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Review on Nanoparticles: An Unseen Drug Delivery System

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Abstract : Particulate systems like nanoparticles are used as a physical approach to vary and enhance the pharmacokinetic and pharmacodynamic properties of varied sorts of drug molecules. The nanoparticles show improved properties like high reactivity, strength, surface area, sensitivity, stability, etc. because of their small size. For adequate drug activity, it is necessary to deliver the drug to the body and its site of action as efficiently as possible. Several polymers have been applied in the formulation of nanoparticles for drug delivery research to improve therapeutic benefit, while minimizing side effects. Delivery of drugs to the target site is accomplished by a colloidal drug delivery system mainly by using nanoparticles. Different fabricated nanoparticles and drugs possessing poor solubility and poor pharmacokinetic profiles are the two major substances extensively distributed to target sites. Among the colloidal carriers, nano lipid dispersions (liposomes, virosomes, and solid lipid nanoparticles) are supreme delivery systems with the advantages of biodegradation and nontoxicity. Targeting the drug to a specific site improves therapeutic efficiency and reduces toxicity. The present review concentrates on the advantages and disadvantages of nanoparticles, preparation of nanoparticles, carriers used, characterization, and applications of nanoparticles. In conclusion, nanoparticles are one of the convenient drug delivery systems, which can be of potential use in controlling and targeting drug delivery.

Keywords : Nanoparticles, Preparation methods, Polymers, Advantage, Disadvantage, Application, Drug release.

Introduction

Nanoparticles are defined as appropriate 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 nano capsules can be acquired. The major intention in designing nanoparticles as a delivery system is to control particle size, surface properties, and release of pharmacologically active agents to accomplish the site-specific action of the drug at the therapeutically excellent rate and dose regimen[1].Nanoparticles even though unseen have the ability to both controlling the

release and protecting the drug against its degradation. Nanoparticles can accomplish tissue targeting of many drugs. It was recognized 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, modulated. Nanoparticles have an exceptional role in targeted drug delivery in the sense that they have all the advantages of liposomes along with particle size, but unlike liposomes, nanoparticles own long shelf life and can usually catch more drugs than liposomes[2].Due to their small particle size, colloidal preparations lend themselves to parenteral administration and may be convenient as sustained-release injections for the delivery to a particular organ or target site. Targeting the drug to the desired site of action would not only enhance the therapeutic efficiency but also enable a reduction of the amount of drug which must be administered to accomplish a therapeutic response, thus minimizing unwanted toxic effects[3].Nanoparticles are not simple molecules as such and therefore composed of three layers i.e. (a) The surface layer, which may be functionalized with a variety of small molecules, metal ions, and polymers. (b) The shell layer, which is chemically distinct material from the core in all aspects, and (c) The core, which is essentially the central portion of the Nanoparticle and generally refers to the Nanoparticle itself[4].Although nanoparticles are built of hydrophobic polymers encapsulating hydrophobic drugs. Nanoparticles made of hydrophobic polymers are usually taken up by the reticular endothelial system (RES) and have a short residence time in blood[5]. The word "nano" can be easily defined, but it covers many areas of application. Fig. 1 represents multiple nano-based systems composed of distinct types of materials, which can be utilized as nanocarriers[6].

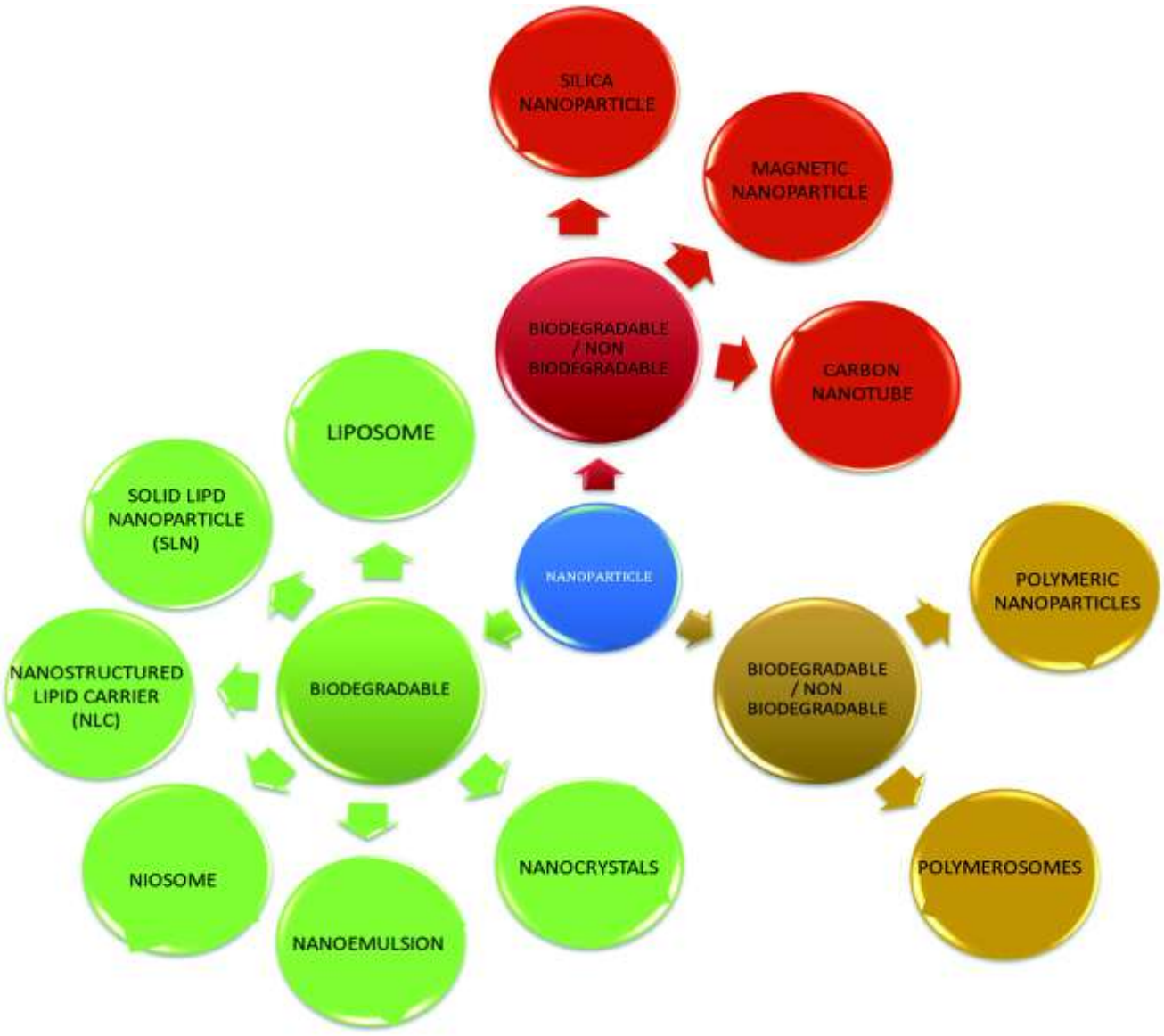

Fig. 1 Schematic diagram of the different types of nanoparticles.

Carriers used in Preparation of Nanoparticles:

The polymers utilized for the preparation of nanoparticles are either amphiphilic macromolecules, acquired from natural sources, hydrophobic polymers, or synthesized chemically. Some of the polymers were originally examined for biomedical applications, consequently for their safety and biodegradation. Numerous natural hydrophilic and synthetic hydrophobic polymers are utilized for the preparation of nanoparticles (Table 1).

Table 1:

Sl No	Synthetic Polymers	Natural Polymers
1	Poly(E caprolactone) (PECL)	Gelatine
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	Polymethyl (methacrylate) (PMM)	Agarose

Adjuvant used in the Preparation of Nanoparticles:

- Adjuvant Used in the Preparation of Nanoparticles:
- 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[2].

Classificastion of Nanoparticles:

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

1. Organic Nanoparticles:

Dendrimers, micelles, liposomes, and ferritin, etc. are generally known the organic nanoparticles or polymers. These nanoparticles are biodegradable, non-toxic, and some particles such as micelles and liposomes have a hollow core (Figure2), also known as nano capsules, and are sensitive to thermal and electromagnetic radiation such as heat and light. The organic nanoparticles are most commonly used in the biomedical field for example drug delivery systems as they are efficient and also can be injected on specific parts of the body that is also known as targeted drug delivery.

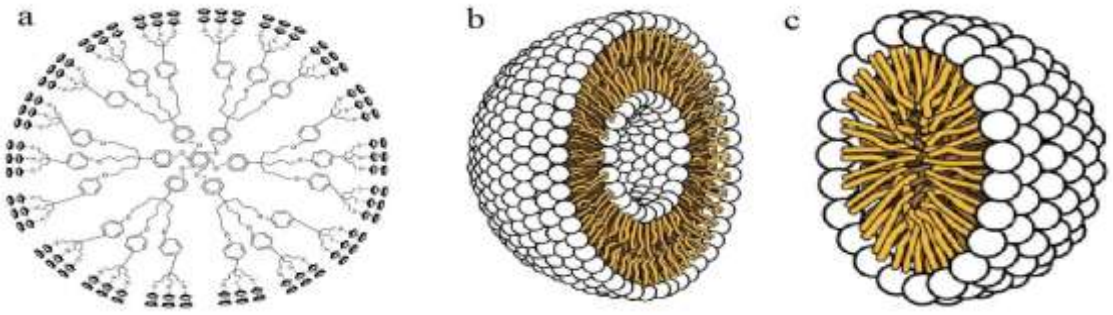

Figure 2.Organic nanoparticles: a – Dendrimers, b – Liposomes, and c – micelles.

2. Inorganic Nanoparticles:

Inorganic nanoparticles are particles that are not built up of carbon. Metal and metal oxide-based nanoparticles are generally categorized as inorganic nanoparticles.

2.1. Metal-Based :

Nanoparticles that are synthesized from metals to nanometric sizes also by destructive or constructive methods are metal-based nanoparticles. Nearly all the metals can be synthesized into their nanoparticles. The frequently 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).

2.2. Metal Oxides Based :

The metal oxide-based nanoparticles are synthesized to alter the properties of their respective metal-based nanoparticles, for example, nanoparticles of iron (Fe) immediately oxidize to iron oxide (Fe2O3) in the presence of oxygen at room temperature that enlarges its reactivity compared to iron nanoparticles.

3. Carbon-Based:

The nanoparticles built completely of carbon are known as carbon-based. They can be categorized into fullerenes, graphene, carbon nanotubes (CNT), carbon nanofibers, and carbon black and sometimes activated carbon in Nano size and are presented in Figure3.

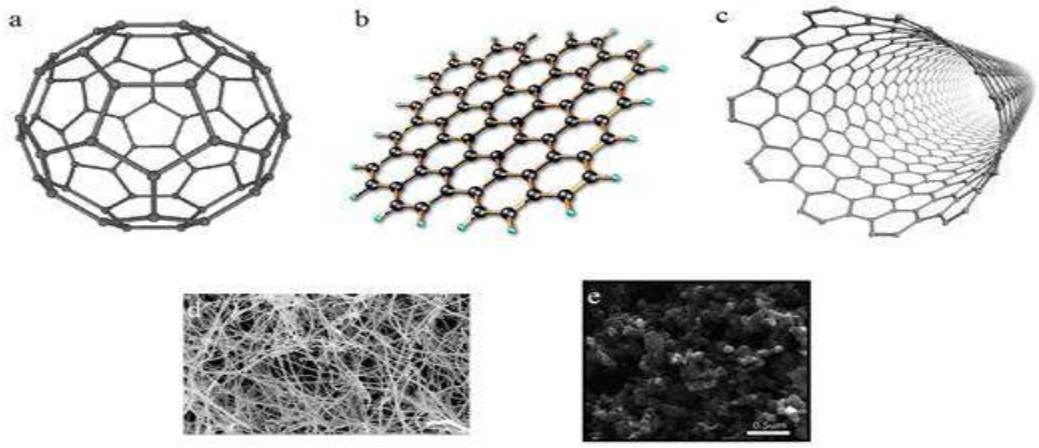

Figure 3. Carbon-based nanoparticles: a – fullerenes, b – graphene, c – carbon nanotubes, d – carbonnanofibers and e – carbon black

3.1 Graphene :

Graphene is an allotrope of carbon. Graphene is a hexagonal complex of honeycomb lattice made up of carbon atoms on a two-dimensional planar surface. Commonly, the thickness of the graphene sheet is around 1 nm.

3.2. Carbon Nano Tubes (CNT) :

Carbon Nano Tubes (CNT), a graphene Nano foil with a honeycomb network 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 micrometers to several millimeters. The ends can also be hollow or closed by a half fullerene molecule.

3.3. Carbon Nanofiber :

The identical graphene Nano foils are used to generate carbon nanofiber as CNT but wound into a cone or cup shape instead of a regular cylindrical tube.

3.4. Carbon Black :

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

3.5. Fullerenes :

A fullerene is a fine carbon molecule composed of at least 60 atoms of carbon. Fullerenes are noticed as good components of future micro-electromechanical systems and in nanotechnology. Compounds of fullerenes may be classed according to two different groups: hexahedral and endohedral[8].

Preparation of Nanoparticles:

For the preparation of nanoparticles, the selection of the appropriate method is based on the drug to be loaded and the physicochemical properties of the polymer. The most Widley used methods are,

A. Emulsion-Solvent Evaporation Method
B. Solvent Displacement/Precipitation method
C. Polymerization method
D. Coacervation or ionic gelation method
E. Salting out method
F. Emulsions - Diffusion method

A Emulsion-Solvent Evaporation Method :

The nanoparticles are usually prepared by using this method. Two steps are mainly involved in this method shown in Fig 4. In an aqueous phase, emulsification of the polymer solution is required in the first step. While in the second step, evaporation of polymer Solution occurs and noospheres are formed by inducing the polymer precipitation. Collection of nanoparticles is done by ultracentrifugation and to eliminate free drug or residue, washed with distilled water and for storage these are lyophilized. This method is also known as the solvent evaporation method and high-pressure emulsification.

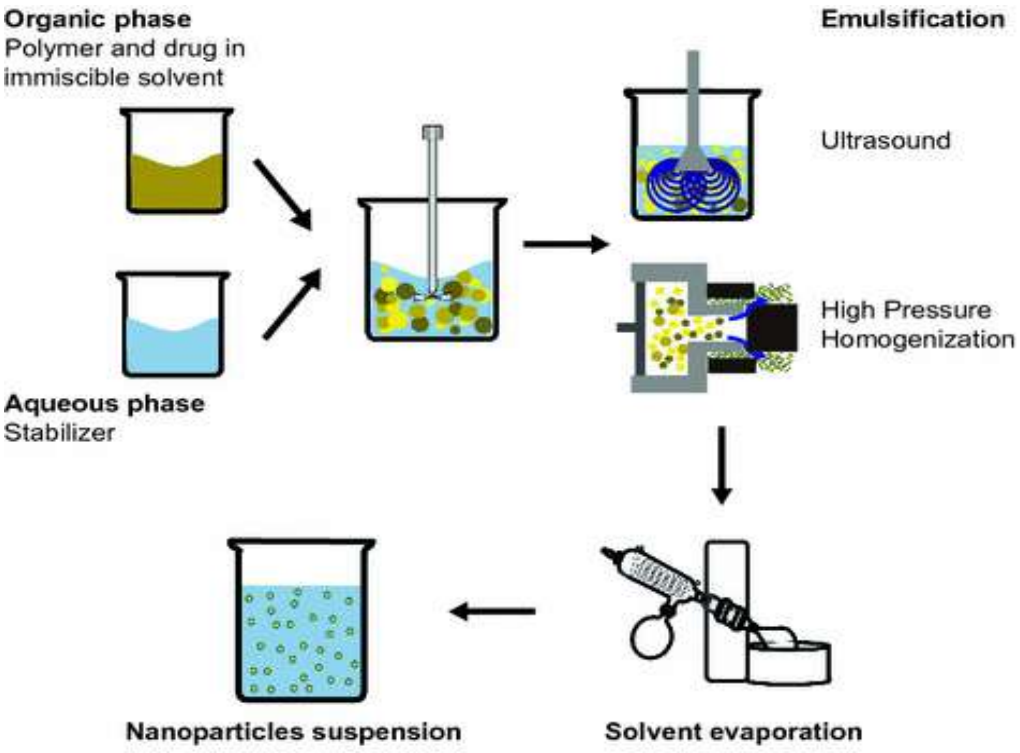

Fig: 4 Nanoparticle preparation using emulsion solvent evaporation methods.

B. Solvent Displacement/Precipitation Method:

Solvent displacement involves from an organic solution, the precipitation of a preformed polymer, and in the aqueous medium the diffusion of the organic solvent in the presence or absence of surfactant. In semi-polar water-miscible solvents like acetone or ethanol, polymers, drug, and lipophilic surfactant are dissolved. Then the solution is injected using magnetic stirring, into a stabilizer containing an aqueous solution. By the rapid solvent diffusion, Nanoparticles are formed. Then under reduced pressure solvent is removed from the suspension. The particles size is also affected by the rate of addition of the organic phase into the aqueous phase. It was observed that by increasing the rate of mixing, both particles size and drug entrapment decrease. For most of the poorly soluble drugs, the nano precipitation method is well suited[9].

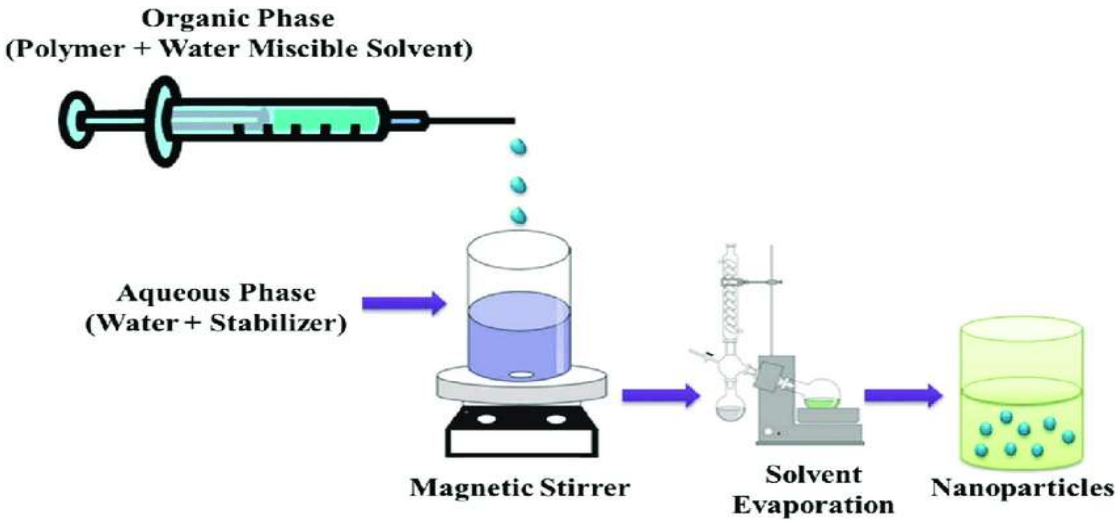

Fig: 5 Nanoparticle preparation using the solvent displacement method

C. Polymerization Method :

In this method, monomers are polymerized to form nanoparticles in an aqueous solution. The drug is included either by being liquefied in the polymerization medium or by adsorption onto the nanoparticles after polymerization is completed. The nanoparticle suspension is then filtered to eliminate various stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. This technique has been described for making poly butyl cyanoacrylate or poly (alkyl cyanoacrylate) nanoparticles. Nano capsule development and their particle size depending on the concentration of the surfactants and stabilizers used.

D. Coacervation Or Ionic Gelation Method :

The preparation of nanoparticles utilize biodegradable hydrophilic polymers such as chitosan, gelatine, and sodium alginate. Calvo and co-workers developed a method for developing hydrophilic chitosan nanoparticles by ionic gelation. The method includes a mixture of two aqueous phases, of which one is the polymer chitosan, di-block copolymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a polyanion sodium tripolyphosphate. In this method, positively charged chitosan links with negatively charged to form coacervates with a size in the range of nanometre. Coacervates are developed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation includes the material undergoing a transition from liquid to gel due to ionic interaction due to ionic interaction conditions at room temperature[1].

E. Salting Out Method :

This technique is based on the separation of water-miscible solvent from an aqueous solution by the salting-out effect. In this method, toxic solvents are not utilized. Polymer and drug dissolved in a solvent which emulsified into an aqueous solution containing salting-out agent but salting out can also be produced by saturation of the aqueous phase using colloidal stabilizer/emulsion stabilizer/viscosity increasing agent such as polyvinyl pyrrolidine or hydroxyethyl cellulose, PVA, PLGA, and poly (trimethylene carbonate). After

preparation of o/w emulsion diluted with the addition of sufficient water to allow the complete diffusion of acetone into the aqueous phase, thus inducing the formation of noospheres. This technique does not require an increase in temperature and stirring energy required for lower particle size. The disadvantage of this technique is its entire application to lipophilic drugs and the extensive nanoparticle washing steps. Solvent and salting-out agents are then eliminated by cross-flow filtration (Fig:6).

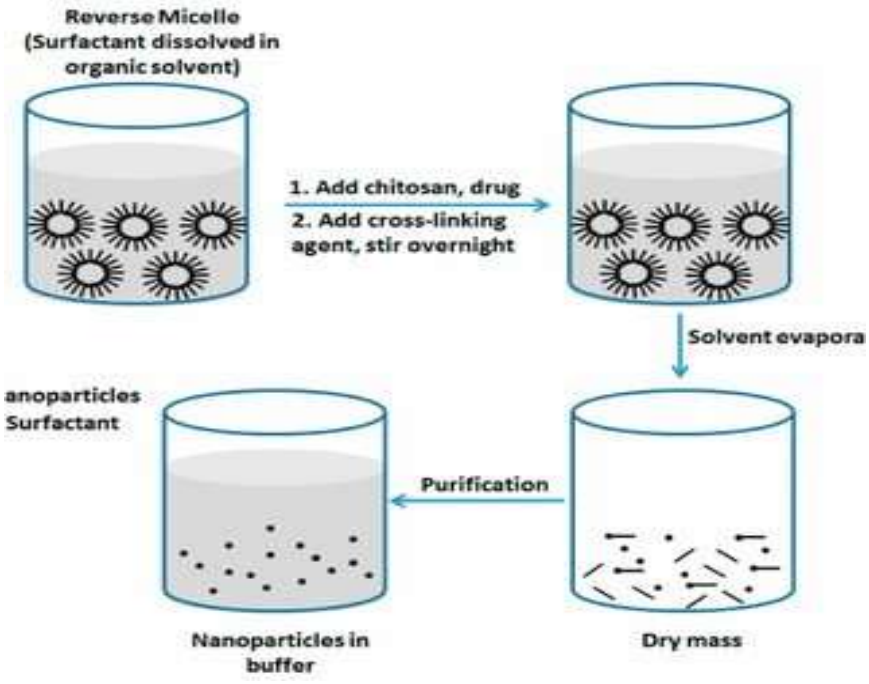

Fig: 6 Nanoparticle preparations using salting-out method

Emulsion-Solvent Evaporation Method The nanoparticles are mostly prepared by using this method. Two steps are mainly involved in this method. In an aqueous phase, emulsification of the polymer solution required in the first step. While in the second step, evaporation of polymer solution occurs and nanospheres are formed by inducing the polymer precipitation. Collection of nanoparticles is done by ultracentrifugation and to remove free drug or residue, washed with distilled water and for storage these are lyophilized. 18 This method is also known as solvent evaporation method and high pressure emulsification. 19 This technique involves homogenization under high pressure and overall stirring to remove organic solvent. 20 By adjusting the stirring rate, viscosity of organic and aqueous phases, temperature, type and amount of dispersing agent the size can be controlled. 21 However to lipid soluble drugs, this technique can be applied and by the scale up issues limitation are imposed. Polymers used are PLA, Poly (β- hydroxybutyrate) (PHB) 22, Poly(caprolactone) (PCL) 23, PLGA 24, cellulose acetate phthalate 25, and EC 26 in this method.

F. Emulsions - Diffusion Method :

In this method, the polymer is liquefied in water-miscible solvent and saturated with water. Polymer-water soaked solvent phase is emulsified in an aqueous solution containing a stabilizer. Then the solvent is eliminated by evaporation or filtration[10].

Characterization of Nanoparticles:

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, average particle diameter, and charge alter the physical stability and the in vivo distribution of the nanoparticles. The surface charge of the nanoparticles alters the physical stability and re-dispersibility of the

dispersion of the polymers as well as their in vivo performance. Electron microscopy techniques are very useful in deciding the overall shape of polymeric nanoparticles, which helps to determine their toxicity.

❖ **Measurement of Particle Size and Zeta Potential:**

Photon correlation spectroscopy (PCS) and laser diffraction (LD are the most powerful techniques for routine measurements of particle size. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by particle movement. This method covers a size range from a couple of fewer nanometers to about 3 microns. The laser diffraction method is based on the dependence of the diffraction angle on the particle radius. Smaller particles cause increased intense scattering at high angles compared to the larger ones. A clear advantage of Laser diffraction is the coverage of a broad size range from the nanometer to the lower millimeter range[11].

❖ **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 quantifying 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 by 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 definite 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 measurements, adsorption of probes, etc. The hydrophobicity and hydrophilicity collectively determine the bio-fate of nanoparticles and their contents. Recently numerous sophisticated methods of surface chemistry analysis have been used. For example, X-ray photoelectron spectroscopy permits the identification of specific groups on the surface of nanoparticles[12].

❖ **In Vitro Release:**

The following methods have been used for the determination of in vitro release.

1. Using diffusion cells with artificial or biological membrane
2. Using dialysis tube
3. Reverse dialysis sac technique
4. Ultracentrifugation
5. Centrifugal ultrafiltration technique

The dissolution media will be a buffer solution of the required pH.

- **Dialysis Tube :**

In-vitro tranquilize discharge studies are for the most part useful for quality control and also for the expectation of in-vivo energy. Discharge outline of medication can be led in dialysis tubing or without tubing. In dialysis, the nanoparticles scattering is transferred into prewashed dialysis tubing, which is then hermetically fixed and after that dialyzed against disintegration medium at a consistent temperature with steady mixing.

Tests were taken at several circumstances, centrifuged, and measured for medication. This technique is not sufficiently touchy to narrate the fast discharge rate of the drug from colloidal transporter[13].

❖ **Drug Release:**

Nanoparticles exhibit their special drug delivery effects in most cases by direct interaction with their environment (biological environment). Drug from the nanoparticles is released by one or more of the following mechanisms, such as, Desorption of surface-bound drug, Diffusion through the matrix or the polymer well, Erosion, Combined erosion and diffusion. The release characteristics of polymeric nanoparticles are one of the most crucial features of the drug/polymer formulations because of the proposed application in sustained drug delivery. Numerous factors that affect the release rate of the entrapped drug. Larger particles have a smaller maiden burst release and longer sustained release than smaller particles. In addition, the greater the drug loading, the greater the burst and the faster the release rate[14].

Advantages:

1. The method of preparations is reproducible.
2. Nontoxic and biodegradable.
3. Relatively cheaper and stable.
4. No swallowing problems in case of oral administration.
5. Circumventing the first-pass metabolism and avoiding systemic toxicity[15].
6. Nanoparticles offer the advantages of high surface area and high selectivity[16].
7. Biodegradable nanomaterials to be used for many biomedical purposes, including bio-imaging, targeted drug delivery, implantation, and tissue engineering[17].
8. Enhanced penetration into tissue and certain nanomaterials can be designed so that they can efficiently transverse specific tissue barriers[18].
9. Various routes of administration are available including oral, nasal, parenteral, intra-ocular etc[19].

Drawbacks:

1) Drawbacks include drug instability in the biological milieu and premature drug loss through rapid clearance and metabolism. Similarly, the high protein binding of certain drugs such as protease inhibitors limits their diffusion to the brain and other organs.
2) Altered physical properties lead to particle–particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms due to smaller size and larger surface area.
3) The smaller the particle's size greater the surface area and this property makes nanoparticles very reactive in the cellular environment.
4) Small particles 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[20].

Applications : NPs can be used in a variety of applications. Some important of these are given below.

1. Application of Nanotechnology in Food and Agriculture.
2. Application of Nanotechnology in Remediation[21].
3. Applications nanoparticles in drug delivery[22].
4. Nanoparticles in Cosmetics[23].
5. Nanoparticles are used to synthesize compounds likes, Dye, Pesticides, Pharmaceuticals, etc[24].
6. Nanotechnology in interfacial tension reduction[25].
7. Nanotechnology in the field of veterinary medicine, Nano vaccines and nano adjuvants, breeding, and reproduction[26].
8. applications of nanomaterials to biology or medicine like bio-detection of pathogens and proteins[27].
9. Gold nanoparticles in biosensor applications[28].

Conclusion:

Nanoparticle technologies have great potentials, being able to turn poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable substances. They possess greater stability when

compared to liposomes. Significant efforts have been made on surface engineering of nanoparticulate transporter to overcome many biological barriers and target to specific tissue sites. Simple methods are employed for the preparation of nanoparticles. The evaluation methods are simple. Nanoparticles are utilized for parenteral, oral, ocular, transdermal, hair care technologies sustained release formulations and transporter for radio nucleotides in nuclear medicine.

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