., Stolnik S., Garnett M.C., Illum L.,Davis S.S., *J. Control. Rel*, 1999, 57, 171-185.

[50] Peracchia M., Gref R., Minamitake Y., Domb A. ,Lotan N. , Langer R., *J Control Release,* 1997, 46, 223-231.

[51] Chen Y., McCulloch R.K., Gray B.N., *J Control Release*, 1994, 31, 49-54.

[52] Fresta M. , Puglisi G., Giammona G., Cavallaro G.,Micali N., Furneri P.M., *Int.J. PharmTech Res*.2009,1(4) 1027.