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Nanoparticulate drug delivery systems: A revolution in design and development of drugs

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Abstract

The recent developments in nanoparticle-based drug formulations have been helping to address issues around treating challenging diseases. Nanoparticles come in different sizes but usually vary between 100nm to 500nm. For the past few years there has been research going on in the area of drug delivery using particulate delivery systems. Various drug molecules have been modified for both pharmacokinetic and pharmacodynamic properties using nanoparticles as physical approach. Various polymers have been used in the formulation of nanoparticles for drug delivery research to increase therapeutic benefit, while minimizing side effects. Here, we review various aspects of nanoparticle formulation, characterization, effect of their characteristics and their applications in delivery of drug molecules and therapeutic genes.

Keywords: nanoparticles, applications in delivery, Liposomes, Dendrimers

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Introduction:

Use of nanoparticles has increased majorly for drug formulations and delivery since the last decade. Efforts are being put to monitor the efficiency of nanoparticles for targeted drug delivery applications. The average time and money spent for the development of a new chemical or biochemical entity are higher than that are needed to develop nanoparticle drug delivery systems[1]. On the other hand, safety, efficiency factors are improved by incorporating medicine into nanoparticles drug delivery systems along with patient compliance[2]. Majority of the latest therapies for cancer are based on nano particles approach which helps improve solubility and bioavailability of the drug at the site targeted. Due to increase in permeation the bioavailability also increases for nanoparticulated drugs especially for topically administered drugs, and so use of nanosuspensions for drug delivery has greatly increased in the recent years.

One of the main problems of drug discovery and development is developing drugs without any side effects to patients. Majority of the drug molecules are large organic molecules and are not soluble in water. So, a lot of effort has been put to nanosized the drug particles in an amorphous or crystalline nanosuspension for applications in passive targeting due to enhanced membrane diffusion[3]. Nanotechnology is a combination of manufacturing science which is advanced and engineering where nanometer scaled material is being used. There is an advantage of more surface to volume ratio for a nanosized particles compared to bulk material. Nanoparticles also proved to have wide applications in various fields like agriculture to medicine.

Nano-sized inorganic particles of either simple or complex nature, display unique, physical and chemical properties and represent an increasingly important material in the development of novel nanodevices which can be used in numerous physical, biological, biomedical and pharmaceutical applications [5,6,7].

Different types of Nanoparticles:

Liposomes:

Liposomes are the first ones to be investigated as drug carriers. Liposomes are of 80 to 300 nm size . They are spherical vesicles contained of phospholipids and steroids. Liposomes are proven to have increased the solubility of drugs and also improve pharmacokinetic properties like therapeutic index of chemotherapeutic agents, rapid metabolism, lower side effects and also increased in vivo and in vitro anticancer activity[4]. For liposomes with size greater than 100 nm, as the size increases clearance rate by mononuclear phagocytic system increased. Liposomes that are multifunctional and containing specific antigens, proteins, biological substances could be used to design drugs

that act at specific tissue. For targeted drug delivery therapy, it is most promising type of drug delivery.

Encapsulation process is used to incorporate drug into liposomes. pH, composition of liposome, osmotic gradient, and environmental conditions regulate the release of drug from liposomes[4]. Lipid transfer, fusion, adsorption realize the interaction of liposomes with cells. Anticancer drugs[4], antibiotics[5,6], anti-inflammatory and anti-rheumatic drugs[7,8] are the drugs with liposomal formulations. Even with long history of investigation liposomes haven't made a significant impact yet. They are being extensively used in cosmetic products. Dior has first prepared the formulation in 1986.

Polymeric nanoparticles:

Nanoparticle structures with diameter ranging from 10 to 100 nm are polymeric nanomaterials. Synthetic polymers like poly e-caprolactone, polyacrylamide, or natural polymers [9,10,11] like Chitosan [12], gelatin[13] are used to obtain Polymeric nanoparticles. Polymeric nanoparticles are further classified as biodegradable and nonbiodegradable. In order to lower immunological and intramolecular reactions between surface chemical groups polymeric nanoparticles are usually coated with nonionic surfactants.

Food and drug administration of US has approved biodegradable polymeric nanoparticles like PLA and PLGA. They are formulated in a way that they are able to encapsulate several low molecular weight compounds[14]. Polymeric nanoparticles are more useful in regard to biocompatibility and biodegradation profiles, when chronic dosing is needed in formulations. One downside of polymeric nanoparticles is that large scale manufacturing and production is an issue. By using a double emulsion solvent evaporation system using oil and water with vinyl alcohol PLGA nanoparticles are formulated as an emulsifier [15,16].

Solid Lipid Nanoparticles:

Solid lipid nanoparticles are first designed in 1990s and are utilized as an alternative for emulsions and liposomes. In biological systems Solid Lipid nanoparticles are more stable than liposomes because of their rigid core that consists of hydrophobic lipids which are solid at room temperature. By including high level of surfactants these aggregates are further stabilized. Solid lipid nanoparticles are less toxic as they are biodegradable. They can be designed with 3 types of hydrophobic designs, and they have pharmacokinetic parameters which can be controllable. These three designs are a drug enriched shell, a drug enriched core and a homogenous matrix. SLNPs could be used to deliver drugs by inhaling, topically and orally. Particles of SLN are made of solid lipids that are like highly purified triglycerides, complex glyceride mixtures or waxes stabilized by various surfactants[17]. Nanostructured lipid carriers and Lipid drug conjugates are modifications of lipid based nanoparticles that have been developed to overcome limitations of conventional SLN. By combining liquid lipids with solid lipids nanostructured lipid carriers are formed and as a result special nanostructured lipids are formed for which payload and prevented drug expulsion have increased. There are 3 types of NLCs, imperfect type, multiple type, and amorphous type NLCs.
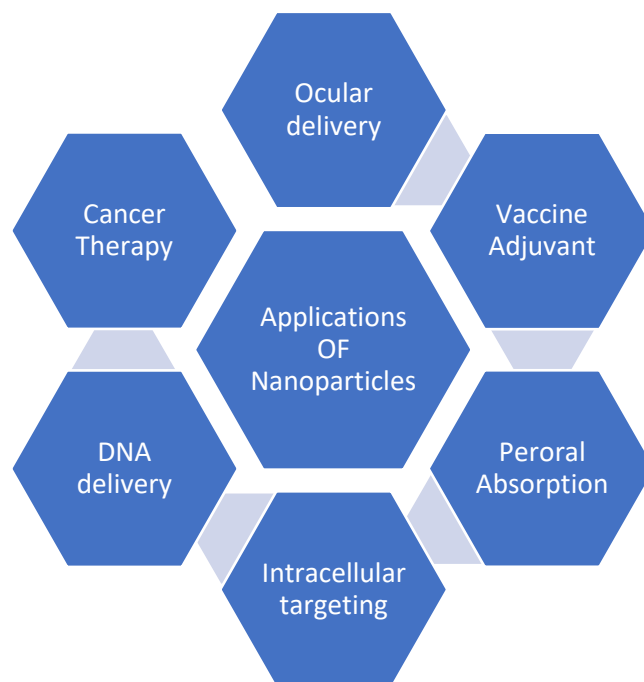

Figure 1: Applications of nanoparticles

Dendrimer nanocarriers:

Dendrimer nanoparticles are unique polymers which has well defined structure and size. Some of the dendrimer nanocarriers are glycogen, amylopectin etc., Dendrimer can do multiple jobs like solubility enhancement, drug targeting. Dendrimers can be used using different routes of drug delivery oral, parenteral, nasal and intra ocular. Dendrimers can also behave like vectors in gene therapy. These 3D tree like branched molecules contain some good characteristics like narrow molecular weight distribution, and 3D structure tuned by dendrimer generation and dendron structure, and flexibility for tailored functional groups with high density on the periphery.

Carbon nanotubes:

Carbon nanotubes are first discovered in 1991.Multi walled nanotubes are prepared by pyrolysis of metallocene's like ferrocene, cobaltocene, and nickelocene under reducing conditions. Single-walled carbon nanotubes (SWNT) were prepared in a related approach using dilute hydrocarbon–organometallic mixtures.70,71 Interestingly, pyrolysis of nickelocene in the presence of benzene at 1100 "C yields primarily MWNT. In contrast, pyrolysis of nickelocene in the presence of acetylene yields primarily SWNT, presumably due to the smaller number of carbon atoms per molecule.

Silica nanoparticles: Sol-gel methods are used to prepare silica nanoparticles. Researcher[18] had demonstrated an efficient co condensation process to monodisperse silica nanoparticles. Apart from this several other methods are described and proved to prepare silica nanoparticles like organic aqueous biphasic system described by Tan group[19.] MCM-41 is a mesoporous silica nanoparticle, which is usually synthesized using sol-gel processes with the presence of surfactant like C12-trimethylammonium bromide versus C16-trimethylammonium bromide, to control pore sizes.

Table 1: Different types of nanoparticle carriers for drug delivery, their structures and characteristics

Type of nanocarrier	Structure	Characteristics
Polymeric nanoparticles	Drugs are attached with a linker to the sides of linear polymer chain	These are water soluble, biodegradable and nontoxic. These type of nanoparticle drugs can target specific cells that has issue, leaving the normal cells out. They are capable of accumulating and being retentive in the tumor.
Dendrimers	Synthetic polymers with units that are repetitive and of regular pattern, which are radially emerging.	There type of nanoparticle drugs are useful in controlled degradation, high structural and chemical homogeneity, and are multifunctional
Liposomes	They are self-assembled structures composed of lipid bilayers	These type of nanoparticle drugs are easy to modify, and are capable of targeting potential areas, and they are biocompatible and amphiphilic.
Carbon nanotubes	Their structure is composed of benzene ring and carbon cylinders.	These types of drugs are water soluble and biodegradable through chemical modification and are multifunctional.
Viral nanoparticles	They contain self-assembled structures that are multivalent	They are capable of targeting specific tumor and are multifunctional. They are uniform and have defined geometry. They are also biologically compatible and are inert in nature.

Synthesis of nanoparticles:
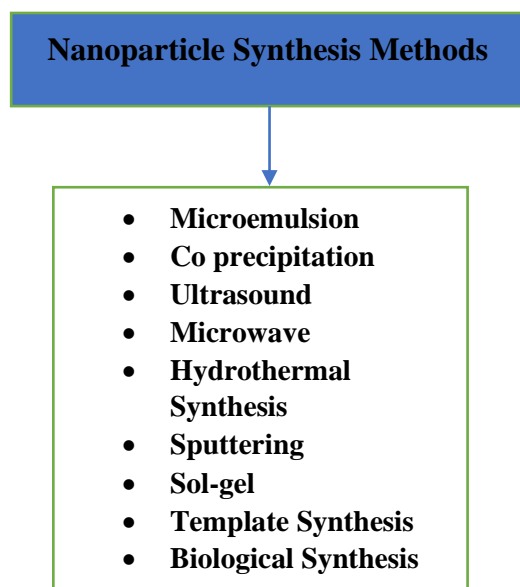
Figure 2: Nanoparticle Synthesis Methods

a. **Chemical reduction:** One of the most commonly used methods to synthesize nanoparticles is chemical reduction of organic and inorganic reducing agents like sodium citrate, hydrogen, tollens reagent, sodium borohydride.

b. **Sol-Gel Process:** Wide different types of materials are used for the synthesis of nanoparticles in the method. Metal oxides like organic, inorganic, metal alkoxide are dissolved to form sol. Once sol in formed and dried a polymer network is formed in which solvent molecules are trapped inside the solid. This is called, gel, and it is dried by calcinations to form the final product.

c. **Polymerization:** In this process nanoparticles are formed by polymerizing monomers in an aqueous solution. Incorporation of drug is being done by either dissolving in the polymerization medium or after polymerizations is completed adsorption of nanoparticles is done. This nanoparticle suspension is purified to remove surfactants and stabilizers. This

technique is used for making polybutylcyanoacrylate or poly (alkyl cyanoacrylate) nanoparticles [20,21].

d. **Hydrothermal technique:** In hydrothermal synthesis technique synthesis is done by chemical reactions of substances in a heated environment. For single nano crystals formation synthesis is done by solubility of minerals in hot water under high pressure. Autoclave is used which contains steel pressure vessel and using this crystal growth is performed.

e. **Microemulsion:** For the synthesis of inorganic nanoparticles microemulsion is quite frequently used. Some researchers also suggested ways to synthesis nanoparticles withing the microemulsion. When the water droplets in the microemulsion collides the reactant exchange happens for microemulsion material like reactants. This reaction exchange is quite fats and precipitation reaction happens in nanodroplets, which in turn is followed by nucleation growth and coagulation of primary particles, that results in nanoparticle formulation.

Characteristics of Nanoparticles, and their effects on Drug Delivery:

Particle size: Particle size is an important factor in deciding nanoparticle characteristics. They decide toxicity, fate biologically and ability of targeting in nanoparticle systems. Along with that they could also affect drug loading, release rate of drug and stability of nanoparticles. Many research studies have proved that nanoparticles of sub micron sized have more uses than microparticles[22]. Intracellular uptake is more in nanoparticles than microparticles and are available to wide range of targets as they are relatively smaller in size and more mobile. It was found in the research that nanoparticles of 100nm had an uptake which is 2.5 times greater than 1μm microparticles. And the uptake is 6 times greater than 10μm microparticles[23]. In another study it was proved that nanoparticles penetrated through submucosal layers in rate in situ intestinal loop model, while microparticles are local to epithelial lining[24]. Nanoparticles that are tween 80 coated have crossed the blood brain barrier. Compared to microparticles some cell line submicron nano particles can be consumed efficiently.

Particle size will have affect on drug delivery. Particles of small size will have large surface area, and major part of the drug associated would be at or near the particle surface, which leads to fast drug release. On the other hand, particles of large size will have large cores which allow drug to be encapsulated and leads to slow diffusion of drug[25]. During the nanoparticle dispersion, transportation and storage smaller particles have greater risk of aggregation. It is difficult to formulate nanoparticles in small size but with good stability. The most commonly used routine method used to determine particle size is photon correlation spectroscopy or dynamic scattering. Viscosity of the medium is necessary to be known in order to determine the diameter of particle.

Surface properties of nanoparticles: Nanoparticles are determined easily by immune system of body when they are administered and are cleared by phagocytes for the circulation[26.] The amounts of proteins adsorbed are determined by size of nanoparticles and their surface hydrophobicity, and in vivo fate of nanoparticles is influenced by this.[27]. The process of binding opsonin to nanoparticles surface is called opsonization and it acts as bridge between phagocytes and nanoparticles.

In order to increase the success rate of nanoparticle-based drug targeting, it is important to lower the opsonization and to extend the nanoparticle circulation in vivo. This process can be achieved by:

- Nanoparticles surface coating using hydrophilic polymers and surfactants.
- Formulation of nanoparticles with biodegradable copolymers with PEG, poloxamer, poloxamine and polysorbate 80.

Drug Loading:

Drug loading capacity is one of the important factors of a successful nanoparticle drug delivery system. Drug loading capacity needs to be high, and that helps reduce the amount of matrix materials needed for administration. Drug loading can be achieved by two methods:

- One method is incorporation method in which drug is incorporated at the time of nanoparticle production
- Drug absorption after nanoparticles are formed by incubating the carrier with a concentrated drug solution, which is called absorption technique.

Drug loading and entrapment efficiency depend on solid state drug solubility in polymer which in turn relates to the drug polymer interactions and molecular weight.

Drug Release:

Drug release is an important factor for a successful nanoparticulate drug delivery system. Usually drug release depends on two factors

- Solubility of drug
- Desorption of the surface drug
- Diffusion of drug through nanoparticle matrix
- Combination of erosion/ diffusion process

When it comes to nanospheres drug will be uniformly distributed and the release happens by erosion of the matrix under sink conditions. If the matrix erosion is slower than drug diffusion, release mechanism is controlled by a diffusion process.

Nanoparticulate Drug delivery systems and applications:

Recently several articles have been published both research and review on nano vehicular intracellular drug delivery systems, one of them includes an article published by Prokop and Davidson[29]. This article includes several aspects of nanodrug delivery systems and their use in biological systems at cellular levels. Various nano systems and their applications has been reviewed. Another researcher has discussed the role of nanotechnology in drug design in a detail way with several drugs and references[30]. Nanoparticles based drug delivery systems and their treatment towards chronic pulmonary disease has been explained in[31]. With all these research studies it was proved that nanoparticulate drug delivery systems show a promising approach to achieve desired drug delivery properties by modifying pharmacokinetic properties. Authors Gupta and Moulik has given a detailed description on nano emulsions[32]. To overcome diseases that are cause through genes, it is good to combat the root cause rather than treating the disease, and gene therapy for it is a promising strategy[33]. Researchers[34] have discussed need for non toxic and efficient gene delivery vectors in nano lipoplex gene delivery.

Liposomes offer good option for delivering chemotherapeutic agents. In addition to that micelles are also great to make insoluble drugs soluble as they have hydrophobic core. Several different forms of nanoparticles have shown good progress in treating cancer, and one of them was carbon nanotubes. It is carbon in allotropic form with framework in cylindrical framework. They are classified into single walled carbon nanotubes and multiwalled depending on the number of sheets in concentric cylinders. Drug can be loaded easily into carbon nanotubes as they have hollow interiors. Use of nanoparticles in diagnostic testing has been explored widely in the recent years [35], as the current technology that has been use for this is hindered by inadequacies of fluorescent markers like fluorescence fading after single use, dyes and restricted usage. Nanoparticles provide good use to overcome these problems. Recently theranostic nanoparticles have gained lot of attention for diagnostic reasons. The primary reasons of stokes are vascular diseases like atherosclerosis and hypertension[36-41]. For the diagnosis and detection nanoparticles have been used for atherosclerotic plaques. Same kind of targeting strategies are used to deliver therapeutic agents to these plaque. Identifying the disease at early stages and intervening it may prevent the worst outcomes that may lead to plaque rupture and thrombosis.

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