REVIEW ARTICLE

Historical Development, Preparation, Characterization, and Pharmacokinetics of Nanoparticles: A Review

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Abstract

In recent years, there has been a considerable research interest in the development of novel drug delivery systems using nanoparticles (NPs) as a drug carrier for small and large molecules. The development of nanoscale carriers is capable of delivering that the active drug has the potential to overcome both systemic and different barriers and also provides specific, sustained, and targeted delivery at the site of action for therapeutic potency. The conventional drug therapies are having some limitations, and they produce fluctuations in plasma drug levels. Conventional drug therapies do not provide linear and sustained action compared to NPs in general. Nanonization technologies established a commercial matured drug delivery platform. Nanotechnology has attained specific importance and platform due to a steadily increase in number of the development of compounds showing poor aqueous solubility. The NPs consist of pure active pharmaceutical ingredients, and these particles are often stabilized with surfactants, and polymeric stabilizers adsorbed onto their surface. The nanoparticulate drug delivery system mainly includes nanoemulsion, nanosuspension, liposomes, nanoimplants, lipid, or polymeric NPs. NPs have been improving the therapeutic effect of drugs and minimize the side effects. The present review paper comprised the advantages and disadvantages, formulation aspects and characterization of NP as drug delivery system.

Key words: Drug release, nanoparticles, nanotechnology, polymeric nanoparticle

INTRODUCTION

Nanoparticle (NP) is defined as solid particles with a size ranging from 10 to 1000 nm in diameter.[1] Nanoparticulate drug delivery system called as colloidal drug delivery system. NPs are prepared from biocompatible and biodegradable polymers where the drug is dissolved, entrapped, and attached to a NP matrix.[2]

The conventional marketed formulations such as solution and suspension are having some limitations such as dose frequency, low bioavailability, first pass effect, intolerability, and instability. Due to these un-unique problems, they used to produce fluctuations in plasma drug levels and does not provide adequate and sustained action.[3] Hence, the major goal of the nanoparticulate system is to reduce these limitations by controlling the particle size, surface properties, and release of pharmacologically active agents to achieve the target specific action of the drug at an optimal rate and dose regimen.[4] In recent developments, nanotechnology is taking a great platform for drug carriers. They exhibit a linear physicochemical and biological property as they have a good ability to cross the cell and tissue barriers.[5]

HISTORICAL DEVELOPMENT OF NP

The originality of discovering NPs is being an interesting and leviathan success in drug targeting or drug-specific field. The progenitor of NP has done by a giant known as Paul Ehrlich.

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Paul Ehrlich called as father of NPs, who has started up the concept of NP after attending Karl Maria von Weber's Opera. His eminent concept was to improve drug therapy by targeting the principle (drug or biologically active materials).[6] In the early years, NPs were trended in the drug targeting field due to their unique pharmaceutical, biopharmaceutical, and pharmacokinetics parameters. The promoter, professor Peter Paul Speiser and his illustrious research team prepared first beads of polyacrylic for oral administration, afterward they have investigated polyacrylic microcapsules and finally they have prepared NPs/nanocapsules for the sustained release of drug in the treatment against vaccine, tetanus, diphtheria, and others infection.[7,8]

Early stage of 1969, "Micelle polymerization" technique was initiated by Gerd Birrenbach to prepare NPs and prepared NPs were applied for antibody responses. Afterward, Helmet Kopf worked on the same principle "micelle polymerization" to establish first NPs for sustained drug delivery through the intravenous route of administration.[9,10] Another pioneer of NPs was Patrick Couvreur who made first rapidly biodegradable NPs. Patrick Couvreur produced acrylic NPs which made up of poly (methyl cyanoacrylate) and poly (ethyl cyanoacrylate).[11] Using the same process NPs were fabricated using different solvents and perpetrated great success.

Later on, NPs were prepared using active drugs materials incorporating with magnetic particles and the prepared NPs were localized at the specific area of the body for the delivery of the drug using an external magnetic field.[12-14] These prepared magnetic NPs were revealed promising results when investigated in rats having tumor.[15,16] Next, in Japan, NPs were prepared by binding of 5-fluorouracil (5-FU) to albumin NPs and checked the drug release study and bio-distribution of NPs in an animal model for the efficacy purposes.[17]

Toward the end of early years, the pioneers worked on the definition of NPs. NPs were defined as the solid colloidal particles having the size range from 1 nm to 1 µm. The NPs mainly comprised micromolecular structural substances which are intended for carrier of therapeutically active drug. NPs were prepared in such a manner where the therapeutically active constituents are dissolved and entrapped or encapsulated.[18-21] In later developments application of NPs was increased tremendously in the different aspect or field for the delivery of the active principle (active drug or active materials). NP was being used for different drug delivery system including delivery of anti-infective drugs, delivery of anti-cancer drugs, drugs targeting for tumor, gene delivery, and AIDS therapy.[22-25]

Advantages of NPs[4,5,26-29]

The advantages of using NPs as a drug delivery system are as follows:

1. Particle size, particle shape and surface characteristics of NPs can be easily manipulated after parenteral administration to achieve both passive and active drug targeting.
2. Using NPs drug can be target to a specific site in the body which can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
3. NPs improve bioavailability by enhancing the aqueous solubility of the drug.
4. NPs increase the residence time or half-life of the drug molecules in the body.
5. NPs can be easily formulated in large scale by various methods to increase the stability of any pharmaceutical agents.
6. By the choice of a polymer and ability to modify the controlled release and particle degradation characteristics can be easily modulated.
7. Small sized NPs can penetrate through the smaller capillary wall, which could allow efficient drug accumulation at the target sites.
8. They offer a significant improvement over oral and intravenous methods of administration in terms of therapeutic efficiency and effectiveness.
9. Nutraceuticals are the essential components for health benefits derived from food sources. In recent times, these nutraceuticals and related standardized components also delivered by the form of NPs.

Disadvantages/Limitations[3,27]

i. Due to the small size and large surface area of NPs can lead to particle-particle aggregation during storage and transportation of NP dispersion which makes the physical handling of NPs difficult in liquid and dry forms.
ii. NPs are very reactive in cellular environment due to their small particle size and greater surface area.
iii. Small particle size and large surface area readily result in limited drug loading and burst release. These practical problems have to be overcome before NPs used clinically.

PREPARATION OF NPs

Many methods are used to prepare NPs. All of methods allow extensive modulation of their structure, composition, and physiochemical properties. The choice of the methods essentially depends on the raw materials intended to be used and on the solubility characteristics of the drugs to be associated with the particles.

The methods for preparation of NPs can be classified as:

A. Methods for preparation of NPs from dispersion of synthetic preformed polymer:
   i. Solvent evaporation method
   ii. Nanoprecipitation method
   iii. Spontaneous emulsification or solvent diffusion method

iv. Salting out method and
v. Supercritical fluid technology.

B. Ionic gelation or coacervation of hydrophilic polymers.

SOLVENT EVAPORATION METHOD[30-34]

In this technique, the preformed polymer and drug are dissolved in water-immiscible organic solvents such as dichloromethane, chloroform, or ethyl acetate. The mixture of polymer and drug solution is emulsified in an aqueous solution containing a stabilizer such as surfactant or emulsifying agent to form oil in water type emulsion. The crude emulsion is then exposed to a high energy source such as sonicators or homogenizers to reduce the globule size. The subsequent removal of the organic solvent by heat results in the formation of a fine aqueous dispersion of NPs.

Lee *et al.,* 2006, prepared self-assembled NPs using this method in which a small amount of an immiscible solvent (chloroform) with water to flue gas conditioning NP suspensions in aqueous media followed by ultrasonification and solvent evaporation led to partial dissociation and subsequent reformation of NPs. In another study, Paswan and Saini, 2017, prepared tamoxifen loaded poly lactic-co-glycolic acid (PLGA) NPs using the solvent evaporation method. In this method, the drug (tamoxifen) and biodegradable polymer (PLGA) were dissolved in a volatile organic solvent (dichloromethane and methanol) which act as the oil phase. The solution (oil phase) was then slowly injected into an aqueous phase containing a surfactant (polyvinyl alcohol [PVA]) under continuous sonication to emulsify. The resulting emulsion was continuously stirred to allow evaporation of volatile organic solvent leaving behind the drug-loaded polymeric NPs suspended in the aqueous surfactant solution. Similar method was used for the preparation of polymer NPs from a clear solution of mixed solvents by Yabu *et al*., 2005. Here, a good solvent (tetrahydrofuran [THF]) and a poor solvent (water) were used for dissolving polystyrene. The solution was then slowly added to the THF solution through a syringe pump with dropping speed of 1 ml/min. Gradual evaporation of the good solvent from the mixed solution at room temperature induces precipitation of the polymer as fine particles. During evaporation of the good solvent, the solution gradually turns turbid from the clear optically transparent solution.

NANOPRECIPITATION METHOD[35-38]

Nanoprecipitation method is also known as the solvent displacement method. It involves the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium in the presence or absence of a surfactant. In this process polymer, drug and a lipophilic stabilizer are dissolved in a semipolar (intermediate polarity) water-miscible organic solvent such as acetone (ACE) or ethanol, leading to the precipitation of nanospheres. Then, this solution is poured or injected into an aqueous solution containing a stabilizer like surfactant under magnetic stirring. Polymer deposition on the interface between the water and the organic solvent caused by rapid solvent diffusion leads to the instantaneous formation of colloidal NPs or suspension and the solvent is then eliminated from the suspension under reduced pressure.

Karmi *et al*., 2011, in their research study used nanoprecipitation method which included dissolving PLGA copolymer and 5-FU in dimethylformamide. When the organic phase was slowly added to the aqueous phase by inserting the syringe directly into the magnetically stirred dispersed phase and continuously stirring for 1 h, nanoprecipitation occurs due to the contact of the organic phase with an aqueous phase, thus allowing for the formation of solid spherical homogenous NPs. The suspension formed was centrifuged 4 times for 15 min and dried using a speed dryer at 35°C for 1 h. Salatin *et al.*, 2017, prepared Eudragit RL 100 NPs containing RHT through a nanoprecipitation or solvent displacement method. First, the drug was dissolved in an aqueous solvent (water). Second, the polymer was dissolved in the organic solvent (ACE). The mixture was formed by injecting the RHT aqueous solution dropwise into the Eudragit RL 100 organic solution and was magnetically stirred at 500 revolutions per minute (RPM). This mixture was then added to an external aqueous solution under agitation containing poloxamer 407 as a suspension stabilizer and was magnetically stirred at room temperature for 2 h at a speed of 400 RPM to evaporate the organic solvent. The NPs obtained were recovered by centrifugation (Eppendorf, Germany) for 60 min at 12,000 RPM and 4°C.

SPONTANEOUS EMULSIFICATION OR SOLVENT DIFFUSION METHOD[39-42]

This is a modified technique of solvent evaporation method. In this method, the water-miscible solvent along with a small amount of water-immiscible organic solvent is used as an oil phase. Formation of small particles occurred due to the spontaneous diffusion of solvents which leads to interfacial turbulence between the two phases and a decrease in the size of the particle can be achieved by increasing the concentration of water-miscible solvent. One technical characteristic of this technique is the use of a binary mixture of a water miscible organic solvent and a water immiscible solvent for the polymeric solution, and the particles are formed by spontaneous emulsification and subsequent solvent evaporation. Both solvent evaporation and solvent diffusion techniques can be used for hydrophilic or hydrophobic drugs.

Trotta *et al*., 2003, prepared glyceryl monostearate NPs using diffusion technique and water used as a solvent. Tween 80, Oramix CG-110, Epikuron 200, taurodeoxycholic acid sodium salt, or cholic acid sodium salts were used as emulsifier which

had been accepted as low toxicity. Glyceryl monostearate (GMS) were dissolved in water-saturated solvent and this organic solution was emulsified at 47 ± 2°C with solvent-saturated aqueous solution containing an emulsifier mixture, using an Ultra Turrax (IKA, Staufen, Germany) at 12,000 RPM for 1 min. On quick addition of water to the preformed emulsion, the lipid NPs were precipitated so as to extract the solvent into the continuous phase. Purification of the suspensions was done after the continual stirring of 60 min. Chen *et al*., 2014, used modified spontaneous emulsification solvent diffusion (modified-SESD) method for synthesizing curcumin-loaded PLGA NPs (PLGA-Cur NPs). In this method, PLGA was dissolved in ACE, and the hydrophobic drug curcumin was dissolved in ethylene (ETH). After dissolving, the curcumin/ETH solution was added in a dropwise manner to the PLGA/ACE solution which was used as the organic phase. To an aqueous PVA solution, the organic phase was further added using a peristaltic pump at a flow rate of 2 mL/min with continuous stirring for solidification of the NPs. The NPs suspensions were collected by ultracentrifugation at 12,000 RPM/min after the removal of residual organic solvents by evaporation under negative pressure for 3 h.

SALTING OUT METHOD[31,43,44]

This method is based on the separation of a water-miscible solvent from aqueous solutions through salting out effect. Salting out method is considered as a modification of solvent diffusion technique. In this method, ACE is generally considered as the water-miscible solvent due to its solubilizing properties and its well-known separation from aqueous solutions by salting out with electrolytes. In this technique, the preformed polymer and drug are initially dissolved in a solvent like ACE and this solution is emulsified under vigorous magnetic stirring in an aqueous gel containing the salting-out agent (electrolytes such as magnesium chloride, magnesium acetate, calcium chloride, or non-electrolytes such as sucrose) and a colloidal stabilizer like polyvinylpyrrolidone. The resulting emulsion is then diluted with a sufficient volume of water to enhance the diffusion of ACE into the aqueous phase, thus indicating the formation of NPs. Then, the solvent and salting out agent are eliminated through cross-flow filtration.

In a study by Eley *et al.*, 2004, Poly (Lactide-co-Glycolide) NPs containing coumarin-6 for suppository delivery were produced by salting out method. A water-soluble polymer, PVA or Mowiol 4–88, and a salting-out agent, magnesium acetate tetrahydrate, were dissolved in distilled water at 40°C to form an aqueous gel. Furthermore, in a solution of ACE and coumarin-6, polymer PLGA was dissolved in a predetermined ratio. To this organic solution containing the drug and the polymer, the formed aqueous gel was added with continuous stirring at a constant temperature of 40°C forming an oil-in-water emulsion. Additional distilled water was then added to this emulsion under constant stirring at an ambient temperature allowing the diffusion of solvent into the aqueous phase which in result formed the drug-containing polymeric NPs in a water-in-oil emulsion. Zweers *et al*., 2004, produced NPs of poly (dl-lactic acid), poly (dl-lactic-co-glycolic acid) (PLGA), and poly (ETH oxide)–PLGA diblock copolymer by the salting-out method. The method consists of the addition of a water-soluble PVA in a highly concentrated salt (magnesium chloride) solution in water (aqueous phase) to a polymer solution in ACE (organic phase). NPs were formed after quick addition of pure water under mechanical stirring (20,500 RPM) for 20 s causing ACE to diffuse into the water phase.

SUPERCRITICAL FLUID TECHNOLOGY[30,45,46]

In recent years, supercritical fluid technology has good enough advantages as compared to conventional methods (solvent evaporation, solvent diffusion, organic phase separation, etc.). Variety of NPs can be produced using supercritical fluids such as water and carbon dioxide. Without using any trace of organic solvent, NPs can be prepared which is safer to the environment as well as human beings.

Using supercritical fluids, two methods developed for the preparation of NPs

1. Rapid expansion of supercritical solution (RESS) and
2. RESS into liquid solvent.

RESSs[27-31]

The steps involved are:

i. Dissolving the solid substance in a supercritical fluids and
ii. Formation of particles due to supersaturation

In this process, initially supercritical fluid-CO_2 is used to pump at a preferred pressure and temperature to extraction chamber which is having the solid substances through heat exchanger. Then, the supercritical fluid percolates and dissolves the solid substances in the extractor. Depressurization of the resulting solution through heated nozzle or capillary at supersonic speed into a low-pressure chamber. The supercritical solution is spread continuously in the chamber, which leads to rapid drops in temperature and pressure and continuous formation of particles. During this process, the density and solvent power decrease significantly, resulting in supersaturation of the solution and consequently precipitation of desire particles which are free of residual solvents. This process is also known as supercritical fluid nucleation.

RESS into Liquid Solvent[47,48]

This is a modified method of RESSs method to use a cosolvent. The main step involved in the solubilization of solute and solid cosolvent in the supercritical fluid followed

by expansion of the resultant solution through the nozzle in the expansion vessel, and finally, the solid cosolvent is removed by sublimation. This method is used to overcome the low solubility of polar drugs in a supercritical fluid and the aggregation of particles in the expansion zone.

IONIC GELATION OR COACERVATION OF HYDROPHILIC POLYMERS[49-51]

In this method, the NPs are prepared using biodegradable hydrophilic polymers such as gelatin, chitosan, and sodium alginate. This method involves a mixture of two aqueous phases in which one is polymer chitosan, a di-block copolymer ethylene oxide/propylene oxide and the other is a poly-anion sodium tripolyphosphate. In this process, positively charged amino group of chitosan react with negatively charged tripolyphosphate to produce coacervates with a size in the range of nanometer. Coacervates are formed as a result of electrostatic interaction between two phases whereas ionic gelation involves the material undergoing a transition from liquid to gel due to ionic interaction conditions at room temperature.

Avadi *et al*., 2010, developed insulin NPs based on ionic gelation between chitosan and Arabic gum. Chitosan was dissolved in acetic acid aqueous solution under magnetic stirring at room temperature, to this solution different amounts of insulin were added. Meanwhile, Arabic gum was dissolved in water under magnetic stirring at room temperature. The Arabic gum solution was added dropwise to chitosan solution containing insulin under gentle magnetic stirring at room temperature to produce the NPs. Similar method had been used by Fan *et al*., 2012, for the preparation of low molecular weight chitosan NPs.

CHARACTERIZATION/EVALUATION OF NPs

Different types of advanced imaging microscopic techniques are used for the study of characterization of NPs for their size, morphology, and surface charge in submicron size. The different techniques such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), scanning tunneling microscopy, and atomic force microscopy (AFM) are developed. The principles are different for all techniques, but one common thing is that they produce a highly magnified image of the surfaces of the NPs.

PARTICLE SIZE AND SHAPE

In the nanoparticulate system, the particle size, size distribution, and morphology are the most important parameters of characterization of NPs.[52] In the nanoparticulate system, particle size determines the *in vivo* distribution, biological rate, toxicity, and targeting ability.[2] One of the parameters affecting the rate of cellular uptake of NPs is its size as it influences their internal mechanism, and thus affects the *in vivo* circulation half-life.[52] Cellular internalization of NPs is majorly dependent on the size of the NPs, and in general, particles in the 40–50 nm range exhibit maximal uptake *in vitro*. It also influences the drug release, drug loading, and stability of the NPs. The smaller particles are having the larger surface area. As a result, most of the drug loaded onto them will be exposed to the particle surface leading to fast drug release.[53] The accepted size range for the development of NPs is 10–100 nm for *in vivo* applications which relates to their *in vivo* clearance and biodistribution patterns. Polymer degradation can also be affected by the particle size.[54]

The majority of NPs developed for drug delivery have a spherical shape. Recent studies have shown that particle shape may be an important factor in the rate of NP cellular internalization. The shape of NPs is also an important factor for the biodistribution and circulation of NPs *in vivo*.[55]

Different methods are used for the determination of the size of NPs. The technology used for the NP size determination includes dynamic light scattering,[56] SEM,[57,58] TEM,[58] and AFM.[59]

ZETA POTENTIAL

Zeta potential is a technique which is commonly used for determining the surface charges of the NPs in colloidal suspension. Hence, the nature and intensity of the surface charge of NPs are very important to characterize their interaction with the biological environment and their electrostatic with bioactive compounds.[60] Zeta potential provides the colloidal stability of the NPs. NPs have a surface charge that attracts a thin layer of ions of opposite charge to the NP surface. This double layer of ions travels with the NP as it diffuses throughout the solution.[61] The electric potential at the boundary of the double layer is known as the zeta potential of the particles and has values that typically range from +100 mV to −100 mV. The magnitude of the zeta potential is predictive of colloidal stability. NPs with zeta potential values >+25 mV or <-25 mV typically have high degrees of stability.[62] Dispersions with a low zeta potential value will eventually aggregate due to Van Der Waal interparticle attractions. High zeta potential values, either positive or negative, should be achieved to ensure stability and avoid aggregation of the particles. The extent of surface hydrophobicity can then be predicted from the values of zeta potential. The zeta potential can also provide information regarding the nature of material encapsulated within the nanocapsules or coated onto the surface. Zeta potential is an important tool for understanding the state of the NP surface and predicting the long-term stability of the NP.[61]

SURFACE HYDROPHOBICITY

Surface hydrophobicity of NPs has been investigated as a function of the NP content. Surface hydrophobicity is the surface chemistry of NP which is key determinant of their fate, transport, and toxicity. Surface hydrophobicity can be determined by several techniques such as hydrophobic interaction chromatography, biphasic partitioning, adsorption of probes, and contact angle measurements. Recently, several sophisticated analytical techniques are reported in the literature for surface analysis of NPs. X-ray photon correlation spectroscopy permits the identification of specific chemical groups on the surface of NPs.[63] Moreover, hydrophobic surfaces of NPs can be easily bound with opsonins and to avoid this interaction; surface modification is carried out with hydrophilic polymers.[63]

DRUG LOADING AND ENTRAPMENT EFFICIENCY OF NP

Drug loading of the NPs can be defined as the amount of drug bound per mass of the polymer (usually moles of drug per mg polymer or mg drug per mg polymer). Nanoparticulate drug delivery has the potential to improve the effectiveness of the small drug molecule.[64] Nanoparticulate drug loading is highly dependent and variable on the method of preparation. A nanoparticulate system should have a high drug loading capacity. The pharmacokinetic and pharmacodynamic parameters of the small drug molecules *in vivo* also depend on the drug loading capacity of the NP. In the nanoparticulate system, the drug loading and entrapment efficiency of the NPs is mostly depending on the solid-state drug solubility in matrix materials or polymer relating to the matrix composition, molecular weight, drug-polymer interactions, and end functional groups present (i.e.,. ester or carboxyl) in either the drug or matrix.[65,66] The macromolecules or protein shows the greatest loading efficacy when the drug loading is carried out at or near the isoelectric point. At the isoelectric point, macromolecules or proteins are having minimum solubility and maximum adsorption. Drug loading can be effectively increased through the interaction between the drug and matrix materials.[67]

DRUG RELEASE AND RELEASE KINETICS OF NP

In the nanoparticulate system, the NPs are prepared and coated with a polymer, which releases the drug by controlled diffusion or erosion from the core across the polymeric membrane or matrix.[68] The polymeric membrane is act as a barrier for drug release. Hence, the solubility and diffusivity of the drug in the polymer membrane become the determining factor in drug release.[69] The drug release capacity is also affected by the interaction between the drug and polymer or additional ingredients. The drug release and polymer biodegradation are the very important factors in an ideal nanoparticulate system. Drug release of NPs is affected by various factors such as solubility of the drug, drug diffusion through the polymeric membrane, erosion or degradation of the polymeric membrane, combination of diffusion and erosion process and release of the drug from the surface of the NPs.[70]

Therefore, the drug release from the NPs depends on three different mechanisms:

I. Release from the surface of NPs due to erosion
II. Diffusion through the swollen polymeric matrix
III. Combination of both the processes, i.e.,. erosion and diffusion.

PHARMACOKINETICS OF NPs

Application of NPs in current time is being remarkable. Development of nanosized range particles increased enhanced the absorptivity of the drug, tissue distribution, and also enhanced bioavailability. The pharmacokinetic parameters of NP are directly influenced by the size and shape of the NPs and surface morphology of NP.[71] Therefore, therapeutic effect as well as tissue distribution of NP mainly influenced by the pharmacokinetic profile of NP. In this part of our review paper, we concentrated to build the relationship between pharmacokinetic and biodistribution of NP. The pharmacokinetic study mainly conducts for the quantitative determination of drug concentration in the biological system until eliminated from the biological system, and various pharmacokinetic parameters comprised maximal concentration, half drug of the drug, clearance, area under curve, and average/mean residence time.

The accumulation of active materials in the specific site is considered as to enhance the therapeutic efficacy but there is also a high chance to accumulate of active materials in the nonspecific site to cause the side effects or toxicity. For this purpose, pharmacokinetic and biodistribution pattern of the NPs are very important to optimize the formulations. The pharmacokinetics parameter of free drug and entrapped drug can be easily understood by studying the serum protein binding behavior. Free drug can be easily affected by the enzyme environment in the biological system but the NPs cannot be easily affect by the enzymes due to have a coat on the active drug, and finally the retention time of NPs in the biological system or blood circulation used to increase to shoe the prolonged therapeutic effect. Primary delivery of the NP is mainly facilitated by the endothelial wall present in the tissue. Pharmacokinetic of NPs is mainly influenced by the physical and chemical behavior of the NPs. The surface morphology can be modified by using different polymer like polyethylene glycol. Modification of the surface of the NP reduced the rate of mononuclear phagocyte system, and the drug formulation retain in the blood circulation for a longer

period of time to produce better pharmacokinetics of NPs. The rate of mononuclear phagocyte system can be also decreased by controlling the size of the NPs and reported average particle size of NP approximately 100 nm. Formulation of neutral NP having a diameter of 200 nm also can improve the pharmacokinetic of the NP.[72-75]

CONCLUSIONS AND FUTURE PROSPECTS

The utilization of the nanoparticulate system is manifold due to the increased drug residence time in biological circulation and also improved the cellular uptake as well as half-life of some hydrophilic drugs. These teeny particles are having the dynamic penetration power through the biological barrier to pose the therapeutic effect. Through the attempt of nanoparticulate system water-insoluble drug also delivered for its better effect. Magnetic NPs with their magnetic properties afford excellent sensitivity for its specific target. Application of the nanomaterials is tremendously increasing in the treatment of numbers of life-threatening diseases. However, the surface morphology and particle size of NPs are major problems in the drug delivery field. The optimization is still needed for manufacturing NPs for the prominent drug delivery and also to profile pharmacokinetic as well as quantification of active materials. In addition, accumulation of NPs with the antibody or others substances is very essential for the targeted drug delivery.

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