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Formulations, Characterization and Applications of Nanoparticle in Drug Delivery: Reviewc

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Review Article

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ABSTRACT

The interest of new drug delivery system has been changed for the some decades by using particulate delivery systems as carriers for small and large molecules. Nanoparticles have been proved to commute and expand the pharmacokinetic and pharmacodynamic effects of various group of drug molecules. The delivery of Nanoparticles always in a controlled and sustained manner to the site of action. Here, review on various feature of nanoparticle formulation, characterization, effect of their characteristics and their applications in delivery of drug molecules.

INTRODUCTION

Nanoparticles are those with a size in the range of <100 nm. The medication is dissolved, trapped, encapsulated or bound into a nanoparticle matrix. Depending on the preparation process Nanoparticles, nanospheres or nanocapsules may be obtained, In nanospheres matrix systems the drug is physically and uniformly dispersed and nanocapsules are systems in which the drug is cramped to a cavity which is surrounded by a unique polymer membrane. Biodegradable polymeric nanoparticles have been used as potential drug delivery devices in recent year because of their capability to circulate for a prolonged period time to target a particular organ [1-4]. Because of various applications of nanoparticles, like control particle size, surface properties and release of pharmacologically active agents, site-specific action, they are gaining popularity day by day. In the row of various nanoparticles, Polymeric nanoparticles gaining popularity day by day because of advantages like they help to increase drug/protein stability and have useful controlled release properties [5,6].

As a system for drug delivery the benefits of using nanoparticles include the following:

• So as to achieve both passive and active drug targeting after parenteral administration, surface characteristics and particle size of nanoparticles can be readily manipulated.

• In the course of transport and at the site of localization, they monitor and manage the release of the drug, altering the organ delivery and eventual clearance of the drug in order to improve the therapeutic effectiveness of the drug and reduce side effects.

• Depending upon the choice of matrix component, controlled release and particle degradation trait can be easily modulated. Without any chemical reaction drug can be introduced into the systems; which is a significant element in maintaining the activity of the drug.

• By adding targeting ligands and using magnetic guidance to the surface of particles it is possible to achieve site specific targeting.

• The framework can be used for different routes, including oral, nasal, parenteral, intra-ocular, etc.

• Due to various advantages, nanoparticles do have some curb.

• Because of small size and large surface area, can create to particle-particle aggregation, which makes it difficult to handle

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nanoparticles physically in liquid and dry forms. Because of small particle size and large surface area can easily lead to less drug loading and burst release.

Nanoparticles preparation

With variety of materials such as proteins, polysaccharides and synthetic polymers nanoparticles can be prepared. The matrix materials selection is dependent on many elements including [7]:

- Nanoparticles size is required.
- Various properties of the drug, e.g., aqueous solubility and stability.
- Surface properties such as charge and permeability.
- Level of biodegradability, biocompatibility and toxicity.
- Drug release profile.
- Antigenicity of the final out-come.

Nanoparticles have been prepared by three methods:

- Diffusion of preformed polymers
- Polymerization of monomers
- Coacervation or ionic gelation of hydrophilic polymers.

Despite, other methods such as supercritical fluid technology [8] and particle replication in non-wetting templates (PRINT) [9] also used for nanoparticles production.

Diffusion of preformed polymers: Diffusion of preformed polymers is a common technique which is 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), [10-12]. This technique can be utilized in different manners as described beneath.

Solvent evaporation method: In this method, the polymer is dissolved in a natural solvent for example, dichloromethane, chloroform or ethyl acetate which is likewise used as the solvent for dissolving the hydrophobic medication. The combination of polymer and drug solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent to shape oil in water (o/w) emulsion. After the development of stable emulsion, the organic solvent is evaporated by reducing the pressure or by continuously stirring. Molecular size was discovered to be affected by the concentrations and type of stabilizer, speed of homogenizer and polymer concentration [13]. High-speed homogenization or ultrasonication may be employed to achieve a uniform size [14].

Unconstrained emulsification or solvent diffusion method: This is another variant of solvent evaporation method [15]. In this method, the water miscible solvent is used with a small amount of water immiscible organic solvent, which is used as an oil phase. Due to the continuous diffusion of solvents an interfacial turbulence is created between the two phases which leads to the formation of small particles. As the convergence of water miscible solvent increases, abatement in the size of molecule can be accomplished. Both solvent evaporation and solvent diffusion methods can be utilized for hydrophobic or hydrophilic drugs.

Polymerization method: In this technique, monomers are polymerized to frame nanoparticles in an aqueous solution. Drug is consolidated either by being dissolved in the polymerization medium or by adsorption onto the nanoparticles after polymerization finished. The nanoparticle suspension is then purified to eliminate different stabilizers and surfactants utilized for polymerization by ultracentrifugation and re-suspending the particles in an isotonic without surfactant medium. This procedure has been accounted for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles [16,17]. Nanocapsule formation and their particle size rely upon the concentration of the surfactants and stabilizers utilized [18].

Coacervation or ionic gelation method: Much research has been entered on the preparation of nanoparticles utilizing biodegradable hydrophilic polymers, for example, chitosan, gelatin and sodium alginate. Calvo and co-workers built up a method for preparing hydrophilic chitosan nanoparticles by ionic gelation [19,20]. In this method they involve a mixture of two aqueous phases, in which one is the polymer chitosan [a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO)] the other is a polyanion sodium tripolyphosphate. Formation of coacervates obtained by positively charged amino group of chitosan with negative charged tripolyphosphate. Coacervates are framed because of electrostatic interaction between two aqueous phases, whereas, ionic gelation involves the material undergoing transition from fluid because of ionic collaboration conditions at room temperature.

Impact of Characteristics of Nanoparticles on Drug Delivery

Particle size: Most important characteristics of nanoparticle systems are particle size and size distribution. In vivo distribution,

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biological fate, toxicity and the targeting ability of nanoparticle systems are determine by the particle size and size distribution. The drug loading, drug release and stability of nanoparticles can also be affected. Due to sub-micron size of nanoparticles have a number of advantages over micro particles as a drug delivery system [21]. As compared to micro particles, nanoparticles have relatively higher intracellular uptake and nanoparticles available to a wider range of biological targets due to their small size and relative mobility. It was also announced that nanoparticles can across the blood-brain barrier following the kick-off of tight intersection by hyper osmotic mannitol, which may provide sustained delivery of therapeutic agents for difficult-to-treat diseases like brain tumors [22]. Tween 80 coated nanoparticles can cross the blood-brain barrier [23]. Drug release is influenced by molecular size, smaller particles have bigger surface area, so majority of the drug associated would be at or near the particle surface, which leads fast drug release. Whereas, larger particles have large cores which allow more drug to be encapsulated and slowly diffuse out [24]. During storage and transportation of nanoparticle dispersion smaller particles also have greater risk of aggregation. It is consistently a test to formulate nanoparticles with the smallest size possible but maximum stability.

Polymer degradation: It can likewise be influenced by the particle size. For example, the rate of PLGA polymer degradation found to increase the particle size in vitro [25]. Panyam et al. arranged PLGA particles with various size ranges and found that the polymer degradation rates in vitro were not generously different for various size particles [26]. Currently, the quickest and most routine strategy for particle size is by photon-correlation spectroscopy or dynamic light scattering. Photon-correlation spectroscopy requires the consistency of the medium to be known and decides the diameter of the particle by Brownian motion and light scattering properties [27]. The outcomes obtained by photon-correlation spectroscopy are generally verified by scanning or transmission electron microscopy (SEM or TEM).

Surface properties of nanoparticles: When nanoparticles are administered intravenously, they are easily recognized by the body immune systems, and are then cleared by phagocytes from the circulation. Except for the size of nanoparticles, adsorbed blood components, mainly proteins (opsonins) determines the amount of surface hydrophobicity. This in turn influences the in vivo fate of nanoparticles [28,29]. Binding of these opsonins onto the surface of nanoparticles called opsonization acts as a bridge between nanoparticles and phagocytes. mononuclear phagocytes system (MPS) such as liver, spleen, lungs and bone marrow leads to modification of the drug biodistribution profile. Indeed, once in the blood stream, surface non-modified nanoparticles (conventional nanoparticles) are rapidly opsonized and massively cleared by the macrophages of MPS rich organs [30]. recognition of foreign substances, it is IgG, compliment C3 components, especially foreign macromolecules. Increasing the success in drug targeting by nanoparticles, minimize the opsonization and to prolong the circulation in vivo achieved by the nanoparticles. This can be achieved by (a) giving nanoparticles surface coating with hydrophilic polymers/surfactants; (b) and formulation of nanoparticles with biodegradable copolymers with hydrophilic segments) (PEG), polyethylene oxide, polyoxamer, poloxamine and polysorbate 80 (Tween 80).

Studies show that PEG conformation at the nanoparticle surface is of utmost importance for the opsonin repelling function of the PEG layer. PEG surfaces in brush-like and intermediate configurations reduced phagocytosis and complement activation whereas PEG surfaces in mushroom-like configuration were potent complement activators and favoured phagocytosis 2, [31].

The zeta potential of a nanoparticle is commonly used to characterise the surface charge property of nanoparticles [32]. Electrical potential of particles reflects and influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (+/-) 30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles. To determine the charged active material is encapsulated within the centre of the nanocapsule or adsorbed onto the surface the zeta potential can also be used.

Drug loading: Nanoparticulate system have a high drug-loading capacity thereby reduce the quantity of matrix materials for administration. By two methods Drug loading can be done:

- Incorporating nanoparticles at the time of production (incorporation method).
- After formation of nanoparticles absorbing the drug by incubating the carrier with a concentrated drug solution (adsorption /absorption technique). Drug loading and entrapment efficiency is dependent on the solid-state drug solubility in material or polymer matrix (solid dissolution or dispersion), which is related to the drug polymer interaction, the molecular weight, polymer composition, and the presence of end functional groups (ester or carboxyl) [33-35]. There is no or little effect on drug loading due to PEG moiety [36]. Studies show the use of ionic interaction between the drug and matrix materials can be a very effective way to increase the drug loading which is effective for small molecules [37,38].

Drug release: Both drug release and polymer biodegradation are important consideration factors for the development of a successful nanoparticulate system. Mostly, drug release rate depends on:

- Solubility of drug.
- Desorption of the surface bound/ adsorbed drug.
- Drug diffusion through the nanoparticle matrix.

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- Nanoparticle matrix erosion/degradation.
- Combination of erosion/diffusion process.

So the release process has been governed by solubility, diffusion and biodegradation of the matrix materials. In the case of nano spheres, in which the drug is distributed uniformly, the release occurs under sink conditions through diffusion or erosion of the diffusion matrix. The mechanism of release is largely controlled by a diffusion process if the diffusion of the drug is faster than matrix erosion, the rapid initial release or 'burst' is mainly due to the large surface of nanoparticles with a weakly bond or absorbed drugs [39]. It is clear that the method of incorporation has an impact on release profile. The system has a relatively small burst effect and better sustained release characteristics, if the drug is loaded by incorporation method [40]. The release is then controlled by diffusion of the drug from the core across the polymeric membrane, If the nanoparticle is coated by polymer. The membrane coating acts as a barrier to release, therefore, the diffusivity and solubility of drug in polymer membrane becomes determining factor in drug release. Due to ionic interaction between the drug and addition of auxiliary ingredients release rate can also be affected. less water soluble complex is formed by when the drug is involved in interaction with auxiliary ingredients, then the drug release can be very slow with almost no burst release effect [41]; whereas if the addition of auxiliary ingredients e.g., addition of ethylene oxide-propylene oxide block copolymer (PEO-PPO) to chitosan, that reduces the interaction of the model drug bovine serum albumin (BSA) with the matrix material (chitosan) due to competitive electrostatic interaction of chitosan with PEO-PPO, then an increase in drug release could be observed [42].

Nanoparticulate delivery systems various applications

Nano particulate delivery systems, tumor targeting: The resonable of using nanoparticles for tumor targeting is based on.

- Nanoparticles would be able to deliver a concentrated dose of drug in the vicinity of the tumor targets through the improved permeability and retention or active targeting of nanoparticle by ligands on the surface.
- By restricting drug delivery to the target organ, nanoparticles can minimize drug exposure to health issues.

In mice treated with doxorubicin integrated into poly(isohexylcyanoacrylate) nanopsheres, Verdun et al. showed that doxorubicin concentrations in the liver, spleen and lungs were higher than in mice treated with free doxorubicin [43]. Studies show that the polymeric composition of nanoparticles such as type, hydrophobicity and biodegradation profile of the polymer along with the associated drug's molecular weight, its localization in the nanospheres and the great influence on the drug distribution pattern in vivo is affected by mode of incorporation technique, adsorption or incorporation. The exact underlying mechanism is not fully understood but the biodistribution of nanoparticles is rapid, within ½ hour to 3 hours, and it likely involves MPS and endocytosis/phagocytosis process [44].

Long circulating nanoparticles: To be successful as a drug delivery system, nanoparticles must be able to target tumors which are localized outside MPS-rich organs. In the past decade, a great deal of work has been devoted to developing so-called "stealth" particles or PEGylated nanoparticles, which are invisible to macrophages or phagocytes [45]. A major breakthrough in the field came when the use of hydrophilic polymers (such as polyethylene glycol, poloxamines, poloxamers, and polysaccharides) to efficiently coat conventional nanoparticle surface produced an opposing effect to the uptake by the MPS [45,46]. These coatings provide a dynamic "cloud" of hydrophilic and neutral chains at the particle surface which repel plasma proteins [47,48]. As a result, those coated nanoparticles become invisible to MPS, therefore, remained in the circulation for a longer period of time. Hydrophilic polymers can be introduced at the surface in two ways, either by adsorption of surfactants or by use of block or branched copolymers for production of nanoparticles [44,45].

Various studies shows that nanoparticles containing a coat of PEG not only have a prolonged half-life in the blood compartment but also be able to selectively expel in pathological sites such as tumors or inflamed regions with a leaky vasculature44. As a result, such long-circulating nanoparticles have increased the potential to directly target tumors located outside MPS-rich regions [44]. The size of the colloidal carriers as well as their surface characteristics are the critical to the biological fate of nanoparticles. A size less than 100 nm and a hydrophilic surface are essential in achieving the reduction of opsonisation reactions and subsequent clearance by macrophages [44]. Coating conventional nanoparticles with surfactants or PEG to obtain a long-circulating carrier has now been used as a standard strategy for drug targeting in vivo.

Extensive efforts have been achieved to "active targeting" of nanoparticles in order to deliver drugs to the right targets, based on molecular recognition processes such as ligand-receptor or antigen-antibody interaction. Folate receptors are over expressed on the surface of some human malignant cells and in metastatic events the cell adhesion molecules such as selectins and integrins are involved, nanoparticles bearing specific ligands such as folate may be used to target ovarian carcinoma while specific peptides or carbohydrates may be used to target integrins and selectins [49]. Oyewumi et al. demonstrated that the benefits of folate ligand coating were to facilitate tumor cell internalization and retention of Gd-nanoparticles in the tumor tissue [50].

Targeting with small ligands appears more likely to succeed since they are easier to handle and manufacture. Furthermore,

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it could be advantageous when the active targeting ligands are used in combination with the long-circulating nanoparticles to maximize the likelihood of the success in active targeting of nanoparticles.

Reversion of tumor cells in multidrug resistance: Anticancer drugs, even if they are located in the tumor interstitium, can turn out to be of limited efficacy against numerous solid tumor types, because cancer cells are able to establish resistance mechanisms [51]. Such mechanisms cause chemotherapy to elude tumors. In chemotherapy Multidrug resistance (MDR) is one of the most serious problems. over expression of the plasma membrane p-glycoprotein (P-gp) MDR mainly occurs, which is capable of expel various positively charged xenobiotics, out of cells, including some anticancer drugs, [51]. Several techniques, including the use of colloidal carriers, have been implemented to restore the sensitivity of tumor cells to anticancer drugs by circumventing Pgp-mediated MDR. The reasoning behind the association of drugs with colloidal carriers, such as nanoparticles, with drug resistance stems from the fact that P-gp is likely to know that the drug is released from tumor cells only when it is present in the plasma membrane and not when it is found after endocytosis in the cytoplasm or lysosomes [52,53].

For oral delivery of peptides and proteins, nanoparticles: Significant developments in biotechnology and biochemistry have led to the discovery of a large number of peptides and protein based bioactive molecules and vaccines. Due to the fact that the bioavailability of these molecules is restricted by the epithelial barriers of the gastrointestinal tract and their susceptibility to gastrointestinal degradation by digestive enzymes, the creation of suitable carriers remains a challenge. Polymeric nanoparticles allow bioactive molecules to be encapsulated and are protected against enzymatic and hydrolytic degradation. For example, insulin-loaded nanoparticles have been found to sustained insulin activity and produced blood glucose reduction in diabetic rats for up to 14 days following oral administration [54].

In general, the gastrointestinal absorption of macromolecules and particulate materials requires either paracellular route or the endocytotic pathway to increase absorption by non-specific interactions. The paracellular route of absorption of nanoparticles utilizes less than 1% of mucosal surface area. The paracellular permeability of macromolecules can be improved by using polymers like chitosan [55], starch [56] or poly (acrylate) [57].

Nanoparticles for gene delivery: Polynucleotide vaccines function by transmitting genes to host cells where they are expressed encoding specific antigens, producing antigenic protein in the vicinity of cells presenting professional antigen to initiate immune response. These vaccines generate both humoral and cell-mediated immunity as intracellular protein development, as opposed to extracellular deposition, stimulates both arms of the immune system [58]. Due to their rapid escape from the degradative endo-lysosomal compartment to the cytoplasmic compartment, nanoparticles loaded with plasmid DNA may also serve as an effective sustained release gene delivery system [59].

Hedley et al. [60] reported that, nanoparticles could release DNA at a sustained rate following their intracellular uptake and endolysosomal escape, resulting in sustained expression of the gene. By using PLGA nanoparticles containing therapeutic genes such as bone morphogenic protein, this gene delivery method could be implemented to promote bone healing.

Nanoparticles for drug delivery into the brain: The most significant factor preventing the production of new drugs for the central nervous system is blood-brain barrier (BBB). Relatively impermeable endothelial cells with tight junctions, enzymatic activity and active efflux transport systems are characterized by BBB. It effectively prevents the movement of water-soluble molecules from the blood circulation into the CNS, through the action of enzymes or efflux pumps may also reduce the brain concentration of lipid soluble molecules [61]. Consequently, the BBB only permits selective transport of molecules that are necessary for brain function. Nanoparticle strategies targeting the brain are focused on the presence of nanoparticle interactions in the BBB with particular receptor-mediated transport systems. For example polysorbate 80/LDL, transferrin receptor binding antibody (such as OX26), lactoferrin, cell penetrating peptides and melanotransferrin have been shown capable of delivery of a self non transportable drug into the brain via the chimeric construct that can undergo receptor-mediated transcytosis [62-66]. It has been reported poly(butyl-cyanoacrylate) 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 [67].

CONCLUSION

Now, as we seen that nanoparticulate systems have great potentials, they able to convert poorly soluble, poorly absorbed and labile biologically active substance into good deliverable drugs. The core of the nanoparticle system can enclose a variety of drugs. With the help of nanoparticles we can formulate any dosage form which can easily cross the biological barriers. But still more advances are needed in order to turn the concept of nanoparticle technology into a realistic practical application.

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