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Review Article

NANOPARTICLES: A PROMISING DRUG DELIVERY APPROACH

RENU KADIAN*

Department of Pharmaceutical Sciences, PDM College of Pharmacy, Bahadurgarh, Jajjhar Haryana, India. Email: renukadian23@gmail.com

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ABSTRACT

Nanoparticles are particles having a size range of 1 and 100 nanometers, defined as a small object behaving as a complete unit with respect to the drug transport and therapeutic properties. They have several advantages such as improvement in the intracellular infiltration, enhanced hydrophobic solubility, and circulation time of the drug. They reduce non-specific uptake and side effects of the conventional drug delivery systems. Nanoparticles offer more effective and convenient routes of administration (oral, pulmonary, parenteral, and transdermal) and used for drug delivery for treatment of cancer, diabetes, pain, asthma, allergy, infections, and so on. They allow targeted delivery and controlled release of the drug. Further research on their mechanism of action to meet better stability of nanoparticles in the biological system could be done.

Keywords: Nanoparticles, Drug delivery, Targeted delivery, Bioavailability, Stability.

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INTRODUCTION

Nanoparticles are small object behaving as a whole entity with respect to its transport of drug to the target site with improved properties [1]. Nanoparticles have varied potential applications in pharmaceuticals, medical diagnostics, imaging, and therapeutic. Research on nanoparticles is of great benefit in surgeries and disease management by newer drug delivery approaches [2]. Nanoparticles are novel compounds which owing to their smallness have emerged as a new scientific field in medicines and technology over the past 10 years [3]. Unique physicochemical properties of nanoparticles are their ultra-smallness, greater surface area to mass ratio, and enhanced reactivity. These properties of nanoparticles help them to overcome the restrictions associated with traditional therapeutic and diagnostic agents [4]. Nanoparticles can integrate distinctive features that cannot be engineered into simple drugs and offer an exciting platform for drug delivery [5]. Nanoparticles are drug carriers with an improved capacity which provides greater stability to the drug entrapped inside it, leading to improved drug bioavailability and reduction in dosage frequency [6]. They could be considered a great candidate for future research on their stability and mechanism of action.

ADVANTAGES OF NANOPARTICLES

Nanoparticles are highly reactive species with unique physicochemical properties such as small controllable size and large surface to mass ratio [7]. They make the drug molecule more suitable for targeted drug delivery by improving their pharmacokinetic and pharmacodynamic properties [8]. Nanoparticles help in molecular targeted cancer therapy, recognition of cancer lesions, and determination of molecular signatures of the tumor by noninvasive imaging [9]. They have been considered an ideal choice for cancer therapy due to their ability to modify drug release from polymeric nanoparticles. They are also considered a good candidate for delivery of vaccines, contraceptives, and targeted antibiotics [10]. Nanoparticles permit more efficient drug use by protecting the drug in the systemic circulation and limiting admission of the drug to the selected sites. They also minimize unwanted side effects and deliver the drug at a controlled and sustained rate at the site of action [11] (Tables 1 and 2).

PREPARATION OF NANOPARTICLES FROM PREFORMED POLYMERS (E.G., POLY [LACTIC ACID], POLY [CYANOACRYLATE], AND POLYSTYRENE)

Emulsion solvent evaporation method

It is two step processes. In the first step, the polymer solution is emulsified into an aqueous phase, and in the second step, polymer solvent is evaporated, inducing polymer precipitation as nanoparticles which are collected by ultracentrifugation, washed with distilled water, and lyophilized for storage [23,24].

Double emulsion and evaporation method

The aqueous drug solution is added to organic polymer solution with vigorous stirring to form w/o emulsions. The w/o/w emulsion is then formed by the addition of second aqueous phase with continuous stirring. The solvent is removed from the emulsion by evaporation, and nanoparticles are separated by high-speed centrifugation [25]. Double emulsion technique is employed for encapsulation of hydrophilic drug [26].

Salting out method

Water-miscible solvent is separated from aqueous solution by means of a salting-out effect [27]. This method is of use for heat-sensitive substances, as it does not need an increase of temperature [28].

Emulsions-diffusion method

The encapsulating polymer is dissolved in a moderately water-miscible solvent and saturated with water. Then, the polymer-water saturated solvent phase is emulsified in stabilizer containing an aqueous solution. The solvent is eliminated by filtration or evaporation. The method does not need homogenization, has high reproducibility, and reduces scale up [29].

Solvent precipitation method

This method involves the preformed polymer precipitation from an organic solution and diffusion of the organic solvent in the aqueous medium in presence/absence of surfactants [30].

Dialysis

The proper molecular weight cutoff polymer is dissolved in an organic solvent and placed inside a dialysis tube. Dialysis is performed. The solvent displacement inside the membrane is followed by the

polymer aggregation and formation of homogeneous nanoparticles suspension [31].

Supercritical fluid technology
Supercritical fluids are an environmentally friendly solvent and have the potential of producing polymer nanoparticles with high purity [32]. It offers an interesting and effective technique of particle production and avoids the drawbacks associated with the traditional methods [33].

PREPARATION OF NANOPARTICLES BY MONOMER POLYMERIZATION (E.G., POLY [ISOBUTYL CYANOACRYLATES] [PICA], POLY [BUTYL CYANOACRYLATES] [PBCA], AND POLY HEXYL CYANOACRYLATES [PHCA])

Emulsion polymerization
One of the first methods used for the production of nanoparticles has become less important due to the use of toxic organic solvents [34,35].

Mini-emulsion polymerization
Mini-emulsion polymerization uses low molecular mass compound as the costabilizer and a high-shear device (ultrasound) [36].

Microemulsion polymerization
The water-soluble initiator is added to the aqueous phase of thermodynamically stable swollen micelles containing microemulsion. The particles are completely covered with a surfactant which possesses an interfacial tension, close to zero at the oil/water interface [37].

Interfacial polymerization
It is a type of step-growth polymerization in which polymerization occurs at an interface between an aqueous solution containing one monomer and an organic solution containing a second monomer [38,39].

PHYSICOCHEMICAL CHARACTERIZATION OF NANOPARTICLES

The transfection efficiency of nanoparticles is characterized by their particle size, morphology, and surface charge, using sophisticated microscopic techniques as scanning electron microscopy, transmission electron microscopy, dynamic light scattering, and atomic force microscopy [40]. The physical stability and distribution of nanoparticles are affected by particle diameter, size distribution, and their surface charge [41-43].

THERAPEUTIC APPLICATION OF NANOPARTICLES

For tumor-targeting drug delivery
Nanoparticles form an ideal solution for the anticancer drugs with improved selectivity and reduced side-effects toward the tumor cells. Drug-loaded nanoparticles can be engineered to perform more complex, cooperative targeting functions [5,44]. Nanoparticle-based drug delivery systems overcome the pharmacokinetic limitations associated with conventional formulations. Nanoparticle causes targeted cell death by interfering with the overexpressed proteins proliferation [45]. Etoposide or paclitaxel lipid nanocapsules showed a 4- to 40-fold higher efficiency in a cancer cell culture as compared to the drug solution. The nanoparticulate system was also found to meet efficient intracellular drug concentrations [46]. Nanoparticles were found to be beneficial for the selective delivery of oligonucleotides to cancer cells. Nanoparticles also show the capacity to overcome multidrug resistance in chemotherapy [47]. Iron oxide nanoparticles were found to act as both magnetic and photothermal agents, which lead to complete apoptosis-mediated cell death. Magnetic mode treatment used singly reduced the tumor growth, treatment with both modes resulted in complete tumor regression [48]. Gold nanoparticles functionalized exclusively to interact with biomolecules of interest because of their smallness and ease of bioconjugation, and thus, have emerged as candidates for targeting cancer cells, at the same time displaying low cytotoxicity [49,50]. Silk fibroin-derived curcumin nanoparticles found to be highly effective against breast cancer due to their local, sustained, and long-term therapeutic delivery [51]. Polymeric micelles represent an effective delivery system for poorly water-soluble anticancer drugs due to their ability to show prolonged circulation time in the blood and enhanced tumor accumulation [52].

For brain targeting drug delivery
The blood-brain barrier (BBB) is a fundamental, unique, and protective boundary which control homeostasis, ion, and molecule movement between blood and neural tissue [53]. Its unique characteristics are its relatively impermeable endothelial cells with tight junctions, enzymatic activity, and active efflux transport systems [54]. Hence, the BBB gives serious challenges to drug delivery into the brain. The use of nanoparticles formulation can target specific transport processes, may enhance drug transport through the BBB, and can target relevant regions in the brain for regenerative processes [55]. The novel apolipoprotein E-functionalized nanoparticles system was created to enter the brain. The system acted by enhancing the binding to low-density lipoprotein receptors present on the BBB of endothelial cells. The system was found to be dynamically stable and capable of an improved and specialized delivery of drugs through the BBB [56]. It is now possible to synthesize brain-targeted pegylated immunonanoparticles using peptidomimetic antibodies to BBB transcytosis receptor. These make possible the delivery of active drug entrapped in the brain parenchyma without inducing permeability alteration of BBB [57].

For oral drug delivery
It is the most common method of drug administration with a higher level of patient acceptance. However still, it is linked with a number of barriers, such as acidic pH of the stomach and digestive enzymes [58]. The nanoparticle delivery in this system occurs by transcytosis and intracellular uptake, and transport occurs through the epithelial cells lining intestinal mucosa and Peyer's patches [59]. It was studied by Sharma *et al*., that wheat germ agglutinin coated lectin-functionalized poly nanoparticles could be used as potential drug carriers for antitubercular drugs through the oral as well as aerosol route [60]. Nanoparticles with peptide ligands can be used for specific targeting in the gastrointestinal tract [61]. VB12-dextran nanoparticle conjugate was found to be a viable carrier for oral insulin delivery in animal models of diabetes [62]. It was studied that nanoparticles offer a suitable method for oral delivery of water-insoluble drugs such as rapamycin. It was reviewed that polymeric nanoparticles prevent inactivation and degradation caused by acidic pH and digestive enzymes [57]. A nanoparticle adheres to the mucosa and thus enhances the absorption of the associated drug [63]. Neonatal Fc receptor present in the small intestine and colon is the target for nanoparticles [64]. It was concluded that FcRn-targeted nanoparticles may enable effective delivery of drugs whose action is limited by low bioavailability through oral administration [65].

For transdermal drug delivery
Topical or transdermal drug delivery is a challenge as the skin acts as a natural and protective barrier [66]. The protective function of the skin is attributed to the epidermal stratum corneum layer. This layer also regulates the transport of compounds into the skin [67]. The nanoparticles act as a reservoir of lipophilic drugs and deliver them to the stratum corneum. Polymeric nanoparticles increase the drug adhesivity and duration for skin permeation [68]. The gelatin pilocarpine hydrochloride (HCl) or hydrocortisone nanoparticles produced using a desolations method showed sustained drug release compared to the aqueous solution of the drugs [69]. Vitamin A-loaded glyceryl behenate solid lipid nanoparticles showed increased drug release as compared to nanoemulsions. It was observed that polymorphic transitions and drug release were correlated [70].

For parenteral drug delivery
Parenteral formulations, mainly intravascular, offer a benefit of direct administration of the drug into the bloodstream and fast onset of drug action [71]. Further, it is also useful as passive drug delivery to inflammatory sites [72]. It was studied that miR-34a and siRNAs coformulated in GC4-targeted nanoparticles, when administered as

Table 1: Method for preparation of nanoparticles: From preformed polymers (advantages and disadvantages)

S.No.	Method	Advantages	Disadvantages	Formulations
1	Solvent evaporation method	Suitable thermolabile drugs Small particle size around 100 nm with narrow size distribution can be achieved	Presence of solvent residues in the final dispersion may create problems The partial solubility of lipids in organic materials leads to dilute dispersions and requires concentration by ultra-filtration, evaporation, or lyophilization Poor entrapment of hydrophilic drugs	Ibuprofen loaded Eudragit-S100 nanoparticles [12]
2	Double emulsion and evaporation method	Used for encapsulation of hydrophilic drugs	Characterization of nanoparticles is affected by the amount of hydrophilic drug to be incorporated, a concentration of stabilizer used, polymer concentration, and the volume of aqueous phase	Daunorubicin-loaded polymeric nanoparticle [13]
3	Salting out method	Minimizes stress to protein encapsulants Does not require an increase in temperature, and therefore, useful for heat sensitive substances	Exclusive application of lipophilic drugs Extensive nanoparticle washing steps	Isoniazid-loaded nanoparticles [14]
4	Emulsions-diffusion method	High encapsulation efficiencies (>70%) Needs no homogenization High batch to batch reproducibility Ease of scale-up Simple and narrow size distribution	High volumes of water to be eliminated from the suspension Leakage of the water-soluble drug into the saturated-aqueous external phase during emulsification Reduced encapsulation efficiency	Nanoparticles loaded Neem oil [15]
5	Solvent precipitation method	Simple and rapid preparation Easy control of particle size and composition Suited for most of the poorly soluble drugs	Particle size is affected by rates of addition of the organic phase into the aqueous phase	Azithromycin nanoparticles [16]
6	Dialysis	Simple and effective method	The solvent used in the preparation of the polymer solution affects the morphology and particle size distribution of the nanoparticles	Vancomycin-loaded N-trimethyl chitosan nanoparticles [17]
7	Supercritical fluid technology	Environmentally safer method Use environmental friendly solvents Produce nanoparticles with high purity and without any trace of organic solvent Avoid drawbacks of the traditional methods	Concentration and degree of polymer saturation have a considerable effect on the size and morphology of the particles	Carbamazepine-loaded solid lipid nanoparticles [18]

Table 2: Method for preparation of nanoparticles: By monomer polymerization (advantages and disadvantages)

S.No.	Method	Advantages	Disadvantages	Formulations
1	Emulsion polymerization	Fastest method Readily scalable	It requires toxic organic solvents, surfactants, monomers, and initiator, which are subsequently eliminated from the formed particles	Organic-inorganic nanocomposite particles [19]
2	Mini-emulsion polymerization	The typical formulation used in mini-emulsion polymerization consists of water, monomer mixture, co-stabilizer, surfactant, and initiator	Critically stabilized, require a high-shear to reach a steady state	Hydrogels in miniemulsions [20]
3	Micro-emulsion polymerization	No specialized equipment required No energy required Scale-up production possible	Particle suspension diluted with water, removal of excess water is needed Surfactants and co-surfactants concentration is high in the formulation, which has to be removed using ultrafiltration, ultracentrifugation, or dialysis	Organic and inorganic nanomaterials [21]
4	Interfacial polymerization	Well-established methods	The organic solvent, which is completely miscible with water, served as a monomer vehicle	Lomustine-loaded PLGA nanoparticles [22]

daily two intravenous injections showed an enhanced anticancer effect [73]. This technology by escalating the amount of drug reaching the target site improves drug delivery to macrophages, and thus, reduces therapeutic dose and adverse effects [74]. Nanocrystalline clofazimine was found to be equally effective when administered as liposomal clofazimine in reducing bacterial loads in the liver, spleen, and lungs of infected mice following i.v. administration [75]. The single subcutaneous dose of poly DL-lactide-co-glycolide nanoparticles of three front-line antitubercular drugs resulted in sustained therapeutic drug plasma levels in the lungs and spleen. The mean residence time and absolute bioavailability of drug were also found to be increased several times demonstrating a better chemotherapeutic efficacy [76].

For pulmonary drug delivery

The potential benefit of the direct delivery of the drug to the lungs is that it reduces systemic toxicity and higher drug concentration at the site of infection can be achieved [59]. The route offers a high surface area and rapid absorption because of high vascularization of the lungs, and another benefit is that it circumvents the first pass effect [77]. A possible obstacle for pulmonary nanocarriers is their small mass median aerodynamic diameter, an essential parameter for the particle deposition in the lungs [78]. Poly DL-lactide-co-glycolide nanoparticles of three frontline antitubercular drugs form a sound basis for improving drug bioavailability and reducing the dosing frequency for better management of pulmonary tuberculosis [79]. It was studied that pulmonary delivery of solid lipid nanoparticles of amikacin by microsprayer reduced its side effects in the kidneys and prolonged the dosing intervals due to the sustained drug release [80]. Gelatin and poly (lactic-co-glycolic) acid nanoparticles of plasmid DNA encoding a yellow fluorescent protein or rhodamine-conjugated erythropoietin for inhalational delivery enhances the duration of protein expression [81]. Biodegradable hydroxybenzyl alcohol-incorporated polyoxalate nanoparticles when studied as antiasthmatic agent remarkably reduced the recruitment of inflammatory cells and expression of pro-inflammatory mediators such as IL-4 and iNOS [82]. Formulation of paclitaxel-loaded poly (glycolide-co-ε-caprolactone)-b-D-α-tocopheryl polyethylene glycol 2000 succinate nanoparticles minimized the side effects of the drug and improved its therapeutic efficacy in lung chemotherapy [83]. Chitosan and glycol chitosan nanoparticles of low molecular weight heparin were evaluated for the systemic delivery after pulmonary administration, and the results illustrated promising features [84].

For ocular drug delivery

Ocular drug transport barriers possess the challenge because of the tear film, blood-aqueous barrier, and blood-retinal barrier [85]. Nanoparticles have the advantage that they show improved topical passage of large, poorly water-soluble molecules such as glucocorticoid and cyclosporine, and are useful in immune-related and vision-threatening diseases [86]. When combined with controlled drug delivery, they reduce the drug dose and administration frequency. They also decrease side effects and help in the site-specific targeting of the drug [87]. Drug-loaded polymeric nanoparticles offer several favorable biological properties such as biodegradability, nontoxicity, biocompatibility, and mucoadhesiveness [88]. Cyclosporine A nanoparticles, when used for the treatment of eye inflammation, was proved to be a useful approach because of improved ocular retention and bioavailability [89]. Brimonidine tartrate-loaded chitosan nanoparticles showed sustained release and confirmed a significant sustained effect as compared to conventional eye drops [90]. It was found that positively-charged pilocarpine HCl-loaded polymeric and lipid nanoparticles were prepared successfully and had potential use for ophthalmic delivery [91]. It was studied that comparison to free drug solution, nanostructured lipid carriers formed by incorporation of liquid oil in the structure of solid lipid nanoparticles were more capable of faster permeation through the excised cornea [92].

For intranasal drug delivery

Oral, parenteral, rectal, and other routes of drug administration are associated with a number of problems, which increased the interest of pharmaceutical scientists toward exploring the possibilities of intranasal drug delivery [93]. The drug delivered by the intranasal route bypasses the BBB. Nanoparticles are taken up by olfactory neurons and conveyed along cell processes to synaptic junctions with neurons of the olfactory bulb [94]. Neurological conditions that could benefit from nose-to-brain delivery of nanotherapeutics are the pain, epilepsy, neurodegenerative disease, and infectious diseases [95]. The rivastigmine-loaded chitosan nanoparticles were found to have better brain targeting efficiency and were considered a promising approach for intranasal delivery for the treatment and prevention of Alzheimer's disease [96]. Bromocriptine-loaded chitosan nanoparticles studied as a delivery system to enhance the brain targeting efficiency following intranasal administration were found to have improved drug targeting index and direct transport percentage [97].

CONCLUSION

Nanoparticles have been shown to have varied prospective applications in pharmaceutics. They have been found to be beneficial in diagnosis, treatment, and surgeries. Nanoparticles improve the stability of drug inside the body by protecting the drug molecule inside systemic circulation. They also confine access of the drug to a specific site at a controlled and sustained rate. The main concern of future research can be done in preparation of nanoparticles which can further withstand the biological diversities and thus further improve drug stability in the biological environment and hence its bioavailability.

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