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An overall review on polymeric nanoparticles

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Abstract
The present conventional drug delivery systems often have side-effects and complication due to their wide distribution throughout the body fluids. The localization of drug action in injured tissue is promising way to solve this problem. The object of drug targeting is to achieve a desired pharmacological response at a selected site without undesirable interaction at other sites. At present drug targeting is achieved at one of two approaches: the first approach involves chemical modification of the parent compound to a derivative which is activated only at the target site. The second approach utilizes carriers such as liposomes, microspheres, nanoparticles, antibiotics, cellular carriers (erythrocytes and lymphocytes) and macromolecules to direct the drug at its site of action.

Keywords: microspheres, nanoparticles, antibiotics, cellular carriers

Introduction

The field of nanotechnology is one of the most active research areas in modern materials science. Nanoparticles exhibit new or improved properties based on specific characteristics such as size, distribution and morphology. There have been impressive developments in the field of nanotechnology in the recent past years, with numerous methodologies developed to synthesize nanoparticles of particular shape and size depending on specific requirements. New applications of nanoparticles and nanomaterials are increasing rapidly [2]. Nanotechnology can be termed as the synthesis, characterization, exploration and application of Nano sized (1-1000nm) materials for the development of science. It deals with the materials whose structures exhibit significantly novel and improved physical, chemical, and biological properties, phenomena, and functionality due to their Nano scaled size. Because of their size, nanoparticles have a larger surface area than macro-sized materials. Nanoparticles, because of their small size, have distinct properties compared to the bulk form of the same material, thus offering many new developments in the fields of biosensors, biomedicine, and bio nanotechnology. Nanotechnology is also being utilized in medicine for diagnosis, therapeutic drug delivery and the development of treatments for many diseases and disorders. Nanotechnology is an enormously powerful technology, which holds a huge promise for the design and development of many types of novel products with its potential medical applications on early disease detection, treatment, and prevention [3].

Nanoparticles are sub nanosized colloidal particles ranging between 1-1000nm size made from natural or synthetic polymers in which drug may be dissolved, entrapped, encapsulated or attached to a matrix. Nanocapsules are reservoir systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed in the polymeric matrix.

Advantages

- Increases the stability of any volatile pharmaceutical agents, easily and cheaply fabricated in large quantities by a multitude of methods.
- They offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.
- Ease of formulating smaller drug doses.
- Less toxicity
- Good control over size and size distribution.
- Protects the encapsulated drug from degradation.
- Stable dosage forms of drug which are either unstable or have unacceptably low bioavailability can be formulated as nanoparticles.
- Increased surface area results in a faster dissolution of active agents in an aqueous environment.
- Faster dissolution generally equates with greater bioavailability.
- Improving drug bioavailability through enhancing aqueous solubility
- Increasing the resistance time in the body (increasing the half-life for the clearance/ increasing specificity for its cognate receptor).
- Relatively higher intercellular uptake.
- Because of their small size, can penetrate through smaller capillaries and are taken up by cells, which allow efficient drug accumulation at the target sites.
- Minimizes non-specific uptake, prevents undesirable off target and side effects
- The use of biodegradable materials for nanoparticle preparation allows sustained drug release within the target site over a period of days or even weeks.

Limitations

- Their small size and large surface area can lead to particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms.

- In addition, small particles size and large surface areas readily result in limited drug loading and burst release.
- The major threat to safety question is yet to be revealed. Due to small size, nanoparticles could gain access to unintended environments with harmful consequences such as a nanoparticle might erroneously cross the nuclear envelope of a cell & cause genetic damage & mutations. Not much research has been done in developing risk assessment models & toxicology studies devoted to nanoparticles.

Type of nanoparticles

According to material used for synthesis, nanoparticle is classified as follows:

a) Polymeric Nanoparticles
b) Solid Lipid Nanoparticles
c) Peglyted Nanoparticle
d) Magnetic Nanoparticle
e) Metallic Nanoparticle

Polymeric Nanoparticle

Potential improvements in the field of polymer chemistry have made polymers the most suitable carrier for delivering small and macromolecules.

Polymeric nanoparticles are made from biodegradable and biocompatible polymers such as either natural polymer (e.g., gelatin, chitosan etc.) or synthetic polymers (e.g., polylactides, polyacrylcyanoacrylates etc.). According to the structural organization biodegradable nanoparticles are classified as nanocapsule, and nanosphere. The drug molecules are either entrapped inside or adsorbed on the surface.

The selection of materials for preparing nanoparticles depends upon consideration of the following factors.

Size and surface characteristics of the particle desired.

- Aqueous solubility and stability of drugs or active ingredients.
- Degree of biodegradability, biocompatibility and toxicity.
- Drug release profile desired.
- Antigenicity of the polymers.

Polymeric materials can be classified broadly as natural polymers and synthetic polymers and are tabulated in table – 01.

Table 1: List of polymers used in nanoparticle preparation.

Material	Full name	Abbreviation or Common names
Synthetic homopolymers	Poly (lactide) Poly (lactide-co-glycolide) Poly (epsilon-caprolactone) Poly (isobutylcyanoacrylate) Poly(isohexylcyanoacrylate) Poly (n-butylcyanoacrylate) Poly (acrylate) and Poly(mathacrylate	PLA PLGA PCL PICBA PIHCA PBCA Eudragit*
Natural polymers	Chitosan Alginate Gelatin Albumin	
Copolymers	Poly (lactide)- poly (ethylene glycol) Poly (lactide-co-glycolide)- poly (ethylene glycol) Poly (epsilon-caprolactone)- poly (ethylene glycol) Poly(hexadecylcyanoacrylate-co-poly(ethylene glycol) cyanoacrylate)	PLA- PEG PLGA-PEG PCL-PEG Poly (HDCA-PEGCA)
Colloid stabilisers	Dextran Pluronic F68 Poly (vinyl alcohol) Co polymers (see above) Tween®20 and Tween® 80	 F68 PVA

Different techniques for preparation of nanoparticles

1) Amphiphilic macromolecule cross-linking
   a) heat-cross linking
   b) Chemical cross linking
2) Polymer precipitation methods
   a) Solvent extraction
   b) Solvent displacement
   c) Salting out
3) Polymerization based methods
   a) Emulsion polymerization
   b) Dispersion polymerization
   c) Interfacial polymerization
4) Miscellaneous

1) Amphiphilic macromolecule cross-linking

It involves aggregation of amphiphile followed by further stabilization either by heat denaturation or chemical cross linking.

Cross linking in w/o emulsion

The cross-linking method is used for the nano-encapsulation of drug. The method involves the emulsification of bovine serum albumin (BSA/Human serum albumin) or protein aqueous solution in oil using high pressure homogenization. The water in oil emulsion so formed is then poured into preheated oil. The suspension in preheated oil maintained above 100 degrees is held stirred for a specific time in order to denaturate and aggregate the protein contents of aqueous pool completely and to evaporate water. Protenacious subnanoscopic particles thus formed where the size of the internal phase globule mainly determines the ultimate size of particulates. The particles are finally washed with an organic solvent to remove any adherent or adsorbed oil traces and subsequently collected by centrifugation. The factors which govern size and shape of nanoparticle are mainly emulsification energy and temperature.

Emulsion Chemical dehydration

It is used for producing BSA nanoparticles with a narrow size distribution. Hydroxy propyl cellulose solution in chloroform was used as a continuous phase of emulsion. A chemical dehydrating agent 2, 2-dimethyl propane was used to translate internal aqueous phase into a solid particulate suspension. This method avoids coalescence of droplets and could produce nanoparticles of small size.

Phase separation in aqueous medium

The protein or polysaccharide from an aqueous phase can be desolvated by pH change or change in temperature or by adding appropriate counter ions. Cross-linking may be affected simultaneously or subsequent to the desolvation step. It contains three steps. Protein dissolution, protein aggregation and protein deaggregation. The appropriate levels of desolvation and resolvation, the aggregate size could be maintained and finally these aggregated nanoparticles are cross linked using glutaraldehyde. Sodium sulphate is the main desolvating agent. Alcohol, Ehanol, isopropanol are added as desolvating agents. The addition can be optimized turbidometrically using nephelometer. Only desolvation gives the final product as nanosphere. Desolvation deaggregates the protein and turns the suspension colloidal and hence milky in appearance. Both lipophilic and hydrophilic drugs can be entrapped in nanoparticle ns using this technique.

2) Nanoparticle preparation using polymer precipitation methods

In these hydrophobic polymer and a hydrophobic drug is dissolved in an organic solvent followed by its dispersion in a continuous aqueous phase in which polymer is insoluble. The external phase also contains stabilizer. Depending upon solvent miscibility techniques they are designated as solvent extraction/evaporation method.

The polymer precipitation occurs as consequence of the solvent extraction/evoparation at which can be brought by

a) Increasing the solubility of the organic solvent in the external medium by adding an alcohol(i.e isopropronolol)
b) By incorporating additional amount of water into the ultra-emulsion
c) By evaporation of organic solvent at room temperature or at accelerated temperature or by using vaccum.
d) Using an organic solvent that is completely soluble in the continuous aqueous phase-nanoprecipitation.

a) Solvent evaporation

Here, polymer solutions are prepared in a volatile solvent and emulsion is formulated. The emulsion is converted into a nanoparticles suspension on evaporation of the solvent for the polymer, which is allowed to diffuse across the continuous phase. In the conventional methods, two strategies are used for formation of emulsion: the preparation of single emulsions (e.g. o/w) and preparation of double emulsions (e.g. w/o/w). These techniques utilize high-speed homogenization or ultrasonication or combination of both, followed by evaporation of solvent. Then the solidified nanoparticles are collected by ultracentrifugation and washed with distilled water to remove additives such as surfactants. Finally, the product is lyophilized to obtain free-flowing powder. Normally, a polymer is dissolved in an organic phase containing the surfactant/ stabilizer forms the water phase. Although the solvent evaporation technique is a simple method for the preparation of nanoparticles, it is time-consuming and possible coalescence of the nano-droplets during the evaporation process may affect the final size and morphology of the particle.

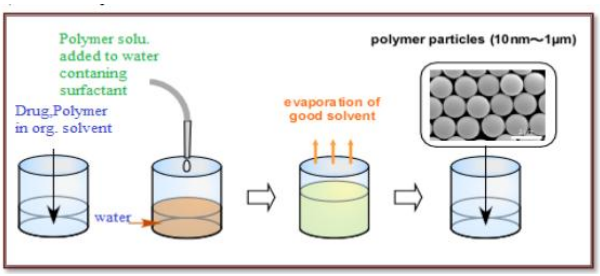


Fig 1: Schematic representation of Solvent evaporation method

b) Nano precipitation

Also known as the solvent displacement method, the basic principle of this method is based on the interfacial deposition of a polymer after displacement of a semipolar solvent, miscible with water, from a lipophilic solution. Rapid diffusion of the solvent into non-solvent phase results in the decrease of interfacial tension between the two phases, which increases the surface area and leads to the formation of small droplets of organic solvent. Nano precipitation system comprises of three basic components: the polymer (synthetic, semi synthetic or natural), the polymer solvent and the non-solvent of the polymer. Organic solvent (i.e., ethanol, acetone, hexane, or dioxane) which is miscible in water and easy to remove by evaporation is selected as the polymer solvent. Due to this reason, acetone is the most commonly employed polymer solvent in this method sometimes, it consists of binary solvent blends, acetone with small amount of water, blends of acetone with ethanol and methanol. On the other hand, the non-solvent phase consisting of a non-solvent or a mixture of non-solvents is supplemented with one or more naturally occurring or synthetic surfactants.

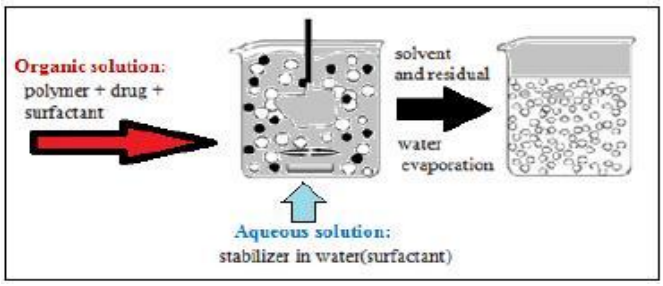


Fig 2: Schematic representation of Nano-precipitation method

Nano-precipitation is an easy, fast and reproducible method which is widely used for the preparation of both nano-spheres and nano-capsules. Although low polymer surfactant concentrations are being used, challenges pertaining to low polymer concentration in the organic phase need to be addressed.

c) Salting out

This process is a modified version of emulsion process which involves a salting-out process, which avoids surfactants and

chlorinated solvents. The emulsion is formulated with a polymer solvent which completely miscible with water and emulsification of the polymer solution in the aqueous phase is achieved, without utilization of any high sheer forces, by dissolving high concentration of salt or sucrose chosen for a strong salting-out effect in the aqueous phase. Magnesium chloride, calcium chloride and magnesium acetate are commonly used suitable electrolytes. The miscibility properties of water with other solvents are modified as these components dissolve in the water. A reverse salting out effect, obtained by dilution of the emulsion with an excess amount of water, results in the precipitation of the polymer dissolved in the droplets of the emulsion. In fact, after dilution, migration of the solvent for the polymer from the emulsion droplets is induced due to the reduction of the salt concentration in the continuous phase of the emulsion.

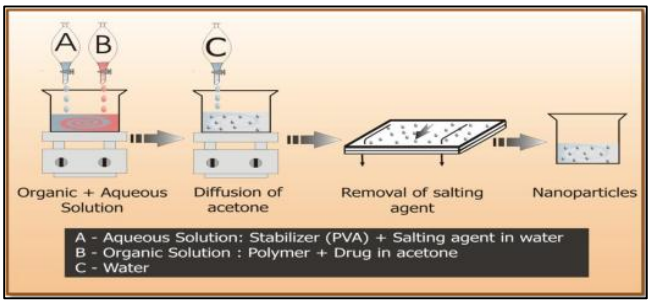


Fig 3: Schematic representation of salting out

3) Polymerization based methods

Polmerization of monomers in an aqueous solution form the basis of this method. Two different techniques are used for the preparation in aqueous solution.

a) Emulsion polymerization: - this method involves emulsification of monomer in non-solvent phase.
b) Dispersion polymerization: - this method involves dispersion of monomer in non-solvent phase.

Incorporation of drug in nanoparticle can be achieved either by dissolving the drug in polymerization medium or by adsorption onto nanoparticle. Suspension of nanoparticles is formed, which contain surfactants and stabilizers that are used in polymerization which has to be removed by method like ultracentrifugation or by suspending them in isotonic medium which is free of surfactant. Polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles are beenprepared by this method. The polmer particle size had been affected by concentration of stabilizer and surfactant involved in preparation.

Interfacial Polymerization

Polymer and drug dissolved in volatile solvent. The solution is then poured into non-solvent for both polymer and core phase. The polymer phase is separated as a coacervative phase at o/w interface. The resultant mixture instantaneously turns milky owing to the formation of nanocapsule. The solvent is removed under vaccum. Size ranges 30-300nm. Drug loading depends on drug solubility in core phase. Surfactant in decreased quantities can be added to stabilize the dispersion. Interfacial polymerization is used for the encapsulation of proteins and enzymes.

4) Miscellaneous

a) Coacervation or ionic gelation method

Chitosan, sodium alginate and gelatin are hydrophilic biodegradable polymers which are used for the preparation of nanoparticles by coacervation method. Preparation of hydrophilic chitosan nanoparticles by ionic gelation was developed by Calvo and Co-worker. This method involves a preparation of two aqueous phases, of which one is the polymer chitosan, adi-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a polyanion sodium tripolyphosphate which are mixed, due to mixing positively charged amino group of chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometer. when electrostatic interaction take place between two aqueous phases coacervates are formed, and when two molecules interact due to ionic force, resulting in transition from liquid phase to gel phase at room temperature this is known as ionic gelation method.

b) Production of nanoparticles using supercritical fluid technology

Various conventional approaches like solvent diffusion, solvent extraction-evaporation and organic phase separtion require the use of organic solvent are hazardous to the environment as well as the physiological systems. Supercritical fluid technology thus has been invested as an alternative to prepare biodegradable micro and Nanoparticles [17]. Solvent which remain fluid in a single phase regardless of pressure above critical temperature are known as supercritical fluid. Super critical CO is the most widely used supercritical fluid. The most common processing techniques involves supercritical fluids are supercritical Anti-solvent (SAS) and rapid expansion of critical solution (RESS). Formation of hydrophilic drug Dexamethsone phosphate by the use of modified SAS had been reported by Thote and Gupta (2005). RESS diffuse from SAS process in that its solute in dissolved in super critical fluid. Thus with solvent power of supercritical fluid decrease and the solute eventually precipitate.

Characterization of Nanoparticles [12-14]

1. Study of drug excipient-interaction
2. Particle size analysis and stability
   - Particle Size
   - Zeta Potential
3. Surface morphology (SEM)
4. Drug content
5. Encapsulation efficiency
6. *In-vitro* drug release studies

1) Study of drug excipient-interaction

There are several methods available to determine drug-excipient interaction. The most commonly used processes are

- Differential scanning calorimetry (DSC),
- X-ray diffraction method (XRD),
- FTIR.

These techniques are able to detect the physicochemical states and interactions of the drug and the polymers in pharmaceutical and nanotechnology [21].

Generally, DSC detects phase transition such as glass transition, crystallization. Crystalline and amorphous states of the drug molecules are determined by XRD techniques.

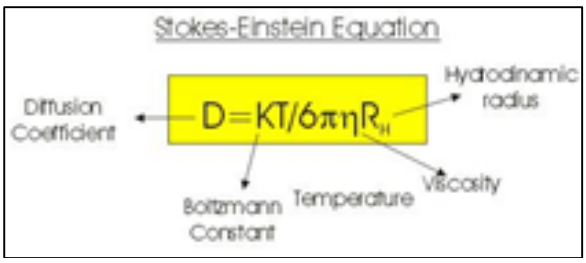
FTIR is a modern and modified form of infrared spectrometry based on mathematical formula, able to determine the structure of the drug molecule and physical interactions between drug and polymers. FT-IR spectroscopy is a form of vibrational spectroscopy, and the FT-IR spectrum reflects both molecular structure and molecular environment. In this technique, the sample is irradiated with infrared radiation from an infrared source and the absorption of this radiation stimulates vibrational motions by depositing quanta of energy into vibrational modes. Therefore, a molecule, when exposed to radiation produced by the thermal emission of a hot source (a source of IR energy), absorbs only at frequencies corresponding to its molecular modes of vibration in the region of the electromagnetic spectrum between visible (red) and short waves (microwaves). These changes in vibrational motion give rise to bands in the vibrational spectrum; each spectral band is characterized by its frequency and amplitude.

Particle size analysis and stability

Particle size analysis and stability study of the nanoparticles are generally determined by zeta sizer. The Zetasizer Nano range of instruments provides the ability to measure three characteristics of particles or molecules in a liquid medium. These three fundamental parameters are particle size, zeta potential and molecular weight. By using the unique technology within the Zetasizer system these parameters can be measured over a wide range of concentrations. The Zetasizer range features pre-aligned optics and programmable measurement position plus the precise temperature control necessary for reproducible, repeatable and accurate measurements. In addition facility is included for measurements of other key parameters such as pH and concentration. The Zetasizer range has been designed with simplicity in mind, so that a minimal amount of user interaction is necessary to achieve excellent results.

Particle Size

Most of the properties of nanoparticle like drug loading and release pattern, in vivo distribution, tissue targeting, toxicity and biological fate are concerned with the size and size distribution of Nanoparticles so they had become an important parameter in characterization of product. It has been reported that micro particles are less effective drug delivers than particle having size ranging in between nanometers for e.g. Nanoparticles having size range greater than 230 nm acquire in the spleen shown by body distribution studies [20]. Drug release is depend upon surface area larger the surface area more is the diffusion and less the surface area less is diffusion and surface area depend upon particle size i.e. smaller the size greater is the surface area and vice–versa. Also large particle has large core which fills more drug and they diffuse out slowly. It has been seen that aggregation occurs with small particle size. So it was considered that large particles will assist fast drug release and polymer degradation.



The Zetasizer system determines the size by first measuring the Brownian motion of the particles in a sample using Dynamic Light Scattering (DLS). Dynamic Light Scattering (also known as PCS - Photon Correlation Spectroscopy) measures Brownian motion and relates this to the size of the particles. It does this by illuminating the particles with a laser and analyzing the intensity fluctuations in the scattered light. The Zeta sizer calculates the particle size in a sample by means of Stokes-Einstein Equation i.e.

Zeta Potential

The zeta potential of a nanoparticle is generally used to characterize the surface charge of the nanoparticles. It exhibits the electrical potential of particles and is influenced by the composition of the particles and the medium in which it is being dispersed. Nanoparticles with a zeta potential above (+/-) 30 mV have been shown to be stable in suspension, as the surface charge prevents the aggregation of the particles. The zeta potential may also be utilized to determine whether a charged active material is encapsulated within the core of the nanocapsule or adsorbed on the surface. The new Zetasizer offers the highest ever sensitivity, accuracy and resolution of zeta potential. This is achieved by a combination of laser Doppler velocimetry and phase analysis light scattering (PALS). Even samples of very low mobility can be analyzed and their mobility distributions calculated.

- Emulsion stability
- Formulation stability
- Water treatment
- Pigment performance
- Impurity determination

The zeta potential limits for colloids in water

0 to ±5	: rapid coagulation or flocculation
±10 to ±30	: incipient instability
±30 to ±40	: moderate stability
±40 to ±60	: good stability
more than ±61	: excellent stability

Scanning Electron Microscope (Particles surface morphology)

Particles surface morphology of the formulation generally determined by scanning electron microscopy technique. Scanning electron microscopy is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition, and other properties such as electrical conductivity. The types of signals produced by an SEM include secondary electrons, back-scattered electrons (BSE), characteristic X-rays, light (cathodoluminescence),

specimen current and transmitted electrons. Due to the very narrow electron beam, SEM micrographs have a large depth of field yielding a characteristic three-dimensional appearance useful for understanding the surface structure of a sample. A wide range of magnifications is possible, from about 10 times (about equivalent to that of a powerful hand-lens) to more than 500,000 times, about 250 times the magnification limit of the best light microscopes.

Drug content

The polymeric nanoparticles were evaluated for drug content in order to know the amount of drug present in certain portion of the formed nanoparticles. Drug content is nothing but the assay procedure conducted to know the actual amount of drug present in the product.

Drug loading

A high drug- loading capacity is the measure of successful nanoparticulate system because it reduces the amount of matrix material for administration. Drug loading can be done by two methods:

a) Incorporation method: - In this drug is incorporated during the formation of nanoparticle.

b) Adsorption/absorption method: - In this method drug is made to be adsorbed on nanoparticle. In this formed nanoparticle is kept in concentrated solution of drug and adsorption phenomenon take place.

$$\% \text{ E.E} = \frac{\text{Total drug added - un entrapped drug}}{\text{Total drug added}} \times 100$$

***In vitro* drug release**

In vitro release kinetics of a drug entrapped in nanoparticles can be evaluated by several experimental methods:

a) Side by side diffusion cells with artificial or biological membranes
b) Dialysis bag diffusion technique
c) Reverse dialysis sac technique
d) Ultracentrifugation
e) Ultrafiltration
f) Centrifugal Ultrafiltration technique
g) Orbitrary shaker technique

There are several factors that affect the release rate of the entrapped drug. Larger particles have a smaller initial burst and a longer sustained release than the smaller particles. Drug release depends on:

1 Structure of nanoparticles
2 Type and length of polymer
3 Degradation or erosion

Therapeutic applications of nanoparticles [4]

Nanoparticles have been widely employed for different therapeutic applications; some of them are listed below.

In tumor targeting

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) Nano particles will reduce the drug exposure of health tissues by limiting drug distribution to target organ. Verdun *et al* showed that in mice treated with doxorubicin loaded into poly (isohexylcyanoacrylate) nanospheres that greater concentrations of doxorubicin manifested in the liver, spleen and lungs than in mice treated with free doxorubicin.

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 lot of work has been devoted to developing so-called "stealth" particles or PEGylated nanoparticles, which are invisible to macrophages or phagocytes. A major breakthrough in the field came when the use of hydrophilic polymers (such as polyethylene glycol, poloxamers, poloxamines, and polysaccharides) to efficiently coat conventional nanoparticle surface produced an opposing effect to the uptake by the mononuclear phagocytic system MPS. These coatings provide a dynamic "cloud" of hydrophilic and neutral chains at the particle surface which repel plasma proteins.

Nanoparticles for oral delivery of peptides and proteins

Significant advances in biotechnology and biochemistry have led to the discovery of a large number of bioactive molecules and vaccines based on peptides and proteins. Development of suitable carriers remains a challenge due to the fact that bioavailability of these molecules is limited by the epithelial barriers of the gastrointestinal tract and their susceptibility to gastrointestinal degradation by digestive enzymes. Polymeric nanoparticles allow encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation. For instance, it has been found that insulin-loaded nanoparticles have preserved insulin activity and produced blood glucose reduction in diabetic rats for up to 14 days following the oral administration.

For gene delivery

Nanoparticles loaded with plasmid DNA could also serve as an efficient sustained release gene delivery system due to their rapid escape from the degradative endo-lysosomal compartment to the cytoplasmic compartment. Hedley *et al*. reported that following their intracellular uptakeand endolysosomal escape, nanoparticles could release DNA at a sustained rate resulting insustained gene expression. This gene delivery strategy could be applied to facilitate bone healingby using PLGA nanoparticles containing therapeutic genes such as bone morph genic protein.

Nanoparticles for drug delivery into the brain

Strategies for nanoparticle targeting to the brain rely on the presence of and nanoparticles interaction with specific receptor-mediated transport systems in the BBB. For example polysorbate 80/LDL, transferrin receptor binding antibody (such as OX26), lactoferrin, cellpenetrating 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.

Nanoparticles for intra-arterial application

They are used for the intra-arterial localization of therapeutic agents. Advantages include their subcellular size, targeted surface

e, good susceptibility, uniform dispersity for catheter-based therapy and an easy penetration into the arterial wall without causing trauma.

Labhasetwar *et al*, 1995 demonstrated that local delivery of drugs like dexamethasone, heparin and U-86983 was facilitated and high regional concentration could be built with prolonged retention in lower doses with reduced systemic toxicity.

Table 2: Marketed products with nanoparticulate formulations

Product	Company	Indication	Formulation	FDA approval
Sirolimus (Rapamune®)	Wyeth	Immunosuppressant	Tablet	1999
Aprepitant (Emend®)	Merck	Nausea, vomiting	Capsule	2003
Fenofibrate (TriCor® 145 mg, 48 mg)	Abbott	Hypercholesterinemia	Tablet	2004
Megestrol acetate (Megace® ES)	PAR	Appetite stimulant	Nanosuspension	2005
Paliperidone (Invega®)	J&J	Schizophrenia	Nanosuspension	Submitted 2007 (FDA requested additional data August 2008)

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