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NANOPARTICLES AS DRUG DELIVERY DEVICES: A REVIEW

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ABSTRACT

For the past few decades, there has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules.

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are 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. This review summarizes the different methods of preparation of polymeric nanoparticlesincluding nanospheres and nanocapsules.

The article summarizes the basic principle of each method of nanoparticle preparation. It presents the most recent innovations and progresses obtained over the last decade and which were not included in previous reviews. Various nanoparticulate systems, general synthesis and encapsulation processes are covered in this review.

INTRODUCTION

Nanotechnology employs knowledge from the fields of physics, chemistry, biology, materials science, health sciences, and engineering. It has immense applications in almost all the fields of science and human life. Nanoparticles can be defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are 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.

Polymeric nanoparticles are nanoparticles which are prepared from polymers of natural or artificial origin ranging in size between 10 and 1000 nm. They present a higher stability when in contact with the biological fluids. The drug is dissolved, entrapped, encapsulated or attached to nanoparticles and depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained.

Nanoencapsulation of medicinal drugs (nanomedicines) increases drug efficacy, specificity, tolerability and therapeutic index of corresponding drugs. These nanomedicines have many advantages in the protection of premature degradation and interaction with the biological environment, enhancement of absorption into a selected tissue, bioavailability, retention time and improvement of intracellular penetration. Nanomedicines formulation depends on the choice of suitable polymeric system having maximum encapsulation (higher encapsulation efficiency), improvement of bioavailability and retention time.

Drug release from nanoparticles and subsequent biodegradation are important for developing successful formulations. The release rate of nanoparticles depends upon

i) Covalent attachment of the drug to the particle surface (Eatock et al., 1999) or to the polymer prior to preparation (Yoo et al., 1999),
ii) Desorption of the surface-bound/adsorbed drug;
iii) Diffusion through the nanoparticles matrix;
iv) Diffusion (in case of nanocapsules) through the polymer wall;
v) Nanoparticle matrix erosion: and
vi) A combined erosion/diffusion process.

The first possibility leads to a new chemical entity (NCE) (Duncan, 2003), the simple adsorption to a preformed carrier system bears the risk of drug loss by desorption processes. Therefore, a promising method appears to be drug incorporation into the particle matrix. Incorporation has been shown to protect pharmacological active substances from degradation during storage as well as from early degradation/inactivation after injection. Thus, diffusion and biodegradation govern the process of drug release.

Advantages:

1) Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.
2) They control and sustain the release of drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.
3) Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction.
4) Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
5) The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.

Limitations:

1) Their small size and large surface area can lead to particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms.
2) In addition, small particles size and large surface area readily result in limited drug loading and burst release.
3) Large amounts of the conventional surfactants and solvents are contained within the formulation, which may cause serious side effects, including hypersensitivity reactions, neutropenia and neuropathy, even death.

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 many factors including

(a) Size of nanoparticles required;

(b) Inherent properties of the drug, e.g., aqueous solubility and stability;

(c) Surface characteristics such as charge and permeability;

(d) Degree of biodegradability, biocompatibility and toxicity;

(e) Drug release profile desired; and

(f) Antigenicity of the final product

Thus the polymeric composition (hydrophobicity, surface charge, and biodegradation profile) of the nanoparticles, any adjuvant substances, and the associated drug (molecular weight, charge, localization in the nanospheres by adsorption or incorporation) have a great influence on the drug absorption, biodistribution pattern, and elimination.

Principle of methods of preparation of drug-loaded nanoparticles:

Many methods for the preparation of nanoparticles include two main steps. The preparation of an emulsified system corresponds to the first step while the nanoparticles are formed during the second step of the process. This second step is achieved either by the precipitation or the gelation of a polymer or by polymerization of monomers. In general, the principle of this second step gives its name to the method. A few other methods do not require the preparation of an emulsion prior to the obtaining of the nanoparticles. They are based on the precipitation of a polymer in conditions of spontaneous dispersion formation or thanks to the self-assembly of macromolecules to form nanogels or polyelectrolyte complexes from a polymer solution.

Methods:

There are now numerous preparation methods available for producing nanoparticles. Many methods have been developed for preparing nanoparticles; these methods can be classified into two main categories according to whether the formulation requires a polymerization reaction or is achieved directly from a macromolecule or preformed polymer.[23] Depending on the physicochemical characteristics of a drug, it is now possible to choose the best method of preparation and best polymer to achieve an efficient entrapment of drug.

Various methods for preparation of drug-loaded polymeric nanoparticles can be classified as:

A) **Nanoparticles obtained by polymerization of a monomer**

1) Emulsion polymerization
2) Interfacial polymerization
3) Interfacial polycondensation

B) **Nanoparticles obtained from preformed polymers**

B1) **Synthetic preformed polymers**

1) Emulsification/solvent evaporation
2) Solvent displacement and interfacial deposition
3) Emulsification/solvent diffusion
4) Salting out with synthetic polymers

B2)**Natural macromolecules**

1) Albumin nanoparticles
2) Gelatin nanoparticles
3) Alginate nanoparticles
4) Chitosan nanoparticles
5) Agarose nanoparticles

C)Nanoparticles produced by **desolvation of macromolecules**

A) Nanoparticles obtained by polymerization of a monomer:

1) Emulsion Polymerization:

Emulsion polymerization is one of the fastest methods for nanoparticle preparation and is readily scalable. By this method, the monomer is dispersed in aqueous solution as a uniform emulsion and stabilized by the surfactants. The surfactants facilitate emulsification of the monomer into the aqueous phase by decreasing surface tension at the monomer–water interface. Dispersion of the surfactant persists until the critical micellar concentration (CMC) is realized. The method is classified into two categories, based on the use of an organic or aqueous continuous phase.

The continuous organic phase methodology involves the dispersion of monomer into an emulsion or inverse microemulsion, or into a material in which the monomer is not soluble (nonsolvent). As one of the first methods for production of nanoparticles, surfactants or protective soluble polymers were used to prevent aggregation in the early stages of polymerization. This procedure has become less important, because it requires toxic organic solvents, surfactants, monomers and initiator, which are subsequently eliminated from the formed particles. As a result of the nonbiodegradable nature of this polymer as well as the difficult procedure, alternative approaches are of greater interest.

In the aqueous continuous phase the monomer is dissolved in a continuous phase that is usually an aqueous solution, and the surfactants or emulsifiers are not needed. Initiation occurs when a monomer molecule dissolved in the continuous phase collides with an initiator molecule that might be an ion or a free radical. Alternatively, the monomer molecule can be transformed into an initiating radical by high-energy radiation, including γ-radiation, or ultraviolet or strong visible light. Chain growth starts when initiated monomer ions or monomer radicals collide with other monomer molecules according to an anionic polymerization mechanism.

The polymerization mechanism is an anionic process. The percentage of drug incorporated or adsorbed decreases generally with the increasing amount of drug in the polymerization medium. This preparation of nanospheres is simple and drugs can be successfully entrapped, but it follows two drawbacks, first, polymerization requires a chemical or physical initiation, and second, nanospheres are not biodegradable.

2) Interfacial polymerization:

Like emulsion polymerization, in interfacial polymerization, the monomers are used to create the solution. High-torque mechanical stirring brings the aqueous and organic phases together by emulsification or homogenization. Polyalkylcyanoacrylate NPs have been polymerized by this method. One of the advantages of these polymers is their very rapid polymerization—occurring during seconds—initiated by ions present in the medium.

Cyanoacrylate monomer and drug were dissolved in a mixture of an oil and absolute ethanol. This mixture was then slowly extruded through a needle into a well-stirred aqueous solution, with or without some ethanol or acetone containing surfactant. Nanocapsules are formed spontaneously by

polymerization of cyanoacrylate after contact with initiating ions present in the water. The resulting colloidal suspension can be concentrated by evaporation under vacuum. PECA, poly (isobutylcyanoacrylate), and poly (isohexylcyanoacrylate) were used in production of nanoparticles by this process.

Besides the monomer, potentially toxic compounds were not used, thus no purification procedure was necessary. The final product was a suspension of nanocapsules in Migliol, which is an acceptable excipient for oral administration. Encapsulation efficiencies reached 50% and 30% for the larger and the smaller capsules, respectively.

An advantage of interfacial polymerization techniques is high-efficiency drug encapsulation (eg, insulin with 95%). In addition, the advantage of obtaining nanocapsules by this method is that the polymer is formed in situ, allowing the polymer membrane to follow the contours of the inner phase of an oil/water or water/oil emulsion. In this case, the main disadvantage is the use of organic solvents required for the external phase. Washing of solvents and replacement by water represents a time consuming and difficult procedure.

3) Interfacial polycondensation:

Polymeric nanoparticles can be also prepared by the interfacial polycondensation of the lipophilic monomer, such as phtaloyldichloride and the hydrophilic monomer, diethylenetriamine, in the presence and absence of the surfactant. These nanoparticles were smaller than 500 nm. A modified interfacial polycondensation method was also developed. In this case, polyurethane polymer and poly (ether urethane) copolymers were chosen and successfully applied as drug carriers for α-tocopherol. Polyurethane and Poly (ether urethane)–based nanocapsules were synthesized by interfacial reaction between two monomers.

B) Nanoparticles obtained from preformed polymers:

Residual molecules in the polymerization medium (monomer, oligomer, surfactant, etc.) can be more or less toxic, requiring meticulous purification of the colloidal material. To avoid these limitations, methods using preformed polymers instead of monomers have been proposed.

B1) Synthetic preformed polymers:

1) Emulsification/Solvent evaporation:

Emulsification-solvent evaporation involves two steps.

The first step requires emulsification of the polymer solution into an aqueous phase. During the second step polymer solvent is evaporated, inducing polymer precipitation as nanospheres. A polymer organic solution containing the dissolved drug is dispersed into nanodroplets, using a dispersing agent and high-energy homogenization, in a nonsolvent or suspension medium such as chloroform or ethyl acetate. The polymer precipitates in the form of nanospheres in which the drug is finely dispersed in the polymer matrix network. The solvent is subsequently evaporated by increasing the temperature

under pressure or by continuous stirring. The size can be controlled by adjusting the stir rate, type and amount of dispersing agent, viscosity of organic and aqueous phases, and temperature.

Even though different types of emulsions may be used, oil/water emulsions are of interest because they use water as the nonsolvent; this simplifies and thus improves process economics, because it eliminates the need for recycling, facilitating the washing step and minimizing agglomeration. However, this method can only be applied to liposoluble drugs, and limitations are imposed by the scale-up of the high energy requirements in homogenization. Frequently used polymers are PLA, PLGA, ethylcellulose (EC), cellulose acetate phthalate, and poly(E-caprolactone) (PCL). Drugs or model drugs encapsulated were albumin, texanus toxoid, testosterone, loperamide, prazinquantel, cyclosporin A, nucleic acid, and indomethacin.

2) Solvent displacement and interfacial deposition:

Solvent displacement and interfacial deposition are similar methods based on spontaneous emulsification of the organic internal phase containing the dissolved polymer into the aqueous external phase. However, solvent displacement forms nanospheres or nanocapsules, whereas interfacial deposition forms only nanocapsules. Solvent displacement 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. The polymer is dissolved in a water-miscible solvent of intermediate polarity, leading to the precipitation of nanospheres. This phase is injected into a stirred aqueous solution containing a stabilizer as a surfactant. Polymer deposition on the interface between the water and the organic solvent, caused by fast diffusion of the solvent, leads to the formation of a colloidal suspension. This method is basically applicable to lipophilic drugs because of the miscibility of the solvent with the aqueous phase, In fact, it seems difficult to choose a drug/polymer/solvent/nonsolvent system in which particles would be formed and the drug efficiently entrapped, because the solvent and the nonsolvent of the polymer must be mutually miscible. The progressive addition of the polymer solution to the nonsolvent generally leads to the formation of nanospheres close to 200 nm in size. Nanoparticles seem to be formed by a mechanism comparable to the diffusion. This phenomenon has been explained by local variations of the interfacial tension between the two immiscible liquids due to the mutual diffusion of the third liquid. This method has been applied to various polymeric materials such as PLA, PLGA, and PCL. This technique was well adapted because entrapment efficiencies as high as 98% were obtained. Interfacial deposition is a process used for the production of nanocapsules; however, this is not a polymerization technique but an emulsification/solidification technique. In interfacial deposition, a fifth compound is introduced, of oil nature, miscible with the solvent of the polymer but immiscible with the mixture. The polymer deposits on the interface between the finely dispersed oil droplets and the aqueous phase, forming nanocapsules. This mixture is injected slowly into a stirred aqueous medium, resulting in the deposition of the polymer in the form of nanoparticles of about 230 nm in size.

3) Emulsification/Solvent diffusion:

Emulsification/solvent diffusion (ESD) is based on the use of organic solvents, and then it was adapted to the following salting-out procedure. The encapsulating polymer is dissolved in a partially water soluble solvent such as propylene carbonate and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. In fact, to produce the precipitation of the polymer and the consequent formation of nanoparticles, it is necessary to promote the diffusion of the solvent of the dispersed phase by dilution with an excess of water when the organic solvent is partly miscible with water. Subsequently, the polymer-water saturated solvent phase is emulsified in an aqueous solution containing stabilizer, leading to solvent diffusion to the external phase and the formation of nanospheres or nanocapsules, according to the oil-to-polymer ratio. Finally, the solvent is eliminated by evaporation or filtration. Figure. 1.

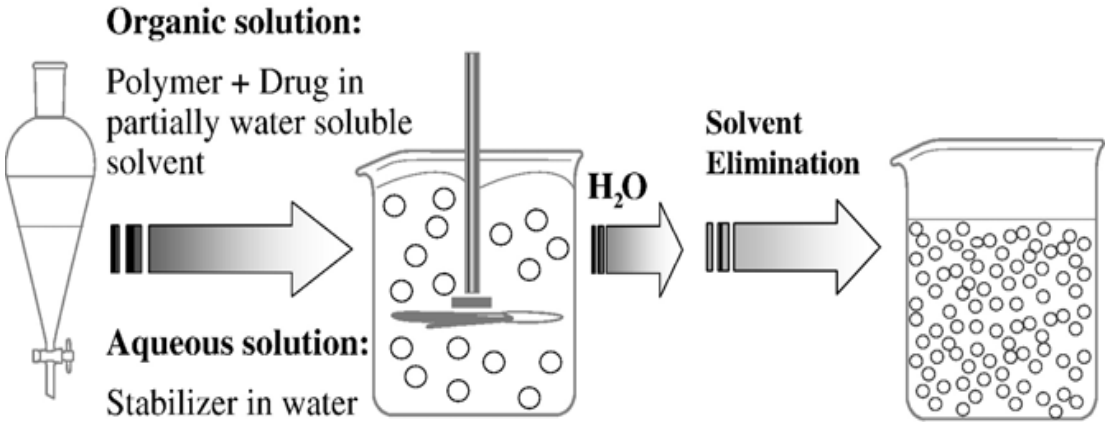

Figure1. Schematic illustration of the ESD technique

This technique presents several advantages, such as high encapsulation efficiencies (generally N70%), no need for homogenization, high batch-to-batch reproducibility, ease of scale-up, simplicity, and narrow size distribution. Disadvantages are the high volumes of water to be eliminated from the suspension and the leakage of water-soluble drug into the saturated-aqueous external phase during emulsification, reducing encapsulation efficiency.

4) Salting out with Synthetic polymers:

Salting -out is based on the separation of a water miscible solvent from aqueous solution via a salting-out effect. Polymer and drug are initially dissolved in a solvent such as acetone, which is subsequently emulsified into an aqueous gel containing the salting-out agent (electrolytes, such as magnesium chloride, calcium chloride, and magnesium acetate, or non- electrolytes such as sucrose) and a colloidal stabilizer such as polyvinylpyrrolidone or hydroxyethylcellulose. This oil/water emulsion is diluted with a sufficient volume of water or aqueous solution to enhance the diffusion of acetone into the aqueous phase, thus inducing the formation of nanospheres. The selection of the salting out agent is important, because it can play an important role in the encapsulation efficiency. Both the solvent and the salting-out agent are then eliminated by cross-flow filtration.

This technique is used in the preparation of PLA, poly- (methacrylic) acid, and EC nanospheres leads to high efficiency and is easily scaled up. Salting out does not require an increase of temperature and, therefore, may be useful when heat sensitive substances have to be processed. The greatest disadvantages are exclusive application to lipophilic drugs and the extensive nanoparticle washing steps.

B2) Natural macromolecules:

1) Albumin nanoparticles:(produced in an external-oily emulsion)

Two main methods are used in the preparation of albumin nanospheres, characterized by the method of stabilization; thermal treatment at elevated temperatures (95–170^{o}C) and chemical treatment in vegetable oil, iso-octane emulsions, or aqueous medium. In this case albumin nanospheres were formed by homogenizing the oil phase containing the albumin droplets and thermally stabilized by heating at 175 to 180^{o}C for 10 minutes. This mixture was cooled and diluted with ethyl ether to reduce the viscosity of the oil phase to permit separation by centrifugation. For this reason, nanoparticles were produced by emulsifying serum albumin aqueous solution in cottonseed oil at 25^{o}C, then denaturing the albumin by resuspending the particles in ether containing the cross-linking agents 2,3-butadiene or formaldehyde. The particles were stirred, isolated by centrifugation, and dried by lyophilization. Particles released the drug much faster than particles formed by heat treatment, but the purification step remains the main problem with the elimination of the cottonseed oil. A technique was proposed based on the desolvation of natural macromolecules, which simplifies the purification step.

2) Gelatin nanoparticles:(produced in an external-oily emulsion)

Emulsified gelatin solution droplets were hardened by cooling the emulsion below the gelation point in an ice bath, resulting in gelation of the gelatin droplets. Gelled nanodroplets were filtered, washed, and cross-linked with formaldehyde. This technique is applicable to heat-sensitive drugs; however, a number of drugs can be covalently bound to the gelatin by formaldehyde treatment, which constitutes a disadvantage.

3) Alginate nanoparticles:

Sodium alginate is a water-soluble polymer that gels in the presence of multivalent cations such as calcium. Alginate particles are usually produced by dropwise extrusion of sodium alginate solution into calcium chloride solution. The smallest particles produced had a minimum size of 1 to 5 Am, obtained by air atomization. The preparation of alginate nanoparticles was first achieved in a diluted aqueous sodium alginate solution in which gelation was induced by the addition of a low concentration of calcium. This leads to the formation of invisible clusters of calcium alginate gels. In an additional advance, alginate particles have been produced by using a modified emulsification/internal gelation methodas illustrated in Figure. The main difficulty of this method is the nanoparticle washing step to eliminate the residual oil droplets. Figure. 2.

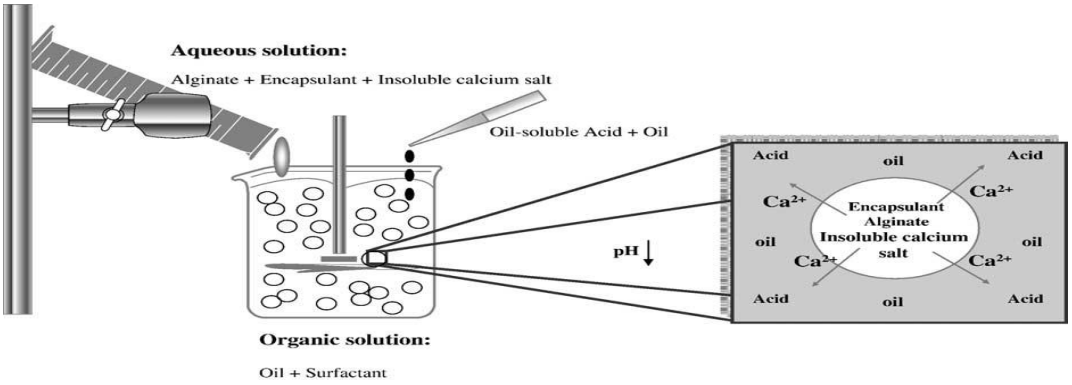

Figure 2: Schematic representation of the emulsification–internal gelation technique using alginate.

3) Chitosan nanoparticles:

Chitosan nanoparticles have been developed to encapsulate proteins such as bovine serum albumin, vaccines, anticancer agents, insulin, and nucleic acids. The methods proposed to prepare chitosan nanoparticles are based on the spontaneous formation of complexes between chitosan and polyanionsor the gelation of a chitosan solution dispersed in an oil emulsion. This technique has a major disadvantage of involving organic solvents during the isolation of the particles; these are difficult to remove and may cause toxicity. Chitosan nanoparticles are produced by promoting gelation in an emulsification-based method as illustrated in Figure, results in a diameter of 400 nm.Figure. 3.

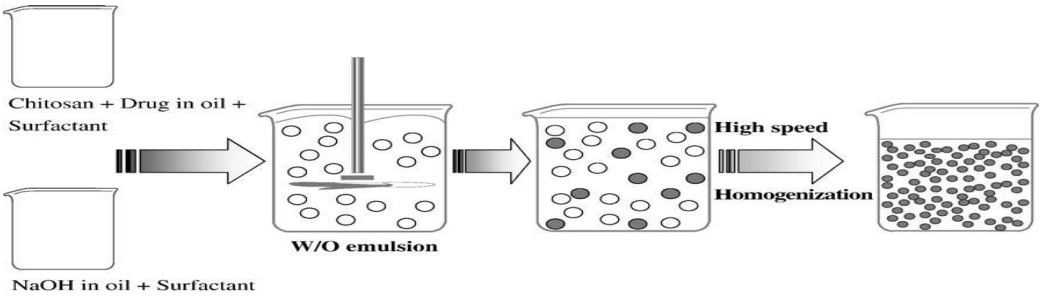

Figure 3: Schematic representation of chitosan nanoparticles preparation by the emulsification technique.

4) Agarose nanoparticles:

Agarose nanoparticles were developed for the administration of therapeutic proteins and peptides. Agarose aqueous solution forms thermally reversible hydrogels while being cooled below the gelling temperature (31–36^{o}C). Thermal gelation results from the formation of helicoidal structures in which large amounts of water can be entrapped. The hydrogel, being hydrophilic, inert, and biocompatible, forms a suitable matrix for proteins and peptides that can be entrapped in the gel during formation. This methodology requires the preparation of an Agarose solution in corn oil emulsion at 40^{o}C. Peptides and proteins to be encapsulated are initially added to the agarose solution. The small size of the dispersed aqueous nanodroplets is achieved by homogenization. Gelation of agarose is then induced by diluting the emulsion with cold corn oil under agitation at 5^{o}C. The liquid nanodroplets then gel to protein-containing agarose hydrogel nanoparticles.

C) Nanoparticles by desolvation of macromolecules:

Another technology applicable to a wide range of polymers is based on desolvation by charge and pH changes, or by addition of a desolvating agent (ethanol or concentrated inorganic salt solutions). The main advantage is that this process does not require an increase in temperature and, therefore, may be useful when heat sensitive drugs are used. Nanoparticles were prepared using the process of reversible swelling of macromolecules using gelatin, human serum albumin, bovine serum albumin, and casein as the macromolecular materials. This process offers the advantage of producing nanoparticles directly in aqueous suspension, but the use of potentially toxic compounds such as glutaraldehyde and desolvating agents requires subsequent purification. Variations in nanoparticle production by the desolvation process were described, but unfortunately the yield is comparatively low.

Polymers Used to Design Nanoparticles for in vivo Delivery of Drugs:

Considering the potential offered by polymer chemistry today, there are only a limited number of polymers which can be used as constituent of nanoparticles designed to deliver drugs in vivo. To explain this fact, one should consider that a suitable polymer needs to fulfil several requirements to be used in such an application.

1) It needs to be biodegradable or at least totally eliminated from the body in a short period of time allowing repeating administration without any risk of uncontrolled accumulation.
2) It must be non-toxic and non-immunogenic. Its degradation products, if any, must also be non-toxic and non-immunogenic.
3) It should be formulated under the form of polymer nanoparticles with suitable properties regarding the drug delivery goal for which the nanoparticles are designed.

In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in drug targeting to particular organs/tissues, as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides and genes through a per oral route of administration. In spite of development of various synthetic and semi synthetic polymers, natural polymers still enjoy their popularity in drug delivery; some of them are listed below.

- Gums (Ex. Acacia, Guar, etc.)
- Sodium alginate
- Gelatin
- Albumin
- Chitosan

A range of materials have been employed to delivery of bioactive agents. However a polymer used in controlled drug delivery formulations, must be chemically inert, non-toxic and free of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging, and be readily processable.Some of these polymeric materials are listed below.

- Cellulosics.
- Poly (2-hydroxy ethyl methacrylate).
- Poly (N-vinyl pyrrolidone).
- Poly (methyl methacrylate).
- Poly (vinyl alcohol).
- Polyacrylamide.
- Poly (methacrylic acid).

However, in recent years additional polymers are designed primarily for medical applications and have entered the arena of controlled release of bioactive agents. Many of these materials are designed to degrade within the body, most popular ones are;

- Polylactides (PLA).
- Polyglycolides (PGA).
- Poly (lactide-co-glycolides) (PLGA).
- Polyorthoesters.
- Polycyanoacrylates
- Polycaprolactone

The main advantage of these degradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways. However, biodegradable materials do produce degradation by-products that must be tolerated with little or no adverse reactions.

Abraxane is the first polymeric nanoparticle based product from American Pharmaceutical Partners, Inc., and American Bioscience, Inc. (ABI). It was approved in year 2005 and is consisting of albumin-bound paclitaxel nanoparticles. This product is free of toxic solvents like cremophor-EL, which is used until now to solubilise paclitaxel in order to administer it intravenously to the patient. Success of Abraxane shows that nanotechnology can bring many exciting products which can overcome many hurdle of formulation scientist.

Human Serum Albumin (HSA):

As a major plasma protein, HSA is selected as a material for nanoparticle as it has a distinct edge over other materials for nanoparticle preparation. It is both bioacceptable and biodegradable. Moreover it is cheap and easily available. The process of preparing nanoparticles from albumin is not complicated and particle size can be controlled by various factors during preparation. Drugs entrapped in albumin nanoparticles can be digested by proteases and drug loading can be quantified.

Nanoparticulate Albumin Based-Paclitaxel (nab-paclitaxel), serves not only as a targeting ligand, but also as a carrier in drug delivery. In this case the albumin contained in the nab-paclitaxel is thought to facilitate receptor-mediated endothelial transcytosis of albumin-based nanoparticles into the extravascular space. This process is initiated by binding of albumin to a cell surface of a brain and has

a high binding capacity to albumin. This binding will lead to combination of gp60 receptor and an intracellular protein (caveolin-1) and subsequently invagination of the cell membrane to form transcytotic vesicles. Thus, agents conjugated or embedded within the albumin are co-transported to the space surrounding the tumours.

HSA nanocarriers can easily be prepared by ethanolic desolvation and process has been proposed to be a robust method which allows the particle size and polydispersity index to be controlled by varying the ion strength, pH, HSA concentration, and stirring speed. Paddle stirring systems show good suitability for their application in an industrial large-scale process. A constant solvent flow was achieved by utilizing a HPLC pump for the addition of ethanol to the protein solution. However, a covalent stabilization or surface functionalization of these nanocarriers is difficult because of the residues of dissolved HSA in the resulting suspension. A benefit of this method is the high desolvation efficiency and the absence of dissolved HSA that may have negative influence on the freeze drying of the colloid system.Thus a cost-effective and reproducible large-scale preparation technique can provide high amounts of these HSA nanoparticles.

Evaluation of Nanoparticles:

1. **Zeta potential:**

The Zeta potential of a nanoparticle is commonly used to characterized the surface charge property of nanoparticles. It reflects the electrical potential of 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 aggregation of the particles.

2. **Particle Shape:**

SEM characterizes the nanosuspension before going for evaluation; the nanosuspension is lyophilized to form solidparticles. The solid particles are coated with platinum alloy using a sputter coater.

3. **Particle size:**

Particle size and size distribution are the most importantcharacteristics of nanoparticle systems. They determine the invivo distribution, biological fate, and toxicity and targetingability of nanoparticle system. In addition, they can alsoinfluence the drug loading, drug release and stability of nanoparticles. Currently, the faster and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM).

4. **Drug Entrapment Efficiency:**

Nanoparticles were separated from the aqueous medium by ultracentrifugation at 10,000 rpm for 30 min at 50C. Then the resulting supernatant solution was decanted and dispersed into phosphate buffer saline pH 7.4. Thus the procedure was repeated twice to remove the unentrapped drug molecules

completely. The amount of drug entrapped in the nanoparticles was determined as the difference between the total amount of drug used to prepare the nanoparticles and the amount of drug present in the aqueous medium. Drug Entrapment efficiency (%) = Amount of released from the lysed nanoparticle X 100 Amount of drug Initially taken to prepare the Nanoparticles.

CONCLUSION

The foregoing show that nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable drugs. The core of this system can enclose a variety of drugs, enzymes, genes and is characterized by a long circulation time due to the hydrophilic shell which prevents recognition by the reticular-endothelial system. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and particle engineering, is still required. Further advances are needed in order to turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system.

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