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Nanoparticles: A smart drug delivery

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ABSTRACT

In recent years, there has been an exponential interest in the development of novel drug delivery systems using nanoparticles. Nanoparticles are defined as particulate dispersions or solid particles with size in the range of 10-1000nm. There has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Nanoparticles have been extensively studied as particulate carriers in the pharmaceutical and medical fields, because they show promise as drug delivery systems as a result of their sustained and targeting release properties, subcellular size, biocompatibility with tissue and cells. Various polymers have been used in the formulation of nanoparticles for targeting drug delivery research to increase therapeutic benefit, while minimizing side effects. Polymeric nanoparticls with a size in the nanometer range protect drugs against *in vitro* and *in vivo* degradation. The use of nanoparticle drug delivery is a universal approach to increase the therapeutic performance of poorly soluble drugs in any route of administration. In this review focused various aspects of nanoparticle formulation, characterization and their applications in targeting delivery.

Keywords: Nanoparticles, Drug Targeting and Controlled Release.

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INTRODUCTION

The control drug delivery alters the pharmacokinetics and pharmacodynamics of drug substance in order to improve the therapeutic efficacy and safety. Besides more traditional matrix or reservoir drug delivery systems, colloidal drug delivery system has gained in more popularity[1]. Colloidal drug delivery systems offer a number of advantages over conventional dosage forms. Due to their small particle size, colloidal preparations lend themselves to parenteral preparations and may be useful as sustain release injections for the delivery to a specific organ or target site. The major colloidal drug delivery systems include liposome and nanoparticles[2].

Nanoparticles in pharmaceutical applications have gained plenty of research attention during recent decades. Although the research concerning formulation of nanoparticles into drug delivery devices has been extensive, only a few polymeric nanoparticulate products have reached the market. Among the drugs used in nanoparticle formulations, particularly cancer therapeutics is widely studied because the formulation might reduce toxicity of the drug while improving efficacy of the treatment[3]. In addition to drug molecules, other candidates to be encapsulated in or coupled with nanoparticles include macromolecules like proteins, peptides and genes (nucleic acids). These kinds of molecules tend to be inactivated in the body by enzymatic degradation. In terms of controlled release, nanoparticles provide protection against the body conditions resulting in sustained release and maintenance of bioactivity before the drug reaches the target[4].

Nanoparticles are colloidal polymeric particles of size below 1µm with a therapeutic agent either dispersed in polymeric matrix or encapsulated in polymer. The term polymeric nanoparticle encompasses nanospheres and nanocapsules. Nanospheres are defined as a polymeric matrix in which the drug is uniformly dispersed and nanocapsules are described as a polymeric membrane that surrounds the drug in the matrix[5].

Advantages: These advantages include

1. Targeted delivery of drugs to the specific site to minimize toxicity
2. Improved bioavailability by reducing fluctuations in therapeutic ranges

3. Improved stability of drugs against enzymatic degradation
4. Controlled release reduces dosing frequency with improved patience compliance.
5. The small particle size also reduces potential irritant reactions at the injection site.

MATERIALS USED FOR PREPARATION OF NANOPARTICLES

A broad range of synthetic and natural polymers available for nanoparticle formation, but their biocompatibility and biodegradability are the major limiting factors for their use in the drug delivery area. Synthetic polymers, on the other hand, offer better reproducibility of the chemical characteristics of the synthesized nanoparticles as compared to the natural polymers

Natural Polymers

Various polymers have been used in the formulation of nanoparticles for drug delivery research to increase therapeutic benefit, while minimizing side effects. Natural polymers have been classified into polysaccharides and proteins. Proteins are gelatin; albumin, lecithin, legumin and vicillin. Polysaccharides are alginate, dextran, chitosan and pollulan[6].

A. Chitosan

Chitosan is a modified natural carbohydrate polymer prepared by the partial N-deacetylation of chitin, a natural biopolymer derived from crustacean shells such as crabs, shrimps and lobsters. Chitosan is also found in some microorganisms, yeast and fungi. After cellulose chitin is the second most abundant polysaccharide in nature. It is physically protected, non poisonous, biocatalyst and eco-friendly polysaccharide[7]. Although chitin is insoluble in most solvents, chitosan is soluble in most organic acidic solutions at pH less than 6.5 including formic, acetic, tartaric, and citric acid.

B. Gelatin

Gelatin is one of the protein materials that can be used for the production of nanoparticles. It is obtained by controlled hydrolysis of the fibrous, insoluble protein, collagen, which is widely found as the major component of skin, bones and connective tissue. The interest was based on the facts that gelatin is biodegradable, non-toxic, easy to crosslink and to modify chemically and has therefore an immense potential to be used for the preparation of colloidal drug delivery systems such as microspheres and nanoparticles[7].

C. Albumin

Albumin is an good-looking macromolecular shipper and extensively use to arrange nanospheres and nanocapsules, due to its availability in pure form and its biodegradability, nontoxicity and nonimmunogenicity. On the other hand, albumin nanoparticles are biodegradable, easy to prepare in defined sizes, and carry reactive groups on their surfaces and also offer the advantage that ligands can easily be attached by covalent linkage[8].

D. Alginate

Alginate, a naturally occurring copolymer of glucuronic acid and manuronic acid, is widely used for pharmaceutical applications. Specifically, the simple aqueous-based gel formation of sodium alginate in the presence of divalent cations such as Ca2+ has been used for drug delivery[9]. Alginate is anionic polysaccharide that it has been widely used in drug delivery High drug encapsulation efficiency was achieved in alginate nanoparticles, ranging from 70%-90%.

Synthetic Polymers

Synthetic polymers offer better reproducibility of the chemical characteristics as compared to the natural polymers. Common classes of polymers used to encapsulate drugs in colloidal systems include polyamides, poly (amino acids), polyesters, polyorthoesters and polyanhydrides.

A. Lactide and Glycolide copolymers

Most popular biodegradable polymers used in drug delivery are polyester copolymers based on lactic and glycolic acids. Poly (d,l-lacticco-glycolic acid) (PLGA) is used for the manufacture of implants and internal sutures and is known to be biocompatible, degrading to produce the natural products lactic acid and glycolic acid[4].

B. Poly (ε-Caprolactones)

PCL is a water permeable polymer with hydrophobic and high crystalline properties. It undergoes bulk erosion by random hydrolytic chain cleavage in the first phase, resulting in a decrease in the molecular weight of the polymer[10].

C. Polyanhydrides

The hydrophobic and crystalline materials have been shown to undergo erosion by surface hydrolysis, minimizing water diffusion into the bulk of the delivery device. The monomeric anhydride bonds have extreme reactivity toward water and undergo hydrolysis to generate the dicarboxylic acids[10]. Although hydrolysis is catalyzed by both acid and base, an increase in pH enhances the rate of hydrolytic degradation.

PREPARATION OF NANOPARTICLES

The nanoparticles prepared by using following methods:

Emulsification–solvent diffusion

It is widely used method for preparing nanoparticles[3]. The drug and polymer dissolved in a partially water soluble solvent. Commonly used solvents are propylene carbonate, benzyl alcohol, ethyl acetate, isopropyl acetate, methyl acetate, methyl ethyl ketone, butyl lactate or isovaleric acid. The organic phase is saturated with water and is then diluted with an extensive amount of pure water to facilitate diffusion of the organic solvent from the organic phase droplets leading to the precipitation of the polymer as presented in Figure: 1. The aqueous phase may contain surfactants such as Pluronic, PVA and sodium taurocholate. Finally, the solvent is eliminated by evaporation.

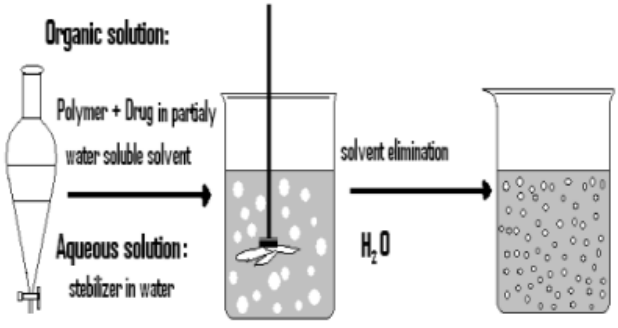

Figure 1: Schematic representation of the emulsification-solvent diffusion method

Nanoprecipitation (Solvent diffusion method)

The easiest and reproducible techniques for preparing nanospheres were the snanoprecipitation method. Three basic ingredients are needed for this method: polymer, polymer solvent and non-solvent for the polymer. In brief, both the polymer and drug are dissolved in a water miscible organic solvent of intermediate polarity[5]. The resulting organic phase is injected into a stirred aqueous phase containing a surfactant as stabilizer. The nanoparticles are formed instantaneously during the rapid diffusion of the organic phase into the aqueous phase as shown in Fig: 2, typically, this method is used for hydrophobic drug entrapment, but it has been adapted for hydrophilic drugs as well. Finally, the solvent is removed under reduced pressure[10].

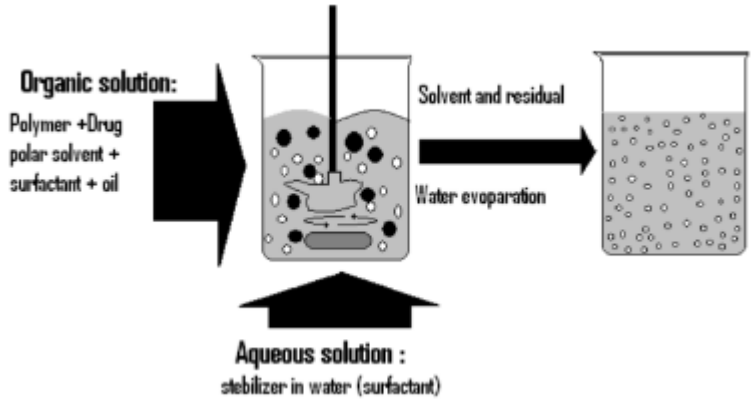

Figure 2: Schematic representation of the solvent displacement technique

Oil in water emulsion method

The method is based on the emulsification of an organic solution which contains the polymer and the active component in an aqueous phase, followed by the evaporation of the organic solvent[5]. Different surfactants can be dissolved in the aqueous phase. The size reduction of the emulsion droplet is done by sonication for miniemulsion formation. The evaporation step is required to eliminate the organic solvent present in the organic phase. This leads to the precipitation of the polymer as nanoparticles with a diameter in the nanometers range.

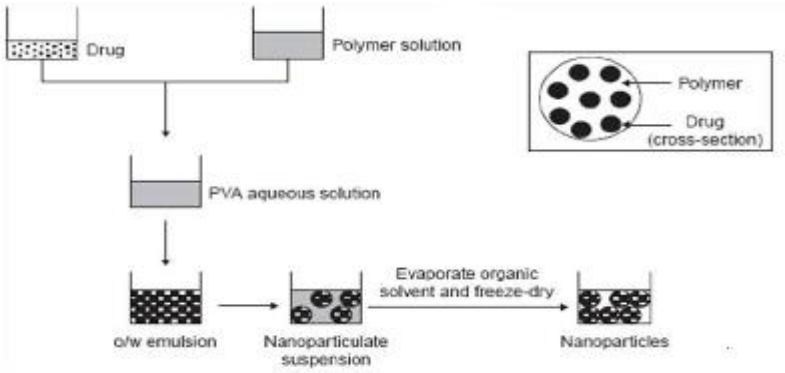

Figure 3: schematic representation of o/w single-emulsion solvent evaporation method

Polymerization method

In this method, 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 surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium[11].

Coacervation or phase separation method

This method involves a mixture of two aqueous phases, of which one is the polymer chitosan, a di-block co-polymer ethylene oxide or propyleneoxide and the other is a polyanion sodium tripolyphosphate[12]. In this method, positively charged amino group of chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometer.

CHARACTERIZATION OF NANOPARTICLES

Particle size and surface morphology

The scanning electron microscope (SEM) is one of the most versatile instruments widely applied to surface microstructure imaging. SEM is a type of electron microscopy that images the sample surface of a solid specimen by using a focused beam of high-energy electrons.

Surface charge of the nanoparticles

The Zeta potential of the nanoparticles was determined by Zetasizer[12]. Zeta potential is important parameter when considering the stability of the nanoparticles *in vitro*. The more negative or positive values of zeta potential are related to more stable particles; more repulsion between particles reduce the particle aggregation.

Table 1: Zeta potential for colloids in water and their stability

Zeta potential (mv)	Stability behaviour of the colloid
0 to +-5	Rapid coagulation/ flocculation
From +-10 to +-20	Incipient instability
From+-20 to +-40	Moderate stability
From+-40 to +-60	Good stability
More than +-61	Excellent stability

Entrapment and loading efficiency

Drug entrapment efficiency is a percentage value that describes the quantity of the drug material in the nanoparticles out of the total amount used in the process. The entrapment into the nanoparticles is described by two important parameters: theoretical drug loading, which is the ratio between mass of drug used in synthesis and mass of polymer used in synthesis, and nanoparticle recovery. The encapsulation efficiency was determined by using the following formula[13]

$$Encapsulation\ efficiency\ (\%) = 1 - \frac{Drug\ in\ supernatant\ liquid}{Total\ drug\ added} \times 100$$

The percentage drug loading capacity was determined using the following formula:

$$\%\ Drug\ loading\ = \frac{Total\ amount\ of\ drug\ -\ Amount\ of\ free\ drug}{Nanoparticles\ weight} \times 100$$

Drug release study

The characterization purposes and for quality control reasons, the determination of the in vitro release of drug from nanoparticles is important[13]. In case of micro and nanoparticulate systems, the apparatus are suitable as following:

1. Side by side diffusion cells with artificial or biological membranes
2. Dialysis bag diffusion technique
3. Reverse dialysis sac technique
4. Ultracentrifugation
5. Ultra filtration (Centrifugal) technique

APPLICATIONS OF NANOPARTICULATE DELIVERY SYSTEMS

Tumor targeting delivery systems: Nanoparticles have able to deliver a concentrate dose of drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or active targeting by ligands on the surface of nanoparticles[14]. Nanoparticles will reduce the drug exposure of healthy tissues by limiting drug distribution to target organ.

Oral delivery of peptides and proteins: Polymeric nanoparticles allow encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation. For instance, it has been found that insulin-loaded nanoparticles have preserved insulin activity and produced blood glucose reduction in diabetic rats for up to 14 days following the oral administration[14].

Epithelial cells in the GI tract: Targeting strategies to improve the interaction of nanoparticles with adsorptive enterocytes and M-cells of Peyer's patches in the GI tract can be classified into those utilizing specific binding to ligands or receptors and those based on nonspecific adsorptive mechanism[15].

Gene delivery: Nanoparticles loaded with plasmid DNA could also serve as an efficient sustained release gene delivery system due to their rapid escape from the degradative endo-lysosomal compartment to the cytoplasmic compartment[14].

Brain targeting delivery systems

It has been reported poly (butylcyanoacrylate) nanoparticles was able to deliver hexapeptide dalargin, doxorubicin and other agents into the brain which is significant because of the great difficulty for drugs to cross the BBB[15].

CONCLUSION

Nanoparticles can offer significant advantages over the conventional drug delivery in terms of high stability, high specificity, high drug carrying capacity, ability for controlled release, possibility to use in different route of administration and the capability to deliver both hydrophilic and hydrophobic drug molecules. Nanoparticle 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.

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