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SCOPE OF NANOTECHNOLOGY IN DRUG DELIVERY SYSTEM

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INTRODUCTION

Nanoscience mainly includes the study the control of matter on an atomic and molecular scale. This molecular level investigation is at range of below 100nm. This is nowadays a widespread and ascertained knowledge that materials in the nano meter range of size have different physical, Chemical and biological properties than materials in large scale.

The most important and promising application in use of nanotechnology for drug delivery which will enhance efficacy and drug potency of therapeutics administered through different routes of administration. Recently, in the field of health care the application of nanotechnologies receiving considerable acknowledgement. Today most of the treatments are considered as very expensive and time consuming, but by usage of nanotechnology provides quicker and cheaper treatments.

The field of nanotechnology was first introduced by Professor Richard Feynman in 1959. The ability to manipulate the physical, chemical and biological properties of these particles provides researchers with the capability to rationally design and use nanoparticles for drug delivery, as image contrast agents, and for diagnostic purposes.[1]

The use of nanoparticles s-drug carriers can play an important role in eliminating the challenging problems associated with conventional drugs used for the treatment of many chronic diseases such as cancer, asthma, human immunodefiency virus, hypertension, and diabetes.[2-7] Polymeric nano-carriers, dendrimers, polymeric micelles, liposome's, solid lipid nanoparticles, metallic nanoparticles, carbon nanotubes, nanosphere, nano capsules, nanogels are examples of nano-based drug delivery systems that are currently under research and development.[8-12]

Some of them, especially cancer treatments have been clinically used and approved by the food and drug administration.

Importance of Nanotechnology System

The materials used in nanotechnology have wide range of different physical, chemical and biological properties. The main aim of development of nano-sized particles in drug delivery is:

1. To enhance the solubility of poorly soluble drugs
2. To overcome the intestinal epithelial barrier.
3. To overcome the mucous barrier.
4. To overcome the harsh GI environment.

The chemical and physical properties of nanoparticles make efficient drug delivery systems that improve the bioavailability, drug carrying capacity, stability within the body, controlled release and target release.[13] Nanotechnology systems increases potency and efficacy of therapeutics administered through different routes. Nanotechnology increases bioavaibility of drugs as a result of their special uptake mechanisms such as absorptive endocytosis and provide the ability to avoid degradation in the GIT. The drug incorporated into the NP is easily diffused through biological membranes and also able to remain in blood for long period.

Advantages of Nano Drug Delivery System

- Nanoparticles formulations that release higher doses of drug for prolonged period of time and inhibit proliferation of nanoparticles into vascular smooth muscle cells.
- Intense investigation has been done for use of nanoparticles in cancer therapy.
- Chemotherapy fails to cure cancer because some tumor cells develop resistance to multiple anti-cancer drugs.
- Cancer cells begin expressing a protein known as p-glycoprotein that is capable of pumping anti-cancer

drugs this quickly cross through cells through the membrane.[14]
- Nanoparticles are the particulate dispersion and they are having different size range of 10-100nm.
- The major goals in designing nanoparticles in a drug delivery system in order to control particle size.
- Nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parental administration.
- Nanoparticles can be used for various routes of administration including oral, nasal, parental, intra-ocular etc.,
- 100nm sized nanoparticles had a 2.5-fold greater uptake than 1nm micro particles, and 6-fold greater uptakes than 10micro meters micro particles.

Principles of Nanoparticle Drug Delivery System

They are usually defined as submicron sized particles. They are of 1-100nm of size and widely used as carrier vectors which are simply made and have high reproducibility. Different kinds of materials and technological methods are used to synthesize nanoparticle- based drug delivery systems.

For the first principle the material should be most suitable according to their actual situation of clinical application. The physical and chemical properties of nanoparticles are, the material size and surface properties, will influence the loading and release characteristics of drugs with nanosized as well as their biocompatibility and degradability.[15] The one type of the delivery system has high loading capacity of the drug and also have the different release behavior which is difficult to control and it is called the "LIPOSOME" nanoparticles -based drug delivery system.[16]

Second type is "POLYMER" nanoparticles -based drug delivery system has low loading capacity and to generate the specific molecular weight and compositions.[17] During the bone regeneration (reformation) the nano based particle drug delivery system with optimal and controlled drug release behavior meets the temporal and spatial demands which is essential to make sure of the second principle. The bone formation takes longer period when compare to the other tissues, which leads to the confirm release of the bioactive factors and these are maintained at the local bone defect area the therapeutic concentrations for long time to which temporal and spatial optimal distributions.

The third principle is that nanoparticle-based drug delivery system which ensures the drug biological activity when filled into the nanoparticle and the Preparation should be mild (little) without the harsh solvents (rough materials), high temperatures or pressures at extreme pH. After the drug incorporated into the nanoparticle the bioactivity of the drug should be examined carefully to avoid any type of the changes.[18] While designing and preparing the nanoparticle-based drug delivery Systems in tissue engineered bone these are the basic principles which are used to achieve better therapeutic outcomes and formation of bone. Different kinds of nanoparticle-based drug delivery systems are introduced during bone reformation.

Properties of Nanoparticles
- The components included in formulas are should be commercially available, safe, affordable, on toxic and bio degradable.
- The nano particles should be stable throughout their shelf life with respect to size, surface morphology, size distribution and other physical and chemical properties.
- The manufacturing process of nano particles might be simple, affordable and the formulation does not include organic solvent and potentially toxic ingredients.

Characterisation of Nano Particles

1. **Particle size and shape:** Particle size and surface characteristics show their effect on interactions of nanoparticles to the cells. Small particles are easily uptake by the cell compared to the large particles. Shape can influence the intracellular nano material trafficking.[19] The circulation time of spherical nano particles are smaller when compared to the elliptical discs. Particle size and shape can be determined by electron microscopy and or atomic Force microscopy.[20-25]
2. **Zeta potential:** zeta potential is a quantitative measure of the surface activity and it unit is 'mv' The absolute value of Zeta potential is less than 10 then the particles got aggregate if it is more close to 0 then the particles show less aggregation causing insufficient charge repulsion Leading to more stable suspension.[26]
3. **Drug release:** An encapsulated drug is released from nanoparticles to exert pharmacological effects. Drug release is mainly influenced by the nature of the drug, nano material composition and Localization of the drug within the nano particle.[27] Drug release kinetics are determined in a well stirred physiological relevant medium such as Phase buffer at pH 7.4 and at 37° C where sink conditions are maintained.[28]
4. **Time-resolved small-angle neutron scattering (TR-SANS):** It is an effective method to study the size, structure development and morphological Changes of lipid.[29] It also provides data regarding coalescence, growth and transformation of lipid molecules.
5. **X-ray diffraction:** It is used to characterize crystallinity, crystal and molecular structure variation, non-Crystalline, periodicity and size nano formulation orientation (crystalline/amorphous), polymorphism and phase transition.[30,31] It is used to examine the state of encapsulated drug.[32]
6. **Differential scanning calorimeter:** Differential scanning calorimeter can be used to quantity and investigate the solid and liquid amorphous phases of

nano material and payload, perfect crystallinity of the sample, polymorphic transition, drug loading efficiency, conformational changes, self-assembly behavior and stability.[33,34]

7. **Fourier transform infrared spectroscopy (FTIR):** Fourier transform infrared spectroscopy can be used to determine the chemical composition, and the presence of chemical bonds and functional groups. FTIR and x-ray diffraction characterize the interactions of drug with nano particle material.[35]
8. **Encapsulation efficiency:** Encapsulation efficiency of a nanoparticle formulation is defined as the fraction of the amount of drug used in the nanoparticle preparation process that was actually encapsulated within the nanoparticles.

Encapsulation efficiency= (mass of drug added to the nanoparticles− mass of free drug) /mass of drug added to the nanoparticles.[36]

Preparation of Nano Particles

- **Preparation of Nanosuspensions:** Nanosuspensions means production of submicron sized particles by combination of drug and emulsifier by the process of high-pressure homogenization. Development of nanoparticles is used for to improve absorption of insoluble compounds. The nanosuspensions are developed to improve the solubility of poorly soluble drugs. Particle size reduction to size of 1mm shows difficulties due to aggregation. The high-pressure homogenization is used to develop nano suspension. Nanosuspensions can be used for parental, ocular and oral preparations.[37]
- **Preparation of Polymeric nanoparticles:** Polymeric nanoparticles can be identified as submicronic colloidal carriers. They have attractive physicochemical properties like size, shape, surface potential, hydrophilic- hydrophobic balance. Solid nanoparticles are very important polymeric nanoparticles. Polymeric Nanoparticles can also be prepared from natural macro molecules by using various methods such as thermal denaturation of proteins or gasification process.[38] The polymers used in the polymeric nanoparticles are polyethylene glycol; polyethyleneimine etc., the incorporation of PEG to lipoid organizes produces better results. The ingredients such as anti-cancer drugs, vaccines, oligonucleotides, and peptides etc., these nanoparticles are prepared by polymerization of monomers, followed by growth phase and emulsion polymerization.
- **Preparation of Polymers for gene delivery:** The delivery of nucleic acid into cells through in vitro involves a critical technique for the study of genes and development of potential gene therapies which will decrease the toxicity. Successful gene transfer techniques, sufficient stability of DNA during extracellular delivery phase, transportation through cell membrane and cytoplasm can be achieved through polymer for gene delivery. These polymers provide anionic stabilization, protection from opsonization and also allow freeze – drying of the vector with little loss of activity. These plays an important role as the gene technology which r is the most important developing department.
- **Preparation of Solid lipid nanoparticles:** Solid lipid nanoparticles are made from solid lipids with diameter ranging between 50-100 mm. Researchers show that the SLN after administration facilitate their uptake by the lymphatics. The preparation of solid nanoparticles includes homogenization techniques, microbial emulsion-based method, solvent emulsification/evaporation method. Particularly the emulsification/evaporation is mostly used. The nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. For homogenization technique the drug is dissolved or solubilized in the lipid and heated.[39] The lipid particles are dispersed in a cold surfactant solution this is homogenized at or below room temperature. This process avoids melting points of lipids. Lipid nanoparticles can also be prepared by using micro emulsions as precursors.

Natural Polymers In Nano Drug Delivery

Starch: Starch is common polysaccharide. It is used as co polymer and excipient in controlled drug delivery[40-42] as drug carrier in tissue engineering ca^{+2} folds[43] as hydrogels[44] and as solubility enhancers.[45] The modified and unmodified form of maize starch was used as polymeric material to formulate different types of nanoparticles. Starch nanoparticles have been employed to deliver insulin via non-invasive routes.[46] Starch extracted from cassava tubes was modified by graft copolymerization using long chain fatty acids before the polymer was made into nanoparticles.

Gelatin: Gelatin is obtained from breakdown and hydrolysis of collagen obtained from connective tissue, bones and skin of animals. Nanoparticles of gelatin prepared by solvent evaporation. Transfection with the aid of gelatin nanoparticles was also used for delivery of DNA plasmids encoding for insulin growth like factor (IGF-1) into chronocytes.[47] The prolonged and localized release of IGF-1 was achieved and used to promote growth in skeletal muscle, cartilage, bones and numerous other tissues. This will show potential application in gene therapy and tissue engineering.

Differences Between Nano Drug Delivery and Traditional Drug Delivery

Traditional drug delivery

- **Specificity:** Drugs will pass through unaffected sites before reaching affected site.
- **Dosage Release:** Higher initial Dosage required. No control ability.
- **Efficacy:** Drug concentration in affected site is low.
- **Side Effects:** Inevitable exposure of unaffected sites to drugs.

Nano drug delivery

- **Specificity:** Delivered in more targeted manner to the affected site.
- **Dosage Release:** Able to control dosage by trigger, requirement, and even time release.
- **Efficacy:** Drug concentration in affected site is more optimized.
- **Side Effects:** Lesser exposure of unaffected sites to drugs.[48]

TYPES OF DRUG DELIVERY SYSTEMS

System	Size	Method	Properties	Uses	Type of release	Product name
LIPOSOMES	Small:25-100nm Large:100-1000nm	Heating spray drying lyophilization	-hydrophobic and hydrophilic -increase therapeutic efficacy and drug stability	Used as model cells for bioactive agents increasing drugs, vaccine, cosmetics and nutraceuticals	Local and sustained release	-vincristine sulfate[49-51] -mitoxantrone[52] -lurtotecan[53]
DENDRIMERS	-	Synthesized by strategies like divergent and convergent	-increase drug solubility, delivery, therapeutic effectiveness -enables targeting to specific sites	-used in cancer therapy, gene delivery, vaccine delivery, diagnostic agents, biomarkers	Local	-sorvivin-A50 -viologen based CX Ry antagonist[54] -Akt siRNA-Paclitaxel (PTX)[55]
LIPID NANOPARTICLES	10-100nm	-ultrasonication -supercritical fluid technology -high pressure homogenization -micro emulsion	-reduce the adverse effects -clinical protection of liable incorporated CAMP's	-enhance drug effects on tumor cells by enhanced permeability and retention effects (EPR)	Controlled release with oral bioavailability	-Antisense[56] -GG 918(elaridar)DOX[57]
POLYMERIC MICELLES	<100nm	-direct dissolution -evaporation -dialysis	Stability of polymeric micelles is dependent on CMC.	-anti cancer therapy -drug delivery to brain -drug delivery of anti-fungal agents.	Below CMC leads to rapid dissociation of micelles	-Genexol PM(Paclitaxel)[58-61] -nano platin (cisplatin)[62]
ORGANIC OR INORGANIC COMPOSITES	65-95nm	Selection of film forming organic phase from starches by following mixing, drying of composites.	Contain inorganic phase and a film forming organic phase	-bioimaging -thermostats -diagnosis of inflammatory diseases	Local and sustained release	-acylated beta cyclodextrin

Liposomers

Liposomers were first discovered by Dr. Alec.D. Bangham and are spherical in shape. The liposomers deliver the drugs which are entrapped in the lipid bilayer. The hydrophilic drugs are encapsulated in the core whereas hydrophobic drugs are encapsulated within the lipid bilayers. These are used to protect the drug from plasma enzymes and provide controlled drug release. Generally, liposomers are classified as

- Unilamellar (composed of single lipid bilayer).
- Multilamellar (composed of several lipid bilayers)[63, 64]

The advantages of liposomers are biocompatible, non-toxic, flexible and used for reducing toxicity. But the major disadvantage with this is loco solubility and cost is high. The liposomes are prepared by mechanical agitation, solvent dispersion methods and detergent removal methods from mixed micelles. The number of lipid bilayers may show its impact on efficiency and drug release. The stability of liposomer is very important and the chemical stability determines the interaction of drug with phospholipids layer. Liposomers plays a wide major role in encapsulating cancer drugs like doxorubicin, cisplatin, paclitaxel and even approved by FDA. The first liposomer pharmaceutical produced is DOXIL in the year 1995.[65] the conclusion research has been going on to get better formulations to improve in vivo circulation time and also to improve tumor delivery and reduce

toxicity for clinical application of liposomers in cancer treatment.[66,67]

Lipid Nanoparticles

Lipid nanoparticles are smaller particles which are less than the one micron. These nano particles have small atomic and molecular scales. These particles may be amorphous or crystalline. The various different materials have been entrapped in lipid nano particles. The examples of various materials are labile compounds, proteins and peptides. The lipid nano particles are classified based on the dimensionality, morphology, composition and uniformity. They are follows

- Solid lipid Nano particles: These are developed during 1990's and consist of solid lipid. The major advantage with solid lipid nanoparticles is controlled release along with oral bioavailability.
- Nano structural lipid carriers: These are composed of both solid and liquid lipids as a core matrix. The major advantage is increased solubility and enhances the storage stability, improved bioavailability; reduce adverse effects and prolonged half-life. The SLN and NLC can be produced by different formulation techniques. Nanoparticles can be prepared from variety of materials such as proteins polysaccharides and synthetic polymers. Particle size and size distribution are the most important characteristics of nanoparticles. They play a vital role in size distribution, toxicity, drug loading and drug release. Lipase/collapse activity is affecting the drug release from lipid nanoparticles in the gastrointestinal track. The stability of lipid nanoparticles can be enhanced by matrix encapsulation. The lipid nanoparticles undergo digestion similarly to food lipids. Pharmacokinetic evaluations of lipid nanoparticles are very difficult and drug loaded lipid nanoparticles need to distinguish from released free form or as the related form. Lipid nanoparticles are widely used to improve oral bioavailability as well as the sustained release and also to overcome hepatic first pass metabolism. The lipids nanoparticles are effectively overcome the various problems linked with oral delivery. The lipid nanoparticles are used to overcome the problems like low solubility, poor permeability, unstable in the gastrointestinal track and undergo extensive first pass metabolism.

Dendrimers

They provide protection against molecular structure. The dendrimers have three different separate Dendrimers are hyper branched globular shaped particles having a unique three-dimensional architecture components such as;

- Core – The central dendrimer, which determines size & shape
- Branches – Tree like or Star shaped or generational structure
- Terminal functional groups – Generally located at the end and useful for the growth of dendrimer.

The dendrimers are used to increasing drug solubilization, enhancing gene and drug delivery and increasing the therapeutic effectiveness of any drug as well as providing targeting to specific site.[68-77] The advantages of dendrimers are monodispersing molecular structure and cross the biological barrier easily. But the major disadvantage is they are not suitable for parental as well as non- specific with variety of toxic cells. The type of polymers used in dendrimer production is triazine, melamine, PEG and carbohydrate based citric acid.

Characterization of dendrimers: There are many methods for characterization of dendrimers. For example, they are

- Ultraviolet-visible spectroscopy.[78, 79]
- Nuclear magnetic resonance.[80-83]
- Mass spectroscopy.[84-87]

The dendrimers play an important role in cancer therapy, photodynamic therapy as well as in solubilization and drug delivery. The dendrimers used in cancer therapy are diaminocyclohexyl platinum (2) and melphalan.

Metal and Metal Oxides of Nanoparticle

The various properties of gold nanoparticles make them in good conditions for therapeutic application. Functionalization of gold nanoparticles is possible by means of gold thiol covalent bonds, which allows for the conjugation of drug molecule to nanoparticle surface.[88] Release of the therapeutic cargo can be triggered by glutathione displacement. Gold nanoparticles may facilitate the delivery of antibiotics, anti-cancer agents and oligonucleotides for gene therapy.[88] Mesoporous silica and ZnO nanoparticles have porous coryamenance to drug loading. Drug release from the pores will be triggered by changes in p^H or by ultrasound.[89] Drug may also be loaded onto metal oxide nanoparticle surfaces by electrostatic interactions between positive charge drug and negative charge citrate surface on Fe_3O_4 magnetic nanoparticle. For example, such particles can be directed to a diseased site by an external magnetic field.[89]

Composite Nanoparticle Based System

Organic nanoparticle such as polymeric and liposome nanoparticles have good biodegradability and biocompatibility, while inorganic nanoparticles have various special properties. For example, magnetic liposome with incorporated RHBMP-2 was prepared and was evaluated in a rat bone defect model. The results show that the combined treatment of topical magnetic rhBMP-2 liposomes and magnetic implantation at injury site was more effective for the treatment of bone defects.[90] In the first step, a drug was released from PLGA nanoparticles, non- bioresorbable calcium phosphate remained the chief part of the particle. The average size was ranging from 65-95 mm. These composite nanoparticles proved to be an adequate system for local, sustained release drug.[91] This system also provides in vitro drug release studies showed that the efficient BMP release from this nanoparticle was maintained for more than 12 days under degradation conditions, and more than 90% of the loaded BMP was

released. No toxicity was found in the composite nanoparticle-based system.[92]

Other Nanostructure Material Based Systems

Other Nanostructures material-based systems are nanofibers, nanogels, nanotubes are also considered as nanoparticles.[93] These are different in functional and affiliate benefits when compared to spherical nanoparticles in case of bone marrow engineering drug delivery.

NANOFIBRES: These are the fibers with diameter less than 100nm used to improve the mechanical strength and architecture of bone tissue.[94] Nanofibers with high surface to volume ratio, high porosity merge with nanostructures and make themselves suitable for drug carriers. The release rate can be varied by changing the morphology, porosity, composition of nanofibers.[95] For example, BMP-2 was immobilized on a membrane surface made of chitosan nanofibers and half of the initial BMP-2 was attached to the membrane surface. This BMP-2-conjugated chitosan nanofiber membrane remarkably upgrades cell proliferation, alkaline phosphatase activity and calcium deposition showing remarkable and confined bone formation.[96]

Nanogel: It is a nanoparticle made of nano scale hydrogel with a network of hydrophilic polymer with diameter ranging 10-100nm. Drug is filled into nanogels with high drug loading capacity for its high surface to volume ratio and heterogenous nanostructure.[97] When they are chemically or physically crosslinked, it can overcome some problems like swelling, degradation and chemical action. Nanogels improve stability, release rate and decrease cytotoxicity in bone tissue engineering.[98] For example, cholesterol-bearing pullulan nanogel-crosslinking hydrogel (CHPA/Hydrogel) helps to transport BMP and embedded into the skull bone deficiency. So, the results show that osteoblastic activation and new bone formation should be persuaded in BMP stuffed nanogel.[99]

Nanotubes: It is a nanoparticle with nanometer-scale tube type nanostructures with a benefit over spherical nanoparticle appliances. Materials such as polymers, metals, and inorganic are used to falsify nanotubes.[100] Due to its unique nanostructure drug can be filled into the inner volumes and open-mouthed nanotubes make drug filling process easier.[101] For example, DEX was filled into the nanotubes and the results showed that the drug is effortlessly encapsulated into nanotubes and it also increases release rate for a longtime to boost up osteoblastic function.[102]

CONCLUSION

Nanotechnology was expected to bring a fundamental change in manufacturing in next few years and will have a huge impact on life sciences, including diagnostics, drug delivery, and nutraceuticals and in production of biomaterials. Nanotechnology is expected to have a revolutionary impact on medicine. Nanotechnology also creating a new smart devices and technologies where existing and more conventional technologies may be reaching their limits. It is reckoning to accelerate scientific as well as economic activities in medical research and development. To the further application of nanoparticles in pharmacy, it is important that the systems are stable, capable of being functionalized, biocompatible and targeted to specific target sites in the body after systemic administration. Finally, a dynamic collaboration is observed within the researchers, government, pharmaceutical-biomedical companies and educational institutions all over the world in developing nanotechnology applications in advanced medicine and patient care, it is surmise that the forthcoming generations of nanoproducts will have target specificity, may carry multiple drugs and could potentially release the payloads at varying time intervals. Further advances are needed in order to turn the concept of nanoparticle technology into a realistic particle application as next generation of drug delivery systems. Pharmaceutical education in India is also taking significant steps in incorporating courses as well as offering specialization in nanotechnology an its application in pharmaceutical scenario.

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