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Nanoparticles – Drug Delivery System for Poorly Bioavailable Drugs

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Abstract

In the recent years, the use of polymeric nanoparticles as carriers for a wide range of drugs for therapeutic applications has been increased due to their versatility and wide range of properties. Nanoparticles provide the action at the desired sites and thus gaining importance nowadays. With these nanoparticles the specific targeting to various cells or which are responsible for cellular internalization and cellular uptake.

Keywords— **nanoparticles, polymers, coacervation, zeta potential, active pharmaceutical ingredients**

Introduction

Colloidal drug delivery system provides number of advantages over conventional dosage forms. Due to their small size colloidal preparations lend themselves to parenteral preparations and may be useful as sustained-release injection for the delivery to specific organ or target site. Nanotechnology has potential for numerous applications in different food industries. Nano encapsulation of bioactive components involved forming nm carriers with diameter ranging from1 to 1000 nm. Such system can be partially useful for control release application in pharmaceutics cosmetics and food industry. Nanoparticles drug delivery system have beneficial advantages such asincreased surface area and enhanced bioavailability of compounds along with limited toxicity. Thereare variety of submicron particles polymer based nanoparticles are unique compared to other nanoparticle system due to their better encapsulation, control release and less toxic properties. Nano particulate drug delivery system is usually intended for oral, parenteral or topical route with theultimate objective being the alteration of pharmacokinetic profile of active molecule. Nanotechnology is a science of the small the prefix nano comes from ancient Greek word means "dwarf". Nanotechnology provides opportunity for the development of material including those for medical application, where conventional techniques reach their limits. Nanotechnology represents thedesign production and application of material at atomic, molecular and macromolecular scale in orderto produce new Nano sized material. The name nanoparticle is combined name for both Nano sphere and Nano capsules. Nano spheres are matrix system in which drug is uniformly dispersed while Nano capsules other system in which drug is surrounded by a unique polymeric membrane. The major goal in designing nanoparticles as a delivery system for control particle size, surface properties and release of pharmacologically active agent so as to achieve site specific action of the drug at rational rate and dose.

Many nanoparticles have a large surface area which enables them to be an integral part of effective drug delivery system. In recent years biodegradable polymeric nanoparticles, particularly those with hydrophobic polymer such as poly ethylene glycol known as long circulating particles havebeen used as a potential drug delivery devices because of their ability to circulate for a prolonged

period of time to target particular organ as a career of DNA in gene therapy and their ability to deliver proteins peptides and genes.

Advantage of nanotechnology is to provide the safe and the effective medicine to influence of both pharmaceutical and biotechnological industry. Application in various fields of life sciences such as separation technologies, histological studies, clinical diagnosis and as a drug delivery systems. The first industrial production of nanomaterial occurs in the early 20th century with the production of carbon black and later in 1940 fused silica. The use of nanotechnology for treatment, identification, monitoring and managing biological system have been recently referred to as Nanomedicine.

Types of Nanoparticles

Depending upon the material used for preparing nanoparticles, they are classified into following three groups

A. Polymer based nanoparticles
B. Lipid based nanoparticles
C. Lipid-polymer hybrid nanoparticles.

Polymer based nanoparticles

Polymer nanoparticles are nano-sized colloidal particles in which a therapeutic agent can be loaded within their polymeric matrix or absorbed or conjugated onto the surface. The nanoparticles have been shown to improve bioavailability and enhance drug solubility because of reduced particle size upto nano size and encapsulating the drug into the water-soluble polymer. This nanoparticles serve as an excellent vehicle for delivery of a number of biomolecules, drugs, genes and vaccines. Nanoparticles were mainly formulated from poly alkyl cyanoacrylate. They easily cross mucosal barrier due to their size but they have short lifespan due to Rapid clearance from the body of phagocytic cells. Surface modification protect nanoparticle from being phagocytized and removal from the vascular system after intravenous injection. The use of polymeric nanoparticles for delivery strategy that to optimize therapeutic effect while minimizing adverse effect. Nanoparticles can be prepared from a variety of materials. Selection of the base polymer is based on many factors such as

- Size of desired nanoparticles.
- Properties of the drug to be encapsulated in polymer.
- Surface characteristics and functionality.
- Degree of biodegradability, biocompatibility and toxicity.
- Drug release profile.
- Antigenicity of final product.

Examples for naturally occurring biodegradable polymers used for preparing nanoparticles are cellulose, gelatin, chitosan and alginate. Examples for synthetic biodegradable polymer used to prepare nanoparticles include poly lactic acid, poly-lactide coglycolide (PLGA), polyunhydrides, Poli-caprolactone, poly alkyl cyanoacrylate and polyphosphazene.

Lipid based nanoparticles.

Due to the toxicity of polymers, presence of solvent residue in compound during production and purification cost, degradability, lack of suitable large scale production unit, requirement of high purity and quality of biodegradable polymers, polymer nanoparticles are limited in use.

Lipid based nanoparticles is composed of lipids with a lipid core. Lipid nanoparticles can be synthesized by combining an oil phace with phospholipids as emulsifiers. They can be synthesized by methods such as high pressure homogenization. Most important lipid based nanoparticles are solid lipid nanoparticles, nanostructured lipid carriers and lipids drug conjugate. Lipid nanoparticles are used commonly because of its characteristics like suitable for drug delivery, use of physiological tolerated lipid, large scale production, protection of drug from degradation, improved bioavailability, minimum level of toxicity and controlled release characteristics.

Due to low cytotoxicity of lipid nanoparticles these are used for application of DNA or RNA.

Lipid polymer hybrid nanoparticles

Lipid-polymer hybrid nanoparticles combines the merits of both lipid based nanoparticles and polymer based nanoparticles. Lipid polymer hybrid nanoparticles has a robust drug delivery platform with high drug encapsulation, tunable and sustained drug release profile with excellent serum stability and differential targeting of cells or tissues.

Lipid polymer hybrid nanoparticles comprised of three distinct functional components.

a) A hydrophobic polymer which is used to encapsulate poorly water soluble drugs.
b) A hydrophilic polymer shell which enhance lipid polymer hybrid nanoparticles stability and increase half life during systemic circulation.
c) A lipid shell at the interface of the core and the shell act as a molecular wall to promote retention of drug inside polymeric core, so as to enhance drug encapsulation efficiency, increasing drug loading and controlling drug release. Polymeric core and shell are associated to hydrophobic interactions, Vander walls forces, electrostatic interactions or non covalent forces. This lipid polymer hybrid nanoparticles have been demonstrated to include unique advantages of both lipid-based and polymer based

nanoparticles by holding great promise as a delivery vehicles for various medical applications.[9]

Preparation of Nanoparticles

In the preparation of nanoparticles different types of matrix materials are used. The selection ofmethod for preparation of nanoparticles based on the following characteristics.

- Nanoparticle size
- Permeability and surface charge of nanoparticles.
- Level of biodegradability and biocompatibility must be optimum.
- Material must be non toxic.
- Solubility profile and stability of drug should not be affected.
- Should show drug release profile.
- Must be immunogenic.

Nanoparticles have been prepared most frequently by

A. Dispersion of preformed polymers

Dispersion of preformed polymers is a common technique used to prepare biodegradable nanoparticles from poly lactic acid (PLA), poly D,L glycolide (PLG), poly D,L- lactide co- glycolide(PLGA), and Poly cyanoacrylate (PCA). This technique can be used in various ways as described below.

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 a 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 an oil-in-water emulsion. After the formation of stable emulsion the organic solvent is evaporated either by reducing the pressure or by continuous stirring. Method was found to be influenced by the type and concentration of stabilizer, homogenizer speed and polymer concentration. In order to produce small particle size often a high speed homogenization or ultrasonication may be used.

Spontaneous emulsification or solvent diffusion method: This is a modified version of solvent evaporation method, in this method the water miscible solvent with a small amount of water immiscible organic solvent is used as an oil phase. Due to spontaneous diffusion of solvents and interfacial turbulence is created between the two phases leading to formation of small particles. The concentration of water miscible solvent increases, a decrease in size of the particle can be achieved. Both solvent evaporation and solvent diffusion method can be used for hydrophobic or hydrophilic drugs. In the case of hydrophilic drug a multiple emulsion w/o/w need to be formed withthe drug dissolved in the internal aqueous phase.

B. 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 nanoparticle suspension is then purified to remove various stabilizers and surfactant employed for polymerization by ultracentrifugation for resuspending the particle in an isotonic surfactant free medium. This technique has been reported for making poly butyl cyanoacrylate or poly alkyl cyanoacrylate nanoparticles depending on the concentration of surfactant and stabilizers used.

C. Coacervation or ionic gelation method

Many research has been focused on the preparation of nanoparticles using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate. The method for preparing hydrophilic chitosan nanoparticles by ionic gelation method involves a mixture of two aqueous phases of which one is the polymer chitosan and the other is a poly anion sodium tripolyphosphate. In this method positively charged amino group of chitosan interacts with negative charged tripolyphosphateto form coacervates with size in the range of nanometers. Coacervates are formed as a result of electrostatic interaction between two aqueous phase where is ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction condition at room temperature.

D. Supercritical fluid technology

Conventional methods such as solvent extraction, evaporation, solvent diffusion and organic phase separation method require the use of organic solvents which are hazardous to the environment as well as to physiological system. Therefore the supercritical fluid technology has been investigatedas 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 about its critical temperature, at which the

fluid remains a single-phase regardless of pressure. Supercritical carbon dioxide is the most widely used supercritical fluid because of its mild critical condition, nontoxicity, non-inflammability and low price. The most common processing techniques involved supercritical fluids are supercritical antisolvent (SAS) and Rapid expansion of critical solution (RESS). The process SAS employs a liquid solvent example methanol which is completely miscible with supercritical fluid to dissolve the solute to be micronized at process conditions because the solute is insoluble in supercritical fluid the extract of the liquid solvent by supercritical fluid leads tothe instantaneous precipitation of the solute resulting the formation of nanoparticles.

RESS differs from the SAS process in that its solute is dissolved in a supercritical fluid and then the solution is rapidly expanded through a small nozzle into a region lower pressure. Thus the solvent power of supercritical fluid dramatically decrease and the solute eventually precipitates. This technique is clean because the precipitate is basically solvent-free. RESS and its modified process have been used for the product of polymeric nanoparticles. Supercritical fluid technology is environment friendly and suitable for mass production and specially designed equipments are more expensive.

Characterization of Nanoparticles

Nanoparticles are generally characterized by their surface morphology by using advanced microscopic techniques such as scanning electron microscopy (SEM), transmission electron microscopy (TEM) and atomic force microscopy. Average particle diameter, distribution and charge affect the physical stability and *in vivo* distribution of nanoparticles. Electron microscopy techniques are very useful in ascertaining the shape of polymeric nanoparticles, which may determine their toxicity, effect of physical stability and redispersibility of the polymer dispersion as well as their in vivo performance.

A. Particle size

Particle size distribution and morphology are the most important parameters of characterization ofnanoparticles. Morphology and size are measured by electron microscopy. The major application of nanoparticles is in drug release and drug targeting. It has been found that particle size affect the drug release, smaller particle offer large surface area as a result most of the drug loaded and will be exposed to the particle surface leading to fast drugs release. The main drawback is that, smaller particles tend to aggregate during storage and transportation of nanoparticle dispersion, hence there isa compromise between a small size and maximum stability of nanoparticles. Degradation can also beaffected by the particle size, for instance the degradation rate of poly (lactic-co- glycolic acid) was found to increase with increasing particle size.

The different tools used for determining nanoparticle size are discussed below

1. Dynamic light scattering (DLS): Currently the fastest and most popular method of determining particle size is photon correlation Spectroscopy (PCS) or dynamic light scattering (DLS). Dynamic light scattering is widely used to determine the size of Brownian nanoparticles in colloidal suspension in the nano and submicron range. Striking monochromatic light on to a solution of spherical particle in Brownian motion causes a doppler shift, when the light hit the moving particles and changing the wavelength of the incoming light this change is related to the size of the particle. It is impossible to extract the size distribution and give a description of the particles motion in the medium in measuringthe diffusion coefficient of the particle and using the autocorrelation function. The photon correlation spectroscopy is the most frequently used technique for accurate estimation of particle size and size distribution based on DLS.

2. Scanning electron microscopy (SEM): Scanning electron microscopy is giving morphological examination with direct visualisation. Technique based on electron microscopy offer several advantages and moreover they provide limited information about the size distribution and true population average. For scanning electron microscopic characterization of nanoparticle solution should be first converted into dry powder which is then mounted on a sample holder by coating with aconductive metal such as gold. The sample is then scanned with a focused fine beam of electrons. The surface characteristics of the sample are obtained from secondary electrons emitted from the sample surface. The nanoparticle must be able to withstand scanning and the electron beam can damage the polymer. The mean size obtained by scanning electron microscope is comparable with the result obtained by dynamic light scattering. Moreover these techniques are time-consuming, costly and frequently need complementary information about sizing distribution.

3. Transmission electron microscopy: Transmission electron microscopy operates on different principle than scanning electron microscope, yet it often brings same type of data. The sample preparation for transmission electron microscope is complex and time-consuming because of its requirement to be ultra thin for the electron transmittence. The nanoparticles dispersion is deposited onto support grids or films. To make nanoparticles, withstand the instrument vacuum and facilitate handling, they are fixed using either negative staining material such as phosphotungstic acid or derivatives uranyl acetate etc or by plastic embedding. Alternate method is to expose the sample to liquid nitrogen temperatures are embedding in vitreous ice. The surface characteristics of the sample obtained when a beam of electron is transmitted through the ultra thin sample interacting with the sample as it passes through.

4. Atomic force microscopy: Atomic force microscopy of ultra-high resolution in particle size measurement and is based on a physical scanning of samples at submicron level using a prob tip of atomic scale. The instrument provides a topographical map of sample based on forces between the tipand the sample surface. Samples are usually scanned in contact or non contact more depending on their properties. In contact mode the topographical map is generated by tapping the prob onto the

surface across the sample and prob moves over the conducting surface in non-contact mode. The mainadvantage of atomic force microscopy is its ability to image non conducting samples without any specific treatment, thus allowing imaging of delicate biological and polymeric nano and microstructures. Atomic force microscopy provides the most accurate description of size and size distribution and requires no mathematical treatment. Moreover particle size obtained by atomic force microscopy technique provides real picture with help understand the effect of various biological conditions.

B. Surface charge

The nature and intensity of the surface charge of nanoparticle is very important as it determines their interaction with the biological environment as well as their electrostatic interaction with bioactive compounds. Stability is analysed through zeta potential of nanoparticles this potential is an indirect measure of surface charge. It corresponds to potential difference between the outer plane and the surface of the shear. The measurement of the zeta potential allows for predictions about the storage stability of colloidal dispersion. High Zeta potential value whether positive or negative should be achieved in order to ensure stability and avoid aggregation of particle. The extent of surface hydrophobicity can then be predicted from the value of Zeta potential. The Zeta potential can also provide information regarding the nature of material encapsulated within the nanoparticles coated onto the surface.

C. Surface hydrophobicity

Surface hydrophobicity can be determined by several techniques such as hydrophobic interaction chromatography, biphasic partitioning, adsorption probes, contact angle measurement etc. Recently several sophisticated analytical techniques are introduced for surface analysis of nanoparticles. X-Ray Photon correlation spectroscopy permit the identification of specific chemical groups on the surface of nanoparticle.

D. Drug loading

Nanoparticle should have a high drug loading capacity thereby reduce the quantity of matrix material for administration. Drug loading can be done by two methods
Incorporating at the time of nanoparticle production (incorporation method)
Absorbing the drug after formation of nanoparticle by incubating the carrier with concentrated drug solution. (adsorption or absorption technique)

Drug loading and Entrapment efficiency very much depend on the solid state drug solubility in matrix material or polymer which is related to the polymer composition, the molecular weight, that drug polymer interaction and the presence of end functional group.

E. Drug release

The main aim of nanotechnology is to deliver drugs, hence understanding the manner and extent to which the drug molecule are released is important. In order to obtain such information most release methods require that the drug and its delivery vehicle be separated. The drug loading of nanoparticle is generally defined as the amount of drug bound per polymer, it could also be given a percentage relative to the polymer. The technique used to find this analysis is classical analytical methods like UV Spectroscopy or high performance liquid chromatography (HPLC), ultracentrifugation, ultrafiltration, gel filtration or Centrifugal ultrafiltration. Quantification is performed with the UV Spectroscopy or HPLC. Drug release assay are also similar to drug loadingassay which is assessed for a period of time to analyse the mechanism of drug release. [3], [4], [11]

Conclusion

Nanoparticles are a contribution to the drug delivery development for formulation by various methods, mainly the interfacial polymerization and interfacial nano-deposition. Nanoparticles can be released as the monodisperse particles with well-defined biochemical, electrical, optical, as well as magnetic properties. In drug delivery system, they are confined to suit the complexity of theapplication as they intend to produce contents in response to a specific bimolecular triggering action mechanism. Nanoparticles have various applications in various fields of the agrochemicals, waste water treatments, genetic engineering, cosmetics, cleaning products, as well as in adhesive component. They are also used in encapsulation of enzymes, adhesives, catalysts, polymers, oils, inorganic micro and nanoparticles, latex particles, and even the biological cells. In conclusion, they can be used in the delivery of active pharmaceutical ingredients. Nanoparticles are the novel effectivedrug delivery systems in the up-coming future.

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