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Review Article

NANOPARTICULATE DRUG DELIVERY SYSTEM - REVIEW

Rashmi .C*, J. Adlino Jino Nesalin and T. Tamizh Mani

Department of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagar, Maddur Taluk, Mandya District, Karnataka, India.

ABSTRACT

Nanotechnology has many implications in our day today life with its core being the synthesizing of nanoparticles. Nanoparticle can easily enter most cells and circulate through the body, are suitable for targeted delivery vehicles to carry large doses of chemotherapeutic agents or therapeutic genes into the target site. Nanoparticles have been improving the therapeutic effect of drugs and minimize the side effects. It possess numerous properties of a suitable and supreme drug carriers, which comprise its high stability, feasibility of incorporation, high carrier capacity, reduce toxicity. The present review focuses on the advantages and disadvantages of nanoparticles, preparation of nanoparticles, carriers used, characterization and applications of nanoparticulate drug delivery system. In conclusion, nanoparticles are one of the promising drug delivery systems, which can be of potential use in controlling and targeting drug delivery.

Keywords: Nanoparticles, Preparation methods, Polymers, Drug release.

INTRODUCTION

An essential requirement of modern drug therapy is the controlled delivery of a drug or an active substance to the site of action in the body in an optimal concentration versus time profile. One attempt to achieve this goal was the development of colloidal drug carriers known as nanoparticles, chiefly because of their small particle size. 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 sustained release injections for the delivery to a specific organ or target site. Targeting the drug to the desired site of action would not only improve the therapeutic efficiency but also enable a reduction of the amount of drug which must be administered to achieve a therapeutic response, thus minimizing unwanted toxic effects[1].

Nanoparticles are solid colloidal particles with diameters ranging from 1-1000 nm. They consist of macromolecular materials and can be used therapeutically as adjuvant in vaccines or drug carriers in which the active ingredient is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Polymers used to form nanoparticles can be both synthetic and natural polymers. There are two types of nanoparticles depending on the preparation process: nanospheres and nanocapsules (Allemann *et al*., 1993). Nanospheres have a monolithic-type structure (matrix) in which drugs are dispersed or adsorbed onto their surfaces (Figure 1). Nanocapsules exhibit a membrane-wall structure and drugs are entrapped in the core or adsorbed onto their exterior (Figure 1).The term “nanoparticles” is adopted because it is often very difficult to unambiguously establish whether these particles are of a matrix or a membrane type[2].

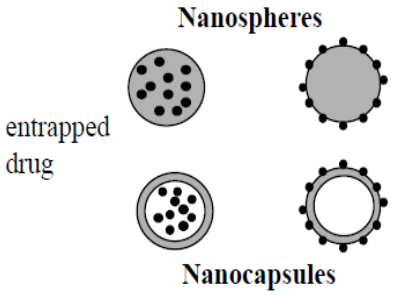

Figure 1. Various types of drug-loaded nanoparticles. Adapted from Allemann *et al.* (1993)

Nanoparticulate system can be formed by entrapped and encapsulated with matrix. By these method we can prepared the nanoparticle, nanosphere or nanocapsules. Now a day's biodegradable and inert polymer used as coating agent upon nanoparticle. These coating improve the potential of the drug delivery system. The aim of nanoparticulate drug delivery system is to control the release of drug at the specific site for longer action. This is achieving by liposome formation which is used as carriers. Carriers have many advantages like protect from the degradation, reduce the toxicity and targeting site of action. Nanoparticles enhance the stability of drug and have the control release property[3]. The proper selection of the polymeric matrix is necessary in order to develop a successful nanoparticulate delivery system[4].

Recent developments in nanotechnology have shown that nanoparticles (structures smaller than 100 nm in at least one dimension) have a great potential as drug carriers. Due to their small sizes, the nanostructures exhibit unique physicochemical and biological properties (e.g., an enhanced reactive area as well as an ability to cross cell and tissue barriers) that make them a favourable material for biomedical applications[5].

Modification and fabrication of polymers is very effective technology which provides the better drug delivery to the system for the treatment of disease. The materials which are used in fabrication are polymers nanostructures. These polymers used with the combination of drug particle and targeted to the site of action. Targeted drug can be conjugated to tissue, ligands or macromolecules to the site of action. Targeted nanoparticulate drug delivery systems are to delivery of anti-cancer, anti-microbial agent, vascular endothelial, brain drug targeting, insulin delivery and neuro disorders[3].

ADVANTAGES OF NANOPARTICLES[6,7]

- NPs is a better carrier than the emulsion if a prolonged and a sustained delivery of the drug is desired.
- Longer clearance time.
- The matrix must be non-toxic and must not exhibit any antigenic behaviour to the body.
- Targeted and drug delivery.
- Good control over size and size distribution.
- Good protection of the encapsulated drug.
- Retention of drug at the active site.
- Increased therapeutic efficacy.
- Increased bioavailability.
- Dose proportionality.

DISADVANTAGES OF NANOPARTICLES

- Extensive use of polyvinyl alcohol as a detergent –issues with toxicity.
- Limited targeting abilities.
- Discontinuation of therapy is not possible.
- Cytotoxicity.
- Pulmonary inflammation and pulmonary carcinogenicity.
- Alveolar inflammation. The disturbance of autonomic imbalance by nanoparticles having direct effect on heart and vascular function.

NEED FOR DEVELOPING NANOPARTICLE[8]

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents so as to achieve the site of action of the drug at the rationate rate and dose. Polymeric nanoparticles offer some specific advantage over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties.

MECHANISM OF DRUG DELIVERY VIA NANOPARTICLE[9]

Nanoparticles exerts its site-specific drug delivery by avoiding the reticuloendothelial system, utilizing enhanced permeability and retention effect and target-specific targeting. Two types of approaches are applied with drug using nanoparticle as carrier:

a. **Surface bound**: The drug molecules are adhered to the surface of nanoparticles
b. **Core bound**: In such methodology the drug particles are concentrated to the matrix of the nanoparticle and carried to the target in the body.

Drugs can be loaded onto Nanoparticles by adding them to a solution that contains previously prepared Nanoparticles or by adding them to the reaction mixture during the polymerization process. Nature of interaction of nanoparticle to the drug may be chemical, surface adsorption, and no binding or interaction at all. The amount of bound drug and the type of interaction of drug and Nanoparticles depend on the chemical structure of the drug and the polymer and the conditions of drug loading.

CARRIERS USED IN PREPARATION OF NANOPARTICLES

The polymers should be compatible with the body in the terms of adaptability (non-toxicity) and (non-antigenicity) and should be biodegradable and biocompatible.

The polymeric drug carriers deliver the drug at the tissue site by any one of the three general physico-chemical mechanisms.

1. By the swelling of the polymer nanoparticles by hydration followed by release through diffusion.
2. By an enzymatic reaction resulting in rupture or cleavage or degradation of the polymer at site of delivery, there by releasing the drug from the entrapped inner core.
3. Dissociation of the drug from the polymer and its de-adsorption/release from the swelled nanoparticles[10].

The polymers used for the preparation of nanoparticles are either amphiphilic macromolecules, obtained from natural sources, hydrophobic polymers or synthesized chemically. Some of the polymers were originally investigated for biomedical applications, consequently fortheir safety and biodegradation. Various natural hydrophilic and synthetic hydrophobic polymers are used for the preparation of nanoparticles.

The use of natural biopolymers specifically polysaccharides in drug delivery has attracted particular interest due to their desirable biocompatible, biodegradable, hydrophilic and protective properties (Barichello JM, 1999). The interaction between biodegradable cationic and anionic biopolymers leads to the formation of polyionic hydrogels, which have demonstrated favourable characteristics for drug entrapment and delivery (Chella F, 2000). Chitosan and Alginate are two biopolymers that have received much attention and have been shown to maintain their structure and activity and protect them from enzymatic degradation (Madan T, 1997)[12].

ADJUVANT USED IN THE PREPARATION OF NANOPARTICLES[11]

- Cross linking agent – gluteraldehyde
- Desolvating agents – sodium sulphate,ethanol, isopropyl alcohol
- Counter ions – tripolyphosphate
- Surfactants – tween-80, span-80
- Stabilizer – poly vinyl alcohol
- Solvents – methanol, isopropyl alcohol, chloroform, dichloromethane, water etc.

Table 1: Polymers used for the preparation of nanoparticles[11]

Sl.No	Synthetic polymers	Natural polymers
1	Poly(E caprolactone) (PECL)	Gelatin
2	Poly(lactic acid) (PLA)	Albumin
3	Poly(lactide-co-glycolide) (PLGA)	Lectins
4	Polystyrene	Alginate
5	Poly hexyl cyanoacrylate (PHC)	Dextran
6	Poly butyl cyanoacrylate (PBC)	Chitosan
7	Poly methyl(methacrylate) (PMM)	Agarose

PREPARATION OF NANOPARTICLES

Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection of matrix materials is dependent on various factors which include:

a. Size of nanoparticle required
b. Inherent properties of the drug, e.g., aqueous solubility and stability
c. Surface characteristics such as charge and permeability
d. Degree of biodegradation, biocompatibility and toxicity
e. Drug release profile desired
f. Antigenicity of the final product[13].

Nanoparticles have been prepared most frequently by three methods:

A) Dispersion of preformed polymers
1. Solvent evaporation method
2. Spontaneous emulsification or solvent diffusion method
B) Polymerization of monomers
C) Ionic gelation or coacervation of hydrophilic polymers
D) Supercritical fluid technology

However, other methods such as supercritical fluid technology39 and particle replication in non-wetting templates (PRINT) have also been described in the literature for production of nanoparticles.

A) DISPERSION OF PREFORMED POLYMERS:

Is the most common technique used to prepare biodegradable nanoparticles from poly (lactic acid) (PLA); poly (D,L glycolide), PLG; poly (D, L-lactide-co-glycolide) (PLGA) and poly (cyanoacrylates) (PCA)[14].

1. Solvent Evaporation Method:[15]

Solvent evaporation method has been widely used in the preparation of both micro and nanosuspension. Briefly, drug and polymer were dissolved in water non-miscible organic solvent, which was then added to the aqueous phase containing copolymer/surfactants (e.g. Poloxamer, Tween 80, and sodium dodecyl sulphate) under high energy homogenization to form an emulsion. Subsequently, the polymer in the emulsion undergoes precipitation, which encapsulates the drug in the polymer matrix resulting in the formation of nanospheres. The residual solvent in the formulation was then removed by increasing the temperature under reduced pressure.

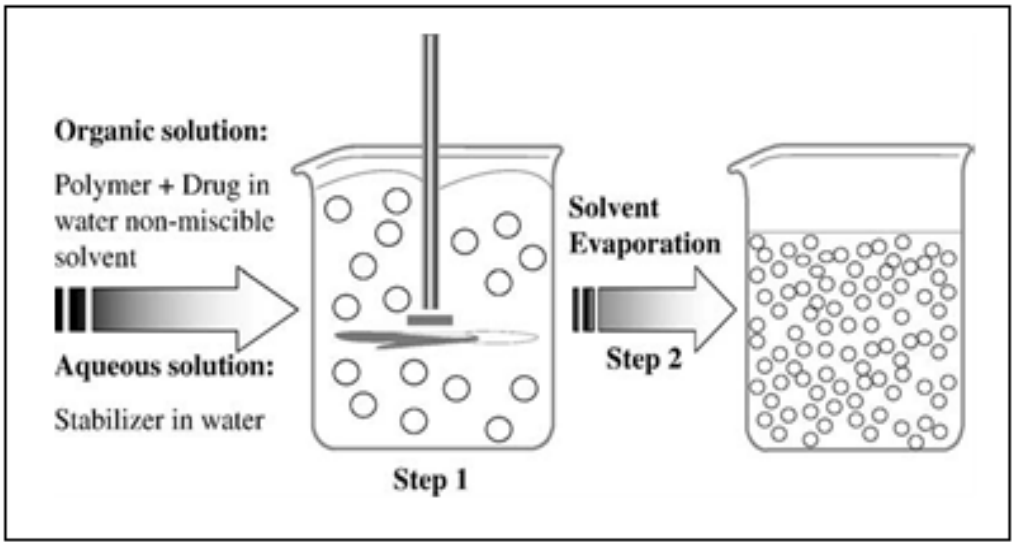

Fig. 2: Schematic representation of the solvent-evaporation technique[16]

2. Spontaneous Emulsification Or Solvent Diffusion Method:[17]

El-Shabouri reported chitosan NP prepared by emulsion solvent diffusion method, (which originally developed by Niwa *et al.*employing PLGA. This method is based on the partial miscibility of an organic solvent with water. An o/w emulsion is obtained upon injection an organic phase into chitosan solution containing a stabilizing agent (i.e. poloxamer) under mechanical stirring, followed by high pressure homogenization. The emulsion is then diluted with a large amount of water to overcome organic solvent miscibility in water. Polymer precipitation occurs as a result of the diffusion of organic solvent into water, leading to the formation of nanoparticles. This method is suitable for hydrophobic drug and showed high percentage of drug entrapment. The major drawbacks of this method include harsh processing conditions (e.g., the use of organic solvents) and the high shear forces used during nanoparticle preparation.

B) POLYMERIZATION OF MONOMER[14]

In this method, monomers are polymerized to form nanoparticles in an aqueous solution in which drug may be dissolved. Drug may also be incorporated 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 resuspending the particles in an isotonic surfactant-free medium. This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles.

C) IONIC GELATION OR COACERVATION OF HYDROPHILLIC POLYMER[16]

Polymeric nanoparticles are prepared by using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate. Calvo and co-workers developed a method for preparing hydrophilic chitosan nanoparticles by ionic gelation. Amir Dustgani *et al* prepared Dexamethasone Sodium Phosphate loaded chitosan nanoparticles by ionic gelation method. The method involves a mixture of two aqueous phases, of which one is the polymer chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a poly anion sodium tripolyphosphate. 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. Coacervates are formed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature.

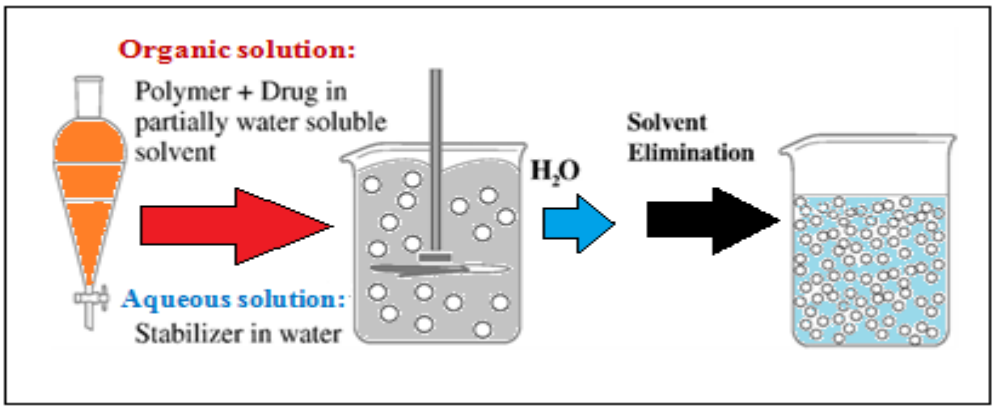

Fig. 3: Schematic representation of the emulsification/solvent diffusion technique[16]

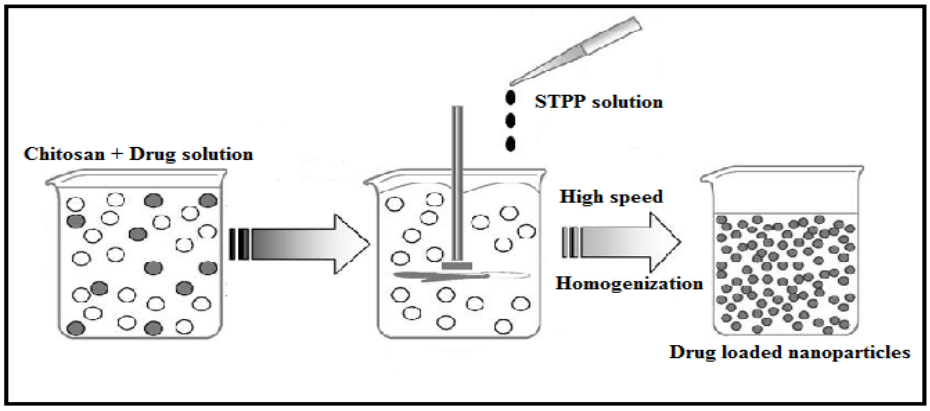

Fig. 4: Schematic representation of ionic gelation method

D) SUPERCRITICAL FLUID TECHNOLOGY

Nanoparticle can be prepared by the use of supercritical fluid. This is the alternative option for the biodegradable polymers and safe for the environment. Conventional method like solvent evaporation, solvent diffusion and organic phase separation, these create the hazardous to the environment due to the organic solvents. Supercritical fluid is defined as a solvent at temperature above its critical temperature which is remain in a single phase regardless of pressure are called supercritical fluid. CO2 (SC CO2) is used as supercritical fluid which is most widely used in pharmaceutical industries and have advantages of low price, nontoxic in nature, and non-inflammable. For the formation of supercritical fluids many processes are involved like supercritical anti-solvent and rapid expansion of critical solution. The process of supercritical anti-solvent methanol is used and it is completely miscible with the supercritical fluid to dissolve the solute at the process condition. Solutes are insoluble in supercritical liquid and extract with supercritical fluid after that precipitation occurs and nanoparticle are formed[3].

CHARACTERIZATION OF NANOPARTCLES

Table 2: Physical characterization of Nanoparticles[18]

Sno.	Property	Analytical method(s)
1.	Presence size	Dark field optical microscopy Size Dynamic light scattering, Static light scattering, Ultrasonic spectroscopy, Turbidimetry, NMR, Single particle optical sensing, FFF Hydrodynamic fractionation, Filtration
2.	Morphology	TEM, SEM, Atomic force microscopy
3.	Surface charge	Electrophoretic light scattering, U-tube electrophoresis, Electrostatic-FFF
4.	Surface hydrophobicity	Hydrophobic interaction chromatography
5.	Surface adsorbates	Electrophoresis
6.	Density	Isopycnic centrifugation, sedimentation-FFF
7.	Interior structure	Freeze-fracture SEM, DSC, X-ray diffraction, NMR

- **Particle size analysis:**[19]

The particle size analysis was done for drug loaded nanoparticles in order to find the diameter of the particles. The mean particle size of the drug loaded nanoparticles was found to be 267 nm.

- **Determination of drug content and entrapment efficiency:**[20]

Freeze-dried nanoparticles were dissolved in suitable solvent and the amount of drug was measured by UV spectroscopy at 245nm (Shimadzu UV 1800).

$$\text{Drug Content (\%)} = \left\{ \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of nanoparticles recovered}} \right\} \text{X } 100$$

$$\text{Entrapment Efficiency} = \left\{ \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of drug used in formulation}} \right\} \text{X } 100$$

- **Determination of zeta potential**[21]

The zeta potential is commonly used to characterize the surface charge property of nanoparticles. It reflects the electrical potential of the particles and is 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 particle aggregation.

- **Density**[11]

The density of nanoparticles is determined with helium or air using a gas pycometer. The value obtained with air and with helium may differ noticeably from each other. The difference is much more pronounced due to specific surface area and porosity of the structure.

- **Surface hydrophobisity**

The hydrophobicity of nanoparticles has an important influence on the interaction of colloidal particles with the biological environment. The hydrophobicity and hydrophilicity collectively determines the bio-fate of nanoparticles and their contents. Several methods including hydrophobic interaction chromatography, two-phase partition, adsorption of hydrophobic fluorescent or radiolabeled probes and contact angle measurements have been adopted to evaluate surface hydrophobicity. Recently several sophisticated methods of surface chemistry analysis have been used. For example X-ray photoelectron spectroscopy permits the identification of specific groups on the surface of nanoparticles.

- **Loading efficiency**[22]

The Nanosuspension with known amount of drug (10mg/20ml) incorporated was centrifuged at 5000 rpm for 15 minutes. The supernatant solution was separated. 5ml of supernatant was distributed with 100 ml of 2% w/v tween 80 solutions and the absorbance was measured using UV spectrophotometer at 306 nm using 2% w/v tween 80 as blank. The amount of drug unentrapped in the supernatant was calculated. The amount of drug entrapped and percentage entrapment was determined from drug unentrapped. Standard deviation was determined for 3 trials.

$$\textbf{Loading efficiency} = \frac{\text{Total amount of drug - Amount of unbound drug}}{\text{Nanoparticles weight}} \times 100$$

- **Fourier transform infrared (ftir) spectroscopy[23]**

The chemical structure of nanoparticles, pure Diclofenac sodium, and polymer was analyzed by FTIR (Schimadzu FTIR-8400) in transmission mode. The sample was prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was used from 4000 to 400 cm^{-1}.

- **x-ray diffraction**

In order to confirm the crystalline or amorphous nature of pure drug, polymer and nanoparticles were subjected to X-ray diffractometer (Bruker, D-8 advance). The data collection was performed using Cu anode and a voltage of the monochromator at 40 kV. The diffraction pattern was determined in the area 30< 2Ɵ <800 using continuous scan.

- ***in-vitro* release studies[12]**

In-vitro release of drug from MTX nanoparticle formulation is determined by dialysis bag method in phosphate buffer saline pH 7.4. The freeze dried MTX nanoparticles (equivalent to 5.0 mg of drug) was taken in a dialysis bag (molecular cut off 12,000, pore size 0.2 µm) and placed in 100 ml of dissolution medium which was continuously stirred at 100 rpm at 37°C using shaker incubator. Definite aliquots of the dissolution medium were withdrawn at specific time intervals and the same volume of fresh dissolution medium was added to the flask to maintain a sink condition. The samples withdrawn were analyzed for drug content spectrophotometrically at 303 nm.

APPLICATION OF NANOPARTICULATE DELIVERY SYSTEM

- **Tumor targeting using nanoparticulate delivery system[24]**

The rationale of using nanoparticles for tumor targeting is based on:

1. Nanoparticles will be 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.
2. Nanoparticles will reduce the drug exposure of health tissues by limiting drug distribution to target organ.

- **Nanoparticles for gene delivery[5]**

Polynucleotide vaccines work by delivering genes encoding relevant antigens to host cells where they are expressed, producing the antigenic protein within the vicinity of professional antigen presenting cells to initiate immune response. Such vaccines produce both humoral and cell mediated immunity because intracellular production of protein, as opposed to extracellular deposition, stimulates both arms of the immune system.

- **Ultrasonic drug and gene delivery[25]**

Ultrasonic drug and gene delivery by nanocarriers has tremendous potential because of the wide variety of drugs and genes could be delivered to targeted tissues by fairly non-invasive means. Liquid emulsions and solid nanoparticles are used with ultrasound to deliver genes *in vitro* and *in vivo.*

- **Parasitic diseases**

Solid liquid nanoparticle and nanostuctured lipid carriers (NLC) are particulate in nature and inherent structure exhibit good potential in the treatment of parasitic infections. With respect to encapsulation ability and target ability, it requires extensive investigations on these systems to arrive at a versatile, effective and economical approach for the delivery of anti-parasitic drugs.

- **Nanoparticles for drug delivery into the brain[26]**

The blood-brain barrier (BBB) is the most important factor limiting the development of new drugs for the central nervous system. The BBB is characterized by relatively impermeable endothelial cells with tight junctions, enzymatic activity and active efflux transport systems. It effectively prevents the passage of water-soluble molecules from the blood circulation into the CNS, and can also reduce the brain concentration of lipid-soluble molecules by the function of enzymes or efflux pumps. Consequently, the BBB only permits selective transport of molecules that are essential for brain function.

- **Nanoparticles for oral delivery of peptides and proteins**

The surface area of human mucosa extends to 200 times that of skin. The gastrointestinal tract provides a variety of physiological and morphological barriers against protein or peptide delivery, e.g., (a)

proteolytic enzymes in the gut lumen like pepsin, trypsin and chymotrypsin; (b) proteolytic enzymes at the brush border membrane (endopeptidases); (c) bacterial gut flora; and (d) mucus layer and epithelial cell lining itself. The histological architecture of the mucosa is designed to efficiently prevent uptake of particulate matter from the environment. One important strategy to overcome the gastrointestinal barrier is to deliver the drug in a colloidal carrier system, such as nanoparticles, which is capable of enhancing the interaction mechanisms of the drug delivery system and the epithelia cells in the GI tract.

CONCLUSION

In conclusion nanoparticles are one of the promising drug delivery systems, which can control the delivery and target the drug to specific site. Nanoparticles represent a technology to overcome solubilities and bioavailability problems of drugs which can be generally applied to all poorly soluble drugs. Any drug can be transformed to drug nanoparticles leading to increasing saturation solubility, dissolution rate and providing in general feature of an increased adhesiveness to surfaces. Nanoparticulate drug delivery system is increasingly viewed as an advantageous solution for biological drugs.

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