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Nanoencapsuation – The Drug Delivery System

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ABSTRACT

Nanoparticles are particles of sizes ranging from 1 to 1000 nm with one or more dimensions. The nanoparticles show enhanced properties such as surface area, strength, high reactivity, stability, sensitivity, etc. because of their small size. For optimal drug activity, it is necessary to deliver the drug to the body and its site of action as efficiently as possible. Delivery of drugs to the target site is achieved by the colloidal drug delivery system mainly by using nanoparticles. Targeting the drug to a specific site improve therapeutic efficiency and reduces toxicity. Due to their exceptional properties like antibacterial activity, high resistance to oxidation, and high thermal conductivity, nanoparticles have attracted considerable attention in recent years. Nanoparticles are one of the promising drug delivery systems, which can be of potential use in controlling and targeting drug delivery. This paper presents a review of nanoparticles, their classification, synthesis methods polymers, carriers, and adjuvant used preparations, advantages, and drawbacks of nanoparticles.

INTRODUCTION

Nanoparticles are solid colloidal particles ranging from 10 to 1000 nm. They consist of macromolecular materials and can be used as an adjuvant in vaccines or as drug carriers, in which the active principle is dissolved, entrapped, encapsulated or to which the active principle is adsorbed or attached.[1] Nanoparticle even though invisible has the ability for both controlling the release and protecting the drug against its degradation. Nanoparticles can achieve tissue targeting of many drugs. It was realized that the nanoparticles loaded bio-actives could not only deliver the drugs to specific organs within the body but the delivery rate, in addition, could be controlled as being bystanders, burst, controlled, pulsatile, or modulated.[2] Nanoparticles have a special role in targeted delivery in the sense that they have all the advantages of liposomes including the particle size, but unlike liposomes, nanoparticles have a long shelf life and can usually entrap more drugs than liposomes[3]. Nanoparticles possess better stability as compared to liposomes. Because of their small particle size, colloidal preparations impart 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 not only improves the therapeutic efficiency but also enables a reduction of the amount of drug which must be administered to achieve a therapeutic response, thus minimizing unwanted toxic effects[4].

CLASSIFICATION OF NANOPARTICLES

The nanoparticles are generally classified as organic, inorganic, and carbon-based.

Organic nanoparticles

Dendrimers, micelles, liposomes, and ferritin, etc. are commonly knows organic nanoparticles or polymers. The nanoparticles are nontoxic, biodegradable and some particles such as micelles and liposomes have a hollow core, also known as nanocapsules, and are sensitive to thermal and electromagnetic radiation such as heat and light. These unique characteristics make them an ideal choice for drug delivery. The organic nanoparticles are widely used in the biomedical field, for example, the drug delivery system as they are efficient, and also they can be injected at specific parts of the body that is also known as targeted drug delivery[5].

Inorganic nanoparticles

Inorganic nanoparticles are particles that are not made up of carbon. Metal and metal-oxides based nanoparticles are generally classified as inorganic nanoparticles.

Metal based

Nanoparticles that are synthesized from metals to nanometric sizes either by destructive or constructive methods are metal based nanoparticles. Almost all the metals can be synthesized into their nanoparticles. The commonly used metals for nanoparticle synthesis are aluminium (Al), cadmium (Cd), cobalt (Co), copper (Cu), gold (Au), iron (Fe), lead (Pb), silver (Ag), and zinc (Zn).

Metal oxides based

The metal oxide based nanoparticles are synthesized to modify the properties of their respective metal based nanoparticles. The commonly synthesized are Aluminium oxide (Al_2O_3), Cerium oxide (CeO_2), Iron oxide (Fe_2O_3), Magnetite (Fe_3O_4), Silicon dioxide (SiO_2), Titanium oxide (TiO_2), Zinc oxide (ZnO). These nanoparticles have possessed exceptional properties when compared to their metal counterparts[6].

Carbon based

The nanoparticles which are made completely of carbon are known as carbon based. They can be classified into fullerenes, graphene, carbon nanotubes (CNT), carbon nanofibers, and carbon black and sometimes activated carbon in nano size.

Fullerenes

Fullerenes (C60) is a carbon molecule that is spherical and made up of carbon atoms held together by sp2 hybridization. About 28 - 1500 carbon atoms form the spherical structure with a diameter up to 8.2 nm for a single layer and 4 - 36 nm for multi-layered fullerenes.

Graphene

Graphene is an allotrope of carbon. Graphene is a hexagonal network of honeycomb lattice made up of carbon atoms in a two-dimensional planar surface. Approximately the thickness of the graphene sheet is around 1 nm.

Carbon Nano Tubes (CNT)

Carbon Nano Tubes (CNT), a grapheme nano foil with a honeycomb lattice of carbon atoms is wound into hollow cylinders to form nanotubes of diameters as low as 0.7 nm for a single-layered and 100 nm for multi-layered CNT and length varying from a few micrometres to several millimetres. The ends can either be hollow or closed by a half fullerene molecule.

Carbon Nanofiber

The same graphene nano foils are used to produce carbon nanofiber as CNT but wound into a cone or cup shape instead of regular cylindrical tubes.

Carbon black

An amorphous material made up of carbon is spherical with diameters from 20 - 70 nm. The interaction between the particles is so high that they bound in aggregates and around 500 nm agglomerates are formed[7].

PREPARATION OF NANOPARTICLES

The nanoparticles are synthesized by various methods that are categorised into a bottom-up or top-down method. Nanoparticles can also be prepared from natural material such as polysaccharides, synthetic polymers and proteins. The selection of inert matrix material depends on several factors like final size of nanoparticles required, drug properties like aqueous solubility, stability, surface charge, permeability, degree of biodegradability, biocompatibility, toxicity, desired drug release profile and antigenicity of the final product.

The following techniques are used for the preparation of nanoparticles:

- ✓ Bottom up technique
- ✓ Chemical reaction technique
- ✓ Top-down technique
- ✓ Combination technique

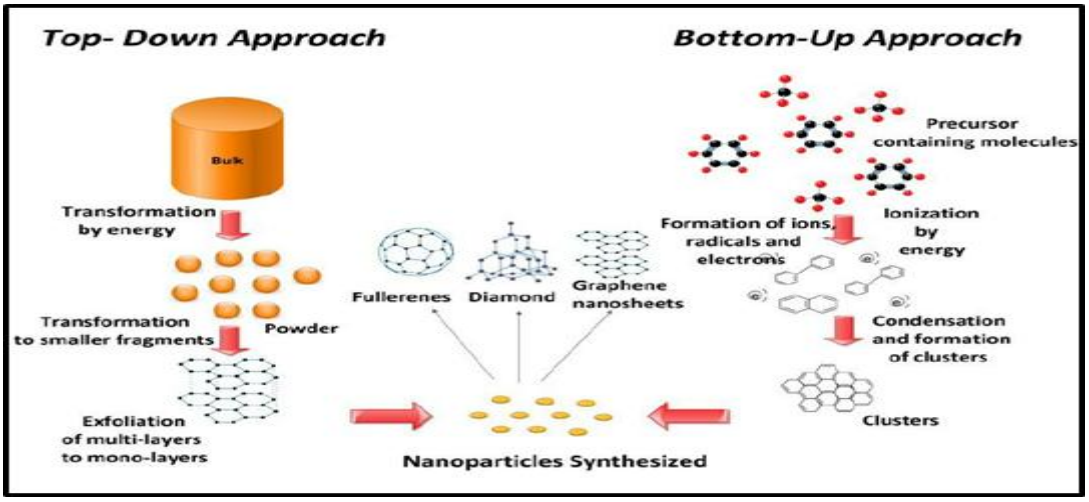

Figure No. 1: A simplified representation of the process is presented.

Nanoparticles can be obtained by using bottom-up processes like precipitation starting from molecular solutions. Furthermore, the reduction of larger particles to nanoparticles (top-down) can be performed (**Figure No.1**). Another approach is the combination of both principles (combination techniques). The last way leads through a chemical reaction step directly to nanoparticles (chemical reaction approach).

Chemical reaction

Chemical reactions such as polymerizations are one of the ways to form nanoparticles; however, they are normally not used for the production of drug nanoparticles consisting of pure API. These techniques are commercially very important such as, for the production of pharmaceutical coating materials in the form of latex dispersions. Chemical reactions can be used to manufacture polymeric nanoparticles consisting of a matrix forming polymer which contains API. The drugs which are a load of such particles is significantly less than 100% hence they must be differentiated from drug nanoparticles produced from standard particle size reduction techniques[8].

Bottom-up method

Bottom-up approaches start with drug molecules in solution. By altering the conditions of the system in solution, the drug molecules begin to precipitate in larger formations. The bottom-up method or constructive method is the build-up of material from atom to clusters and finally to nanoparticles. Sol-gel, spinning, chemical vapour deposition (CVD), pyrolysis, and biosynthesis are the most commonly used bottom-up methods for nanoparticle production[5].

Sol-gel

The sol is a colloidal solution of solids suspended in a liquid phase. The gel – a solid macromolecule submerged in a solvent. Sol-gel is the most selected bottom-up method due to its simplicity and most of the nanoparticles can be synthesized from this method. It is a wet-chemical method containing a chemical solution behaving as a precursor for an integrated system of discrete particles. Metal oxides and chlorides are the most widely used precursors in the sol-gel process. The precursor is then dispersed in a host liquid either by shaking, stirring or sonication and the resultant system contains a liquid and a solid phase. Phase separation is carried out to recover the nanoparticles by various methods such as sedimentation, filtration and centrifugation and the moisture is further removed by drying[9].

Spinning

The synthesis of nanoparticles by spinning is done by a spinning disc reactor (SDR). It contains a rotating disc inside a chamber or reactor where the physical parameters like temperature can be controlled. The reactor is generally filled with nitrogen or other inert gases to remove oxygen inside and avoid chemical reactions [10]. The disc is rotated at a different speed where the liquid i.e. precursor and water is pumped in. The spinning causes the atoms or molecules to fuse and is precipitated, collected and dried. The various operating parameters such as the disc rotation speed, liquid flow rate, location of feed, disc surface, liquid/precursor ratio etc. which determines the characteristics nanoparticles synthesised from SDR[11].

Chemical Vapour Deposition (CVD)

Chemical vapour deposition is the deposition of a thin film of gaseous reactants onto a substrate. This is carried out in a reaction chamber at a medium temperature by combining gas molecules. A chemical reaction occurs when a heated substrate comes in contact with the combined gas[7]. This reaction produces a thin film of product on the substrate surface that is recovered and used. The substrate temperature is the influencing factor in CVD. The advantages of CVD are uniform, hard, highly pure, and strong nanoparticles. The disadvantages of CVD requires special equipment and the gaseous by-products are highly toxic[12].

Pyrolysis

Pyrolysis is the most commonly used process in industries for large scale production of the nanoparticle. It involves burning a precursor with flame. The precursor is either in liquid or vapour state that is fed into the furnace at high pressure through a small hole where it burn[13]. The combustion or by-product gases are then air classified to recollect the nanoparticles. Some of the furnaces use laser and plasma instead of the blaze to produce high temperature for easy evaporation. The advantages of pyrolysis are simple, efficient, cost-effective and continuous process with high yield[14].

Biosynthesis

Biosynthesis is a green and environmentally friendly method for the synthesis of nanoparticles that are biodegradable and nontoxic. Biosynthesis uses bacteria, plant extracts, fungi, etc. together with the precursors to get nanoparticle instead of convention chemicals for bioreduction and capping purposes. The biosynthesized nanoparticles have unique and enhanced properties that find its way in biomedical applications[15].

Top-down method

The top-down method or destructive method is the reduction of a bulk substance to nanometric scale particles. Mechanical milling, nanolithography, laser ablation, sputtering and thermal decomposition are some of the most widely used nanoparticle synthesis methods[5].

Mechanical milling

Among the various top-down methods, mechanical milling is one of the most widely used to produce various nanoparticles. This method is also used for milling and post-annealing of nanoparticles during synthesis where different elements are milled in an inert atmosphere[16].

Nanolithography

Nanolithography is the study of fabricating nanometric scale structures with the least of one dimension in the size range of 1-100 nm. There are several nanolithographic techniques for instance optical, multiphoton, nanoimprint, electron-beam and scanning probe lithography[17]. In general, lithography is the process of printing a required shape or structure on a light sensitive material that selectively removes a portion of the material to create the desired

shape and structure. The main advantages of nanolithography are to produce from a single nanoparticle to a cluster with the desired shape and size. The disadvantages are the requirement of complex equipment and the cost associated[18].

Laser ablation

Laser Ablation Synthesis in Solution (LASiS) is a common method for nanoparticle production from different solvents. The irradiation of metal submerged in a liquid solution by a laser beam condenses a plasma plume that produces nanoparticles. It is a reliable top-down method that provides an alternative solution to conventional chemical reduction of metals to synthesis metal based nanoparticles. As this method provides a stable synthesis of nanoparticles in organic solvents and water that does not require any stabilizing agent or chemicals it is a 'green' process[19].

Sputtering

Sputtering is the deposition of nanoparticles on a surface by releasing particles from it by colliding with ions[20]. This technique is usually a deposition of a thin layer of nanoparticles followed by annealing. The thickness of the layer, duration of annealing, substrate type temperature, etc. regulates the shape and size of the nanoparticles[21].

Thermal decomposition

Thermal decomposition is an endothermic chemical decomposition produced by the heat that breaks the chemical bonds in the compound. The accurate temperature at which an element chemically decomposes is the decomposition temperature. The nanoparticles are produced by decomposing the metal at specific temperatures undergoing a chemical reaction producing secondary products[6].

1. Amphiphilic macromolecule cross-linking

✓ Heat cross-linking

✓ Chemical cross-linking

2. Polymerization based methods

✓ Polymerization of monomers in situ

✓ Emulsion polymerization vs Dispersion polymerization

- ✓ Interfacial condensation polymerization
- ✓ Interfacial complexation

3. Polymer precipitation methods

- ✓ Solvent extraction/ evaporation
- ✓ Solvent displacement (nanoprecipitation)
- ✓ Salting out

The most commonly used methods are,

- ➢ Emulsion evaporation
- ➢ Solvent displacement
- ➢ Salting out
- ➢ Emulsification diffusion
- ➢ Interfacial polymerization
- ➢ Desolvation technique

A. Emulsion evaporation

This method was patented by Vanderhoff et al.[22] for the preparation of pseudo-latexes or artificial latexes. This is the common method for the preparation of solid polymeric nanoparticles (**Figure No. 2**). This technique has been successful in encapsulating hydrophobic drugs. Briefly, the preformed polymer and drug are dissolved in a water immiscible organic solvent which is emulsified in an aqueous solution. This crude emulsion is then passed through a sonicator or homogenizer to reduce the globule size. The organic solvent is then evaporated by heat, vacuum, or both and the nanoparticles are usually collected by centrifugation and lyophilization[23-26].

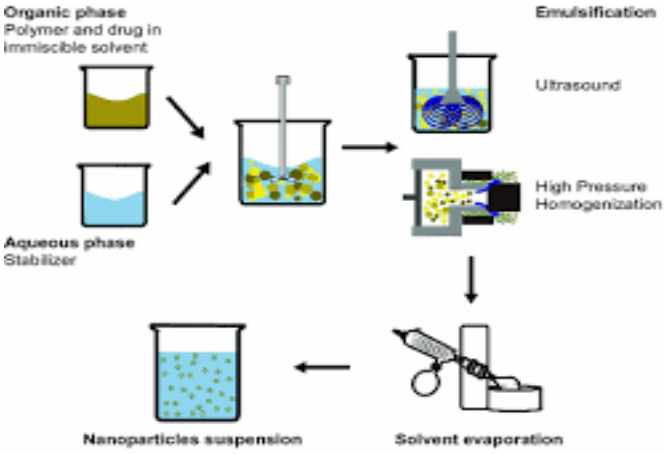

Figure No. 2: Nanoparticle preparation using emulsion solvent evaporation methods.

A modification of this procedure led to the favor of the encapsulation of hydrophilic compounds which is called the multiple emulsion technique. In the emulsification technique, mostly chlorinated solvents (Chloroform and methylene chloride) were used because of their water insolubility, easy emulsification, solubilizing property, and low boiling point[27,29].

B. Solvent displacement

This technique was first described and patented by Fessi et al.[30] In this method polymer, drug, and optionally a lipophilic stabilizer are dissolved in semi-polar water solvents such as acetone or ethanol. This solution is then poured under magnetic stirring into an aqueous solution containing stabilizer which leads to the preparation of nanoparticles by rapid diffusion. This technique is also called as nanoprecipitation method. The usefulness of this technique is limited to water-miscible solvents, in which the diffusion rate is enough to produce spontaneous emulsification. Also, the technique can be used only for drugs soluble in this type of solvents. A major drawback of this technique is the difficulty to choose a drug /polymer/solvent/nonsolvent in which nanoparticles would be formed and the drug efficiently entrapped[31]. Stainmesse et al.[32] found that poly (E-caprolactone) nanoparticles could be prepared under restricted conditions corresponding to a very narrow area of the PCL/Acetone/ Water phase diagram. Solvent displacement is not an efficient method to encapsulate water soluble drugs. Niwa et al.[33] studied the efficiency of this technique to entrap indomethacin and 5- fluorouracil as examples of poorly water soluble drugs respectively (**Figure No. 3**). They found that indomethacin was efficiently encapsulated in PLGA nanoparticle than 5-fluorouracil. 5-fluorouracil was poorly encapsulated because of considerable leakage of the drug into the aqueous phase during preparation.

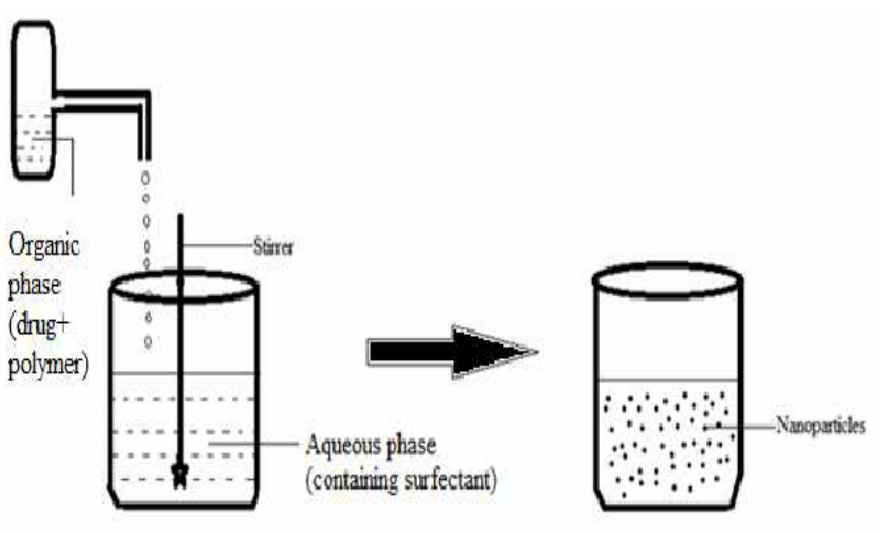

Figure No. 3: Nanoparticle preparation using the solvent displacement method

C. Salting out

This method was patented by Bindschaedler et al.[34] in 1988 to prepare pseudo-latexes. This method is based on the separation of a water miscible solvent from aqueous solutions via the salting-out effect. Acetone is generally chosen as the water miscible solvent because of its solubilizing properties and it's well known separation from aqueous solutions by salting-out with electrolytes. Briefly, polymer and drug are dissolved in acetone and this solution is emulsified under vigorous mechanical stirring in an aqueous gel containing the salting-out agent and a colloidal stabilizer. The o/w emulsion is diluted with a sufficient volume of water or an aqueous solution to enhance the diffusion of acetone into the aqueous phase, thus inducing the formation of nanospheres. Solvent and salting-out agent are then eliminated by cross flow filtration (**Figure No. 4**).

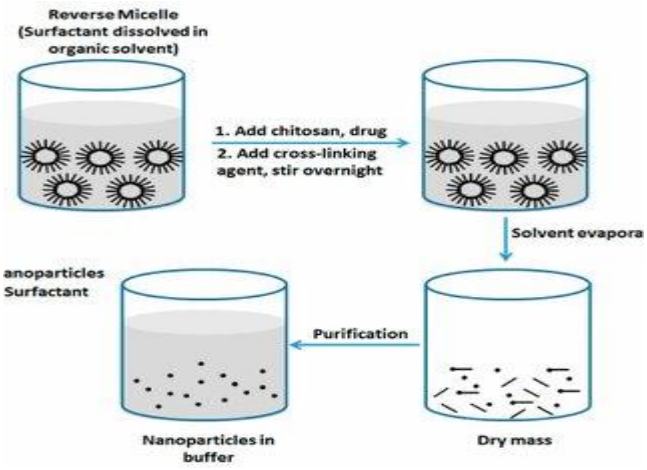

Figure No. 4: Nanoparticle preparations using the salting-out method

D. Emulsification diffusion

This method is a modification of the salting out procedure and was first patented by Quintanar-Guerrero D et al.[35]. This method used a partially water soluble solvent like acetone or propylene carbonate. The polymer and bioactive compounds are dissolved in the solvent and emulsified in the aqueous phase containing the stabilizer. The stabilizer prevents aggregation of emulsion droplets. Water is added to the emulsion to allow for the diffusion of the solvent to the water. The solution is stirred leading to nanoprecipitation of the particles. Murukami et al.[36]effectively modified the solvent diffusion technique by using two water miscible solvents one with more affinity for PLGA and one with more affinity for the stabilizer, PVA, such as acetone and ethanol.

E. Interfacial polymerization

This method involves the interfacial deposition of biodegradable polymers at the o/w interface, following the displacement of a semipolar solvent miscible with water from a lipophilic solution. This method is used for the preparation of nanocapsules[25](**Figure No. 5**). Polymer properties may alter the physicochemical properties at the interface as explained in the Marangoni effect[37].

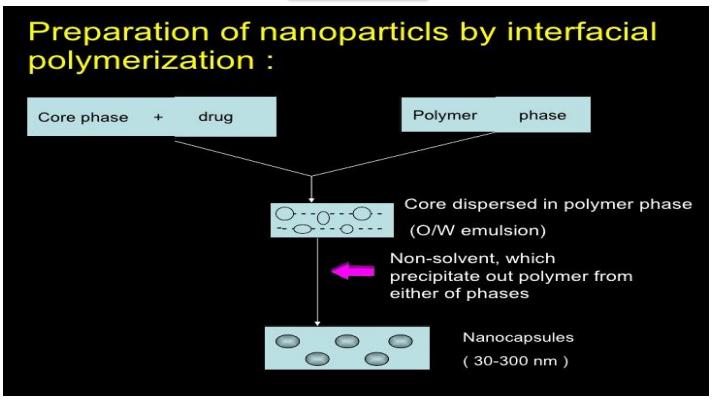

Figure No. 5: Nanoparticles prepared by using interfacial polymerization

F. Emulsion polymerization

In this method the liquid is dispersed under agitation in a continuous phase in which it is immiscible. The polymerization is usually initiated by the reaction of the initiators with the monomer molecules that are dissolved in the continuous phase of the emulsion[38]. The growing polymer chain remains soluble until it reaches a certain molecular weight for which it becomes insoluble leading to phase separation (**Figure No. 6**). Satheshkumar et al.[39]

prepared polystyrene nanoparticles containing cefotaxime sodium by emulsion polymerization method.

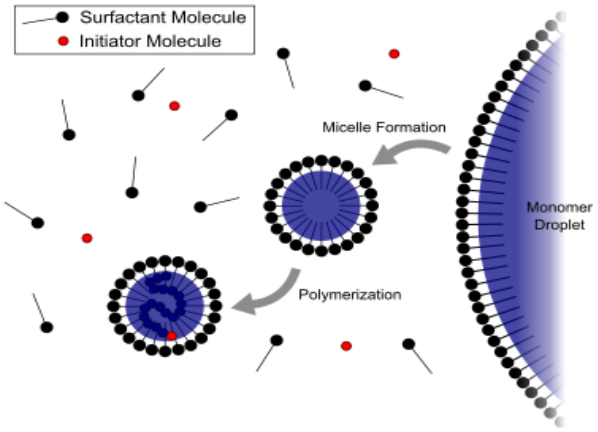

Figure No. 6: Nanoparticles prepared by using emulsion polymerization

G. Desolvation technique[40]

To prepare nanoparticles a solution of the natural macromolecule and an active ingredient associated with it is prepared. This system is then desolvated by adding a solvent competing solutes such as sodium sulfate or alcohol. By controlling the desolvation process colloidal size particles can be obtained. Suman Ramtake et al.[41] prepared clarithromycin based oral sustained release nanoparticulate drug delivery system by desolvation method using pluronic F-68 as a stabilizing agent. From a pharmaceutical point of view nanoparticles prepared using the above mentioned methods should be free from potentially toxic impurities, should be easy to store and administer, and should be sterile if the parenteral route is advocated. Accordingly, three important process parameters are performed before releasing them for clinical trials. They are, purified, freeze drying, and sterilized (**Figure No. 7**).

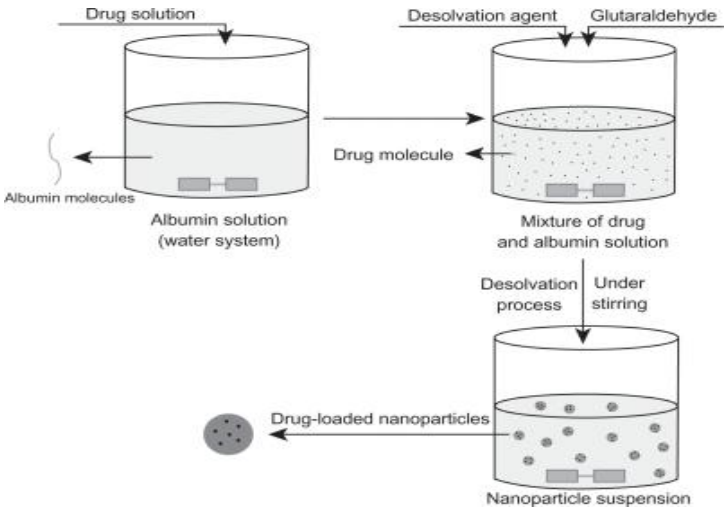

Figure No. 7: Nanoparticles prepared by using desolvation technique

CARRIERS USED IN THE PREPARATION OF NANOPARTICLES[1]

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 for their safety and biodegradation. Various natural hydrophilic and synthetic hydrophobic polymers are used for the preparation of nanoparticles (Table 1).

Table No. 1: Polymers used for the preparation of nanoparticles [1]

Sr. 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

Natural hydrophilic polymers have certain disadvantages such as batch to batch reproducibility, the specific condition for their degradation, and potential antigenicity. The relevant information provided in the literature is deficient, thus more *in vivo* toxicity studies

will have to be performed to assess the safety of carriers based on these polymers. For example, alginate, which has been approved for oral and ophthalmic administration, was recently reported to have adequate hemocompatibility and not to elicit in immunogenic responses. Consequently; it may represent a new candidate for parenteral administration. On the other hand, dextran, albumin, and gelatin are acceptable for parenteral administration, however, their aggregation and the introduction of a cross-linking agent during nanosphere preparation may render them immunogenic. The polysaccharide chitosan is not hemocompatible and requires the presence of some specific enzymes to undergo degradation. Therefore, the present application of chitosan should be restricted to extra-parenteral routes of administration.

Most synthetic biodegradable polymers that have been used in the preparation of colloidal dispersions have been previously employed to prepare microspheres. Most of them are typically hydrophobic. Polymers can be synthesized before or during nanoparticle preparation. The first group includes polyesters such as poly(e caprolactone) (PECL) and the family of poly(lactic acid) and poly(lactic-glycolic acid) copolymers. The second group is represented by the poly(alkyl cyanoacrylates) (PACA) which have received the greatest attention as polymeric colloidal drug carriers. For the design of nanoparticulate drug carrier's criteria such as preparation condition of nanospheres, drug-polymer compatibility, expected drug release behaviour, and final purpose of the formulation (i.e., route of administration) should be taken into account for the final choice of the polymer carrier.

ADJUVANTS USED IN THE PREPARATION OF NANOPARTICLES[1]

Cross-linking agent – glutaraldehyde

Desolvating agents – sodium sulphate, ethanol, isopropyl alcohol

Counter ions – tripolyphosphate

Surfactants – tween-80, span-80

Stabilizer – polyvinyl alcohol

Solvents – methanol, isopropyl alcohol, chloroform, dichloromethane, water, etc.

NEED FOR DEVELOPING NANOPARTICLES

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties, and release of pharmacologically active agents to achieve the site specific action of the drug at the rationale rate and dose[27]. Polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties[42].

FUTURE OPPORTUNITIES AND CHALLENGES[43]`

Nanoparticles and nanoformulations techniques have already been applied as drug delivery systems with huge success; and nanoparticulate drug delivery systems have still greater potential for many applications, including gene therapy, AIDS therapy, radiotherapy, anti-tumor therapy, in the delivery of proteins, antibiotics, virostatics, vaccines and as vesicles to pass the blood-brain barrier.

CHARACTERIZATION OF NANOPARTICLES[44]

The nanoparticles are generally characterized for size, density, electrophoretic mobility, angle of contact, and specific surface area using such advanced microscopic techniques as scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM). Their size distribution, the average particle diameter, and charge alter the physical stability and *in vivo* distribution of the nanoparticles. The surface charge of the nanoparticles changes the physical stability and redispersibility of the dispersion of the polymers as well as their *in vivo* performance. Electron microscopy techniques are very useful in determining the overall shape of polymeric nanoparticles, which helps to determine their toxicity.

Size and morphology

The particle size is one of the most important parameters of nanoparticles. Two main techniques are being used to determine the particle size distribution of nanoparticles and include photon correlation spectroscopy and electron microscopy. The latter include scanning electron microscopy (SEM), transmission electron microscopy (TEM), and freeze-fracture techniques. Atomic force microscopy is an advanced nanoscopic technique that has been applied for the characterization of PLA nanospheres. Mercury porosimetry is an equally suitable technique for the sizing of nano-particulates.

Surface charge and electrophoretic mobility

The nature and intensity of the surface charge of nanoparticles are very important as it determines their interaction with the biological environment as well as their electrostatic interaction with bioactive compounds. The surface charge of colloidal particles in general and nanoparticles, in particular, can be determined by measuring the particle velocity in an electric field. Laser light scattering technique,i.e. Laser doppler anemometer or velocimetry has become available as a fast and high-resolution technique for the determination of nanoparticle velocities. The surface charge of colloidal could also be measured as electrophoretic mobility. The charge composition critically decides the biodistribution of drug carrying nanoparticles. Generally, the electrophoretic mobility of nanoparticles is determined in phosphate buffer (PBS, pH 7.4) and human serum. The zeta potential can be obtained by measuring the electrophoretic mobility applying the Helmholtz-Scoluchowski equation.

Density

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

Surface hydrophobicity

Surface hydrophobicity can be determined by various techniques such as biphasic partitioning, hydrophobic interaction chromatography, contact angle measurement adsorption of probes,etc. X-ray photon correlation spectroscopy permits the identification of specific chemical groups on the surface of nanoparticles[44].

ADVANTAGES

1. Ease of manipulation of the particle size and surface characteristics of nanoparticles to achieve both passive and active drug targeting after parenteral administration.

2. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents.

3. Reduction of toxicity and occurrence of adverse reactions

4. Better drug utilization

5. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving drug activity.

6. The methods of preparations are reproducible

7. Easy handling of nanoparticles prepared in the powder form

8. Nontoxic and biodegradable

9. Relatively cheaper and stable

10. Site-specific targeting can be achieved by attaching targeting ligands to the surface of particles or the use of magnetic guidance.

11. Small sized nanoparticles can penetrate through smaller capillaries which could allow efficient drug accumulation at the target sites.

12. Various routes of administration are available including oral, nasal, parenteral, intra-ocular, etc.

DRAWBACKS

1. Altered physical properties that lead to particle-particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms due to smaller size and larger surface area.

2. Smaller the particle size greater the surface area and this property makes nanoparticles very reactive in the cellular environment.

3. Small particle size results in limited drug loading and burst release. These practical problems have to be sorted out before nanoparticles can be used clinically or made commercially available.

4 .Drug instability in the biological milieu and premature drug loss through rapid clearance and metabolism.

5. High protein binding of certain drugs such as protease inhibitors limits their diffusion to the brain and other organs.

6. Nanotechnology for drug delivery applications may not be suitable for all drugs, especially those drugs that are less potent because the higher dose of the drug would make the drug delivery system much larger, which would be difficult to administer.

7. Their characterization is quite difficult and expensive Long processes of synthesis and purification are major drawbacks of nanoparticles.

TOXICITY[43]

These tiny particles can easily get the entry inside the body through the skin, lungs or intestinal tract depositing in several organs and may cause severe adverse biological reactions by altering the physicochemical properties of tissue. Non-biodegradable particles when used for drug delivery may show accumulation on the site of drug delivery, leading to chronic inflammatory reactions. Most of the nanoparticulate toxicity reactions are observed due to inhalation of particulate matter leading to lung and cardiovascular diseases.

A***PPLICATIONS***[43-45]

- Cosmetics and Sunscreens
- Electronics
- Medicine
- Food
- Cancer therapy
- Intracellular targeting
- Vaccine adjuvant
- Ocular delivery
- DNA delivery
- Nanoparticle as drug delivery systems
- Gastrointestinal tract
- Tumor cell targeting

- Respiratory tract
- Brain
- Gene delivery
- Diagnosis and bioimaging
- Tissue repair

CONCLUSION

Nanoparticles a present highly attractive platform for a diverse array of biological applications. Due to their incredible properties, nanoparticles have become significant in many fields in recent years such as energy, healthcare, environment, agriculture, etc. Nanoparticle technologies have great potentials, being able to convert the poorly soluble, poorly absorbed, and labile biologically active substance into promising deliverable substances. They possess better stability when compared to liposomes. Significant efforts have been made on surface engineering of nanoparticulate carriers to overcome various biological barriers and target specific tissue sites.

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