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Nanoparticle in Pharmaceutical Drug Delivery System: A Review

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ABSTRACT

The most emerging branch in pharmaceutical sciences is "nanotechnology." Nanopharmaceuticals comprised of nano- sized products which can be transformed in numerous ways to improve their characteristics. Nanoparticles reveal enormous potential in tissue engineering, carriers in drug delivery, understanding of basic biological processes, imaging, sensing, disease diagnostics and therapeutics. Application of nontechnology in drug delivery and medicine has paved new pathways and opened many doors for providing customizable and safer treatment option. There are significant advantages of nanoparticles which make them more potential and effective than the conventional drug delivery system in terms of high stability, high specificity, high drug carrying capacity,ability for targeted release, controlled delivery, possibility to use in different route of administration and the capability to deliver both hydrophilic and hydrophobic drug molecules, site specific targeting. Nanomaterials like polymeric nanoparticles, magnetic nanoparticles, liposomes, carbon nanotubes, quantum dots, dendrimers, metallic nanoparticles, polymeric nanoparticles, etc. have brought about revolutionary changes in drug delivery systems and in many other fields. So that, through the manipulation of molecular size and surface properties, researchers are able to deliver drugs for longer period of time with less frequent dosing and with greater precision and penetration in difficult to access tissues.The present chapter summarizes the types of nano pharmaceuticals with the properties, characterization and methods of preparation, advantages, and applications of nanoparticles in pharmaceutical and medical sector.

Keywords: Nanotechnology, Nanoparticles, Preparation, Characterization, Applications.

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INTRODUCTION

The emergence of nanoscience and nanotechnology, which is creation and utilization of materials and tools at the nanometer scale,has been a great influence on a number of industries and particularlythe pharmaceutical industry. Nanotechnology is a known field of research since last century. Delivering therapeutic compound to the desirable site is a major problem in treatment of many diseases. Conventional utilization of drugs is characterized by poor biodistribution, limited effectiveness, undesirable side effects, and lack of selectivity. Controlling drug delivery can potentially overcome these limitations by transporting drug to the place of action, so the drug delivery system provides protection against rapid degradation or clearance. It also enhances drug concentration in target tissues; therefore, lower doses of drug are required. Size reduction of targeted formulation and designing a suitable drug delivery system is a more fundamental and successful approach of nanotechnology. (1)

Recent discovery in nanotechnology has proven that nanoparticle has a great potential as drug carriers. Size reduction methods and technologies yields different types of nanostructures that exhibit unique physicochemical and biological properties which enhance the performance in various dosage forms. The important factor of nanoparticle is that the size can influence the physiochemical properties of a substance. These nanoparticles showed characteristic colors and properties with the variation of size and shape, which can be utilized in bioimaging applications. (2) Nanotechnology is a multi-disciplinary scientific field applying engineering and manufacturing principles at the molecular level. Nanoparticles are solid, colloidal particles with size range from 10 nm to <1000 nm; however, for nanomedical application, the preferential size is less than 200 nm. "Nano" word is originated from Latin word, which means dwarf. Ideal size range offered by nanotechnology refers to one thousand millionth of a particular unit thus nanometer is one thousand millionth of a meter (i.e. 1 nm = 10 −9 m). Nanoparticless are not simple molecules itself and therefore composed of three layers i.e. (a) The surface layer,

which may be functionalized with a variety of small molecules, metal ions, surfactants and polymers. (b) The shell layer, which is chemically different material from the core in all aspects, and (c) The core, which is essentially the central portion of the nanoparticle and usually refers the nanoparticle itself. [3] In this review article, we aim to focus on different types, advantages, preparation, characteristics and applications with future scope of nanoparticles.

VARIOUS TYPES OF PHARMACEUTICAL NANOSYSTEMS

There are many types of nanoparticles platforms with differing size, shape, compositions, and functions. They are mentioned below.

1. Liposomes

Liposomes are spherical vesicles that contain a single or multiple bilayered structures of lipids that self-assemble in aqueous systems. Their size ranges from 50-100 nm.Advantages of liposomes are their diverse range of compositions, abilities to carry and protect many types of biomolecules, as well as theirbiocompatibility and biodegradability.They also have good entrapment efficiency. They are long circulatory, offer passive and active delivery of gene, protein and peptide can also be functionalized with targeting ligands to increase the accumulation of diagnostic and therapeutic agents within desired cells. [1]

2. Solid lipid nanoparticles

The use and scope of solid lipid nanoparticleis increasing day by day in pharmaceuticals because it represent an alternative and suitable system to traditional colloidal carriers such asemulsions, liposomes and polymeric micro andnanoparticles. They have size 50–1000 nm. [4] They are made up of solid lipids (high melting fat matrix), are developed to conquer the weaknesses such as polymer degradation and cytotoxicity, lack of a suitable large scale production method, inferior stability, drug leakage and fusion, phospholipid degradation, high production cost, and sterilization problems) their aim is to provide biocompatibility, storage stability and to prevent the incorporated drug from degradation. [5] The solid core of solid lipid nanoparticle is hydrophobic with a monolayer coating of phospholipids and the drug is usually dispersed or dissolved in the core. Widely used in targeted brain drug delivery, anticancer drug delivery, topical use, cosmetics, anti-tubercular chemotherapy, adjuvant for vaccines. [6]

3. Carbon nanotubes

They are cylindrical molecules which having size of 0.5–3 nm indiameterand20–1000 nm inlength. Third allotropic crystallineform of carbon sheets either single layer or multiplelayer nanotube. They haveremarkable strength andunique mechanical, thermal and electrical properties(conducting, semi conducting,or insulating). Their functions are enhanced solubility, penetration to cell cytoplasm and to nucleus, as carrier for gene delivery, peptide delivery. They are used as diagnostic tool in cancer at their early stage. [7]

4. Dendrimers

Dendrimers arebranched macromolecules made up of synthetic or natural elements including amino acids, sugars, and nucleotides.They have a central core, interior layers of branches, and an exterior surface. They are highly branched, nearly, monodisperse polymer system produced by controlled polymerization. Small molecules in the cavities of the cores are loaded in dendrimersthrough chemical linkage, hydrogen bond, and or hydrophobic interaction. They have size <10 nm. They are useful incontrolled delivery of bioactives, targeted delivery of bioactives to macrophages and liver targeting. [1]

5. Polymeric nanoparticles

Polymeric nanoparticles are formulated through block-copolymers of different hydrophobicity.These copolymers spontaneously assemble into a core-shell micelle formation in an aqueous environment. They are biocompatible and biodegradable. They are especially formulated to encapsulate hydrophilic and/or hydrophobic small drug molecules, proteins and nucleic acid macromaoleculesans offer complete drug protection. They have particle size 10-1000 nm. Excellent carrier for controlled and sustained delivery of drugs, stealth and surface modified nanoparticles can be used for active and passive delivery of bioactives. [8]

6. Polymeric micelles

Polymeric micelles are nanosized core/shell structures formed by amphiphilic block copolymers. They have particle size 10-100 nm. The properties likehigh drug entrapment, payload, biostability, small size, unique nanoscopic architecture, enhance the solubilization of poorly soluble molecules and ability of block copolymer micelles to be tailored for good compatibility with the drug of choice are all highly desirable properties for a drug delivery system. [9]

7. Metallic nanoparticles

Metallic nanoparticles such as iron oxide, gold and silver nanoparticles, nanoshells, and nanocages have been continuously used and modified to enable their use as a diagnostic and therapeutic agent. Generally it has particle size <100. [8]

Gold nanoparticles

Gold Nanoparticles Colloidal gold, also known as gold nanoparticles, is a suspension (or colloid) of nanometer-sized particles of gold. Gold nanoparticles offer many size and shape dependent optical and chemical properties, biocompatibility, and facile surface modification. Gold NPs can strongly enhance optical processes such as light absorption, scattering, fluorescence, and surface-enhanced Raman scattering (SERS) due to the unique interaction of the free electrons in the NP with light. Their probes are used to detect cancer biomarkers and heart diseases and have various biomedical and therapeutic applications. [10]

8. Iron Oxide Nanoparticles

Iron (III) oxide (Fe_2O_3) nanoparticle is a mangnetic nanoparticle in reddish brown, inorganic compound which is paramagnetic in nature and also one of the three main oxides of iron, while other two being FeO and Fe_3O_4. Due to their ultrafine size, magnetic properties, and biocompatibility, paramagnetic iron oxide nanoparticles are potentially used in various biomedical applications, such as enhanced resolution contrast agents for MRI, targeted drug delivery and imaging, hyperthermia, gene therapy, stem cell tracking, molecular/cellular tracking, magnetic separation technologies. [10]

9. Quantum dots

Quantum dots are semiconductor particles that are 2- 10 nm in diameter. Technically they are 'small crystals containing a variable number of electrons that occupy well-defined, discrete quantum states and have electronic properties intermediate between bulk and discrete fundamental particle. They consist of semiconductor core, over coated by a shell, and a cap enabling improved solubility in aqueous buffers. Quantum dots are used in multitasking purposes such as medical diagnostics, drug delivery andgene

therapy.Toxicity is a major obstacle when considering quantum dots for various biomedical applications. [11]

PROPERTIES OF NANOPARTICLES

- Decrease drug resistance
- Decrease toxicity
- Increase oral bioavailability
- Enhance rate of dissolution
- Enhance solubility
- Increase the stability of drug and formulation
- Increase drug targeting ability
- Decreased patient-to-patient variability and increase patient compliance
- Increase surface area
- Less amount of dose required [8]

CHARACTERIZATION OF NANOPARTICLE DRUG FORMULATIONS

Nanoparticles can enter the human body, via three main route, direct injection, inhalation and oral intake. If something is recognized as foreign, macrophages will engulf and clear it from the body. This tends to be the struggle with nanoparticle based drug delivery; however, clearance can be influenced by the size and surface characteristics of particles, which is discussed in following subsection.

Surface Charge

Surface charge and intensity determines the interaction of nanoparticles with the biological environment as well as their electrostatic interaction with bioactive compounds. Stability of colloidal material is usually analyzed through zeta potential of nanoparticles. Zeta potential is an indirect measure of the surface charge. [8]

Surface properties

In order to create an optimum nanoparticle drug delivery system, the incorporation of appropriate targeting ligands, surface curvature and reactivity is important to address the prevention of aggregation, stability, and receptor binding and subsequent pharmacological effects of the drug. Surface properties primarily detect the agglomeration state of particles and colloidal properties therefore their effective size, especially under physiological conditions. [12]

Drug loading capacity and release

The size and surface properties of nanoparticles have been explored to optimize bioavailability, decrease clearance, and increase stability. By controlling these characteristics, it is possible to get the drug to tissues in the body. However, this whole practice is useless if the drug cannot then be released from the nanoparticle matrix. Depending on the type of nanoparticle being used, the release of drug will differ. The release of drug from the nanoparticle-based formulation depends on many factors including, pH, temperature, drug solubility, desorption of the surface-bound or adsorbed drug, drug diffusion through the nanoparticle matrix, nanoparticle matrix swelling and erosion. Various techniques such as UV spectroscopy or high performance liquid chromatography after ultracentrifugation, ultra filtration, gel filtration, or centrifugal ultrafiltration are used to determine this parameter. [13]

Particle size

As particles size gets smaller, their surface area to volume ratio gets larger. This would imply that more of the drug is closer to the surface of the particle compared to a larger molecule. Being at or near the surface would lead to faster drug release. The shape and size of nanoparticles affects how cell in the body react to them and thus dictate their distribution, toxicity, and targeting ability. [3]

Table 1: Various methods and characterization tools for nanoparticles. [8]

S.N.	Parameter	Characterization method
1	Carrier-drug interaction	Diffential scanning calorimetry
2	Charge determination	Laser Doppler Anemometry & Zeta potentiometer
3	Chemical analysis of surface	Static secondary ion mass spectrometry & Sorptometer
4	Drug stability	Bioassay of drug extacted from Nanoparticles& Chemical analysis of drug
5	Nanoparticle dispersion stability	Critical flocculation temperature (CFT)
	Particle size and distribution	Atomic force microscopy Laser defractometry Photon correlation spectroscopy (PCS) Scanning electron microscopy Transmission electron microscopy
6	Release profile	In vitro release characteristics under physiologic and sink conditions
7	Surface hydrophobicity	Rose Bengal(dye) binding Water contact angle measurement X-ray photoelectron spectroscopy

METHODS OF PREPARATION OF NANOPARTICLES

The selection of appropriate method for the preparation of nanoparticles depends on the physicochemical properties of polymer and drug to be loaded. Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides, lipids, natural and synthetic polymers. Selection of matrix material is depends on following factors. [8]

- Surface characteristics (charge and permeability)
- Aqueous solubility and stability of the drug
- Size of nanoparticles required
- Biocompatibility and toxicity
- Antigenicity of the final product
- Drug release profile desired
- Degree of biodegradability

1) Solvent Emulsification-Evaporation Method

This method involves two steps. First step is emulsification of the polymer solution into an aqueous phase and second step is evaporation of polymer solvent, inducing polymer precipitation. This method is based on the solubility of polymer and hydrophobic drug since both polymer and

hydrophobic drug are dissolved in an organic solvent. Mixture obtained from polymer and drug solution is then emulsified in an aqueous solution. This aqueous solution contains surfactant or emulsifying agent to form oil in water (o/w) emulsion. [15] Under appropriate conditions, the subsequent evaporation of the organic solvent by continuous stirring or reducing the pressure induces polymer aggregation in the form of nanoparticles. In order to produce small particle size, ultrasonication or high-speed homogenization may be often employed. Drugs with lipophilic characteristics are then incorporated into the organic phase. [16] Purification stages can be performed by recovering polymer nanoparticles by ultracentrifugation and consecutive washes with distilled water to remove the stabilizer and release the drug. [17]

2) Emulsification-Diffusion Method

Emulsification-Diffusion Method thermodynamic principles that involve, firstly, the use of partially water-miscible solvents in equilibrium with another immiscible solvent, generally water (saturation). This step is performed to avoid mass transference during the process. [18] In general, the method consists of preparing a conventional oil-in-water emulsion (1:2).The internal organic phase includes preparing the drug or drugs for encapsulation and the polymer, both dissolved in the water-saturated solvent. The external aqueous phase consists of one or more hydrophilic stabilizers dissolved in the solvent-saturated water. The emulsion is formed conventionally by adding the organic phase into the aqueous phase under mechanical stirring.

The diffusion can be performed by using two ways. The first is fast diffusion by dilution with water. In this case, the amount of water required should be sufficient to dissolve the inner-organic phase while the second comprises rapid displacement of the solvent from the internal into the external phase by evaporation under reduced pressure, depending on the boiling point of the solvent. Sometimes this modality is denominated "emulsification-solvent displacement." In both cases, the presence of a nonsolvent medium gives rise to polymer aggregation in nanoparticles if the stabilizing effect is suitable. [19]

This technique provides several advantages, such as

- High encapsulation efficiencies (generally 70 %)
- No need for homogenization
- Highbatch-to-batch reproducibility
- Ease of scale-up
- Narrow size distribution [20]

3) Double Emulsion and Evaporation Method

Double emulsion also termed as emulsion of emulsion, are complex system, in which the dropletsof dispersed phase themselves comprises even small of dispersed phase. Double emulsion (DE) droplets are mostly polydispersed in size. To overcome the limitation ofpoor entrapment of hydrophilic drugs double emulsion technique is employed. There are two common types of double emulsion; water-oil-water (w/o/w) and oil-water-oil (o/w/o).[21] This involves the addition of aqueous drug solutions to organic polymer solution under vigorous stirring to form w/o emulsions. This w/o emulsion is added into second aqueous phase with continuous stirring to form the w/o/w emulsion. The solvent removal in emulsion is done by evaporation and nano particles can be isolated by centrifugation at high speed. The stability and release properties of double emulsions can be greatly improved by a change in the type and concentration of stabilizer employed in the system. Such systems are biocompatible, biodegradable and versatile with respect to different oils and emulsifiers being employed. Both hydrophobic and hydrophilic kinds of drugs can be protectively encapsulated separately and simultaneously. Some limitations are also linked with this technique are large and non-uniform particles (polydisperse), two step process, leakage of the hydrophilic active into external aqueous phase, difficult to scale up. [22]

4) Solvent Displacement/Precipitation Method

The solvent displacement method is a convenient, reproducible, fast, and economic one-step manufacturing process for the preparation of monodisperse, polymeric nanoparticles in a size range of approximately 50–300nm. This method is more suitable for poorly soluble drugs. This technique requires the use of amphiphilic organic solvents that are completely miscible with water, for example acetone. Progressive addition of polymer dissolved in acetone to an aqueous phase under stirring leads to the formation of colloidal particles. This step is followed by the removal of solvent from the suspensions under reduced pressure. [23] Particles size is dependent on the extent of addition of the organic phase into the aqueous phase. It was also found that as the mixing rate of the two phase increases, particles size and drug entrapment decreases. Regulating the concentration of polymer in the organic phase was reported to be useful in the production of smaller sized nanospheres. [20]

5) Coacervation or Ionic Gelation Method

Inotropic gelation technique was first reported by Calvo and has been widely examined and developed by Janes. Biodegradable polymers such as gelatin and sodium alginate have been focused now to yield biodegradable nanoparticles having features like biocompatibility and low toxicity. Chitosan can be dissolved in acetic acid in the absence or presence of stabilizing agent, such as poloxamer, which can be added in the chitosan solution before or after the addition of polyanion. [24] Polyanion or anionic polymers was then added and nanoparticles were spontaneously formed. Coacervates are formed by existence of strong electrostatic interaction between two aqueous phases. In contrast ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature.[25] This method has some limitations such as defects such as improper surface morphology, fragile particulate system, high dispersibility index and lack of proper surface modification sites to attach functional moieties. [26]

6) Supercritical Fluid Technology

The methods mentioned above use organic solvents which are hazardous to the environment as well as to physiological systems. Therefore, there is requirement of suitable technology which avoid the usage of organic solvents or any other ingredient hazardous to health. The supercritical fluid technology has been investigated as an alternative to prepare biodegradable micro- and nanoparticles and it is environmentally safe.Supercritical fluid technologyreplaces organic solvents in a number of chemical processes. Supercritical fluids are those fluids which are at a temperature above its critical temperature remains in a single phase regardless of pressure. [27] CO_2($SCCO_2$) is the most widely used supercritical fluid because of its mild critical conditions, non-flammability, low price and nontoxicity.However, in recent years the materials processing which covers all the set of processes is being carried out using not only the scH2O or scCO2, but also supercritical ammonia, supercritical amines, supercritical alcohols, etc. SCF technology produces nanoparticles with

solvent levels below 25 ppm. There are several variants in SCF technology like static supercritical fluid process (SSF), rapid expansion of supercritical solutions (RESS), particles from gas-saturated solutions (PGSS),supercritical antisolvent process (SAS), supercritical fluids drying (SCFD), supercritical fluid extraction emulsions(SFEE),etc. [28]

APPLICATIONS OF NANOPARTICLES IN PHARMACEUTICAL DEVELOPMENT AND DRUF DELIVERY SYSTEM

1) Nanoparticles for Gene Delivery

Gene therapy is an approach of treating disease by either replacing a defective gene or modifying the expression of a gene by introducing genetic material/DNA into the cells. Nanoparticles emerged as the most promising vehicles for clinical gene therapy due to their size, shape, surface, and biological behaviors. Gene therapy has drawn significant attention as a promising strategy for specific treatment of numerous gene-associated human diseases ranging from cancer, hemophilia, hypercholesterolemia, neuro-degenerative diseases to autoimmune diseases. This strategy is to introduce genes into the target pathological tissues or cells by altering the expression of the endogenous genes to cure or prevent the progression of the related disease. [29] The challenges in gene delivery are encapsulation efficiency, stability of nanoparticles, degradation in blood circulation and endocytosisby target cells, endosomal escape, delivery efficiency, and toxicity of pharmacology. To overcome these obstacles, many types of nanoparticles have been evaluated as gene carriers, which include lipid-based nanoparticles, polymer-based nanoparticlesand inorganic nanoparticles. The recent example of polynucleotide vaccine producing the antigenic protein within the vicinity of professional antigen presenting cells to initiate immune response.Polynucleotide vaccines are composed of a key ingredient called as DNA can be produced economically and has much better storage and handling properties than the ingredients of the majority of protein-based vaccines. [30]

2) Nanoparticles for Drug Delivery into the Brain

One of the most challenging obstacles for an effective treatment of CNS related disorders is the low efficiency penetration of drugs to CNS due to the presence of the BBB. The BBB is a dynamic barrier which protects the brain against invading organism and unwanted substances. Small hydrophilic compounds with a mass lower than 150 Da and highly hydrophobic compounds with a mass lower than 400–600 Da are able to cross the BBB by passive diffusion.To achieve this, formation of nano sized particle is important. Nanoparticles should be non-toxic, biodegradable and biocompatible, non-inflammatory and non-immunogenic. [31] There are no effective therapies for many diseases include neurodegeneration(e.g., amyotrophic lateral sclerosis, Alzheimer's, Parkinson's, Huntington disease, and Prion disease), genetic deficiencies and several types ofbrain cancer.Nanotechnology has shown to be useful toolfor crossing the BBB, a key aspect for an effective treatment of neurodegenerative disorders, offering a brain target delivery and a sustained release profile. [32]

3) Nanoparticles for targeted imaging

Molecular imaging refers to the development of molecular probes for the visualization of the cellular function, characterization and the measurement of molecular processes in living organisms at the cellular and molecular level without perturbing them. On conjugation with tumor targeting ligands (e.g., peptides, small organic molecules, antibodies, etc.), nanoparticles can be successfully used as tumor-specificprobes with high specificity. Emerging nanoparticle technologiesare joined by intense development of imaging modalities to assist with disease detection. [33] Particle charge, size, shape and hydrophilicity remain among the most important properties of nanoparticles for effective delivery to the desired target. Nanomaterialssuch as gold nanoparticles, quantum dots, iron oxide nanoparticles and dendrimers are widely used in biomedical imaging applications. Utilization of gold nanoparticles as ultrasensitive fluorescent probes to detect cancer biomarkers in human blood is highly sensitive approach and direct detection of viral or bacterial DNA is possible. Metallic nanoparticles possess immense potential as X-ray contrast imaging agents owing to their potent X-ray absorption and low toxicity profiles observed over short durations in animals. [34]

4) Nanoparticle delivery to subcellular organelles

Targeting of the drug to cells or tissue of choice is the potential area in drug delivery. In delivery systems targeting is the ability to direct the drug-loaded system to desirable site. Targeted nanoparticles can bind to targets situated on the cell surface and enter the cell through endocytosis. There are two mechanisms involved in this process. [8]

1) Passive targeting of nanoparticles to a particular organelle by varying characteristicsof nanoparticles such as size, shape, and composition. In passive targeting ligand–receptor interactions can be highly selective; hence targeting at the site of interest is possible. Example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors. 2) Active targeting allows the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Nanoparticles can be significantly used in targeted drug delivery at the site of disease to improve the drug bioavailability, targeting of drugs to a specific site and to improve the uptake of poorly soluble drugs. [35]

CONCLUSION

Nanotechnology and nanoparticles have a wide range of applications in biology and medicine. As mentioned above, nanoparticles enables novel techniques in imaging, sensing and it is best suited to creating systems that can better deliver drugs to tiny areas within the body. Nanoparticle drug delivery system will helps to lower drug toxicity, reduced cost of treatments, improved bioavailability. Nano-enabled drug delivery also makes it possible for drugs to permeate through cell walls, which is of critical importance to the expected growth of genetic medicine over the next few years. Some recently found health risk evidences limits their utilization in pharmacy and medical field. Some concerning issues like safety, bioethical issues, toxicity hazards, physiological and pharmaceutical challenges should be overcome. We are still lacking sufficient data and guidelines regarding safe use of these nanotechnology based devices and materials and medications. In future expansion of nanotechnology is likely to affect just about every route of administration from oral to injectable and offer significant impact on drug delivery sector.

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