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NANOPARTICLES: AN OVERVIEW

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ABSTRACT

Nanotechnology is most emerging technique in Pharmaceutical sciences. It has been used to improve pharmacokinetic & pharmacodynamic properties of any drug molecule. Nanoparticles ranging from 1 to 100nm with different dimentions. Nanoparticles are used to restrict acess of drug to chosen sites, To deliver the drug at controlled & sustained rate to the site of action and to protect the drug entity in the systemic circulations. Various Polymer have been used in the formulation of nanoparticles to increase therapeutic benefit, whileminimizing the side effect. Several techniques used for preparation of nanoparticle like Double emulsion method, Emulsion-diffusion method, Solvent evaporation, Nanoprecipitation, Coacervation method, Salting out method, Dialysis & Supercritical fluid technology. Nanoparticles are subjected to several evaluation parameters such as yield of nanoparticles, Drug Content / Surface entrapment / Drug entrapment, Particle Size and Zeta Potential, Surface Morphology, Polydispersity index, In-vitro release Study, Kinetic Study, Stability of nanoparticles.

KEYWORDS: Nanoparticles, Nanotechnology, Techniques, Polymer.

INTRODUCTION

Nanotechnology is the science of material featuring between 10 −9 and 10 −7 of a meter.[1] Or in another words it's the science of materials and devices whose structures and constituents demonstrate novel and considerably altered physical, chemical and biological phenomenon due to their nanoscale size. Thus nanotechnology is defined as the manipulation of matter on an atomic, molecular, and supramolecular scale involving the design, production, characterization and application of different nanoscale materials in different potential areas providing novel technological advances mainly in the field of medicine. This forms an independent branch of nanostructures, referred as nanomedicine which is specifically utilized for medicines. Nanomedicine involves utilization of nanotechnology for the benefi t of human health and well being.[2]

Nano word is originated from Latin word, which means dwarf. Ideal size range offered by nanotechnology refers to one thousand millionth of a particular unit thus nanometer is one thousand millionth of a meter (i.e. 1 nm = 10 −9 m). Recent exploration of nanotechnology in biomedical and pharmaceutical science results in successful improvement of conventional means of drug delivery system. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen.[3] The application of the nanoparticle for the DDS is of particular interest because they have some advantages such as easy purification and sterilization, drug targeting possibilities, and sustained release action. However, they have some disadvantages such as they can be easily recognized by the reticuloendothelial system (RES) within seconds or minutes after injection, which is due to phagocytosis by macrophages present in the liver and spleen. The surface modification of nanoparticles by albumin or hydrophilic poly(ethylene oxide) chains have reduced the recognition of nanaoparticles and thus they are available for the more prolonged circulation, increased half-life in blood and a reduced rate of uptake by the liver.[4]

In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly (ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time. 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.[5]

Classification of Nanoparticles[6]

- **One dimension nanoparticle**

One dimensional system (thin film or manufactured surfaces) has been used for decades. Thin films (sizes 1–100 nm) or monolayer is now common place in the field of solar cells offering, different technological applications, such as chemical and biological sensors, information storage systems, magneto-optic and optical device, fiber-optic systems.

- **Two dimension nanoparticles**

Carbon nanotubes.

- **Three dimension nanoparticles**

Dendrimers, Quantum Dots, Fullerenes (Carbon 60), (QDs).

Method of preparation for Nanoparticles

1. Solvent Evaporation Method

Solvent evaporation method is one of the most frequently used methods for the preparation of nanoparticles. This method involves two steps (fi rst is emulsifi cation of the polymer solution into an aqueous phase and second is evaporation of polymer solvent, inducing polymer precipitation as nanospheres). This method is based on the solubility of polymer and hydrophobic drug since both polymer and hydrophobic drug are dissolved in an organic solvent (dichloromethane, chloroform or ethyl acetate) which is also used as the solvent for dissolving the. Mixture obtained from polymer and drug solution is then emulsified in an aqueous solution. This aqueous solution contains surfactant or emulsifying agent to form oil in water (o/w) emulsion. Once the stable emulsion forms, the organic solvent is evaporated either by continuous stirring or by reducing the pressure. Size range of nanoparticles was found to be infl uenced by the concentrations and type of stabilizer, polymer concentration and homogenizer speed.[7] Ultrasonication or high-speed homogenization may be often employed in order to produce small particle size.[8] The nano particles are collected by ultracentrifugation and washed with distilled water to remove stabilizer residue or any free drug and lyophilized for storage.[9] Modifi cation of this method is known as solvent evaporation method and high pressure emulsifi cation.[10] This method involves preparation of a emulsion which is then subjected to homogenization under high pressure followed by

overall stirring to remove organic solvent.[11] The size can be controlled by adjusting the stirring rate, type and amount of dispersing agent, viscosity of organic and aqueous phases and temperature.[12] However this method can be applied to liposoluble drugs and limitation are imposed by the scale up issue. Polymers used in this method are PLGA, 13 PLA][14], cellulose acetate phthalate,[15] EC[16], Poly (β -hydroxybutyrate) (PHB)[17], Poly (β-caprolactone)\ (PCL).[18]

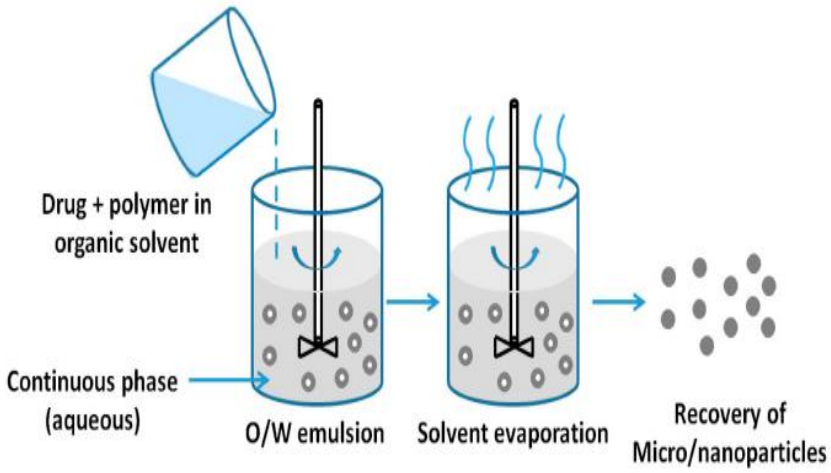


Fig. No. 1: Solvent Evaporation Method.

2. Double Emulsion and Evaporation Method

Most of the emulsion and evaporation based methods suffer from the limitation of poor entrapment of hydrophilic drugs. Therefore to encapsulate hydrophilic drug the double emulsion technique is employed, which involves the addition of aqueous drug solutions to organic polymer solution under vigorous stirring to form w/o emulsions. This w/o emulsion is added into second aqueous phase with continuous stirring to form the w/o/w emulsion. The emulsion then subjected to solvent removal by evaporation and nano particles can be isolated by centrifugation at high speed. The formed nanoparticles must be thoroughly washed before lyophilisation.[19] In this method the amount of hydrophilic drug to be incorporated, the concentration of stabilizer used, the polymer concentration, the volume of aqueous phase are the variables that affect the characterization of nanoparticles.[19,20]

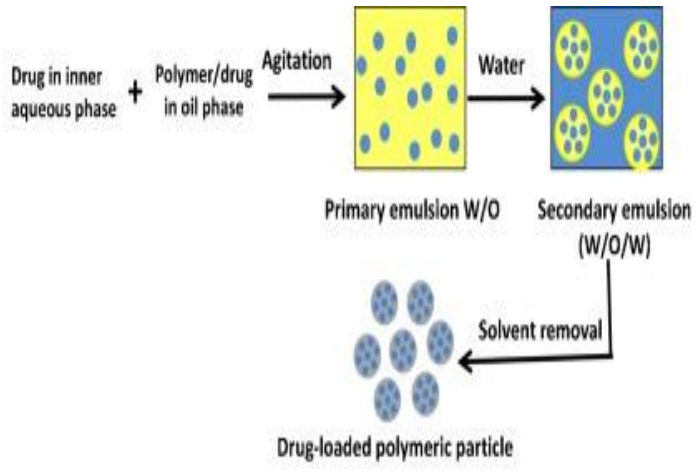


Fig. No. 2: Double Emulsion and Evaporation Method.

3. Emulsions-Diffusion Method

This is another widely used method to prepare nanoparticles. The encapsulating polymer is dissolved in a partially water-miscible solvent (such as propylene carbonate, benzyl alcohol), and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. Subsequently, the polymer-water saturated solvent phase is emulsifi ed 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 fi ltration, according to its boiling point. This technique presents several advantages, such as high encapsulation effi ciencies (generally 70 %), no need for homogenization, high batch-to-batch reproducibility, ease of scaleup, simplicity, and narrow size distribution.[2]

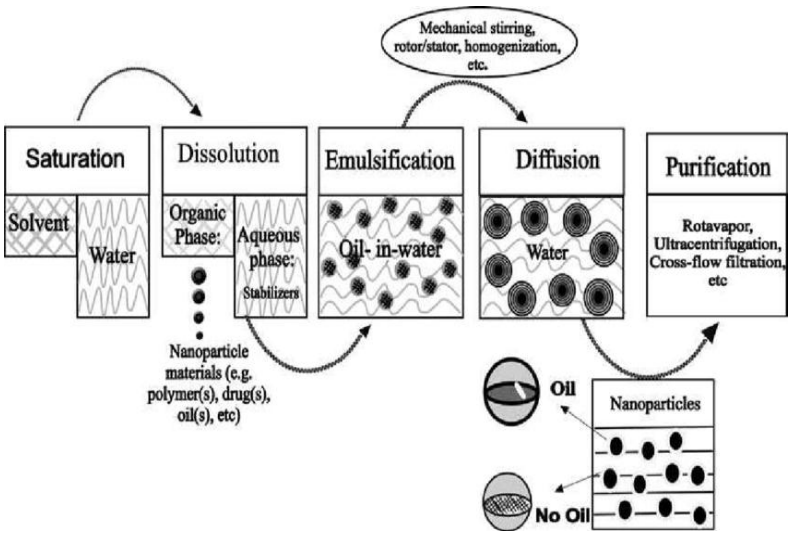


Fig. No. 3: Emulsion-Diffusion Method.

4. NanoPrecipitation Method

Nanoparticles can be synthesized by the nanoprecipitation method. In this method, polymer and drug are dissolved in acetone, ethanol, or methanol and incorporated under magnetic stirring into an aqueous solution of the surfactant. The organic solvent diffuses instantaneously to the external aqueous phase, followed by precipitation of the polymer and drug. After formation of the nanoparticles, the solvent is eliminated and the suspension concentrated under reduced pressure. The advantage of this method is that no surfactant is employed; however, the method is limited to drugs that are highly soluble in a polar solvent.[21]

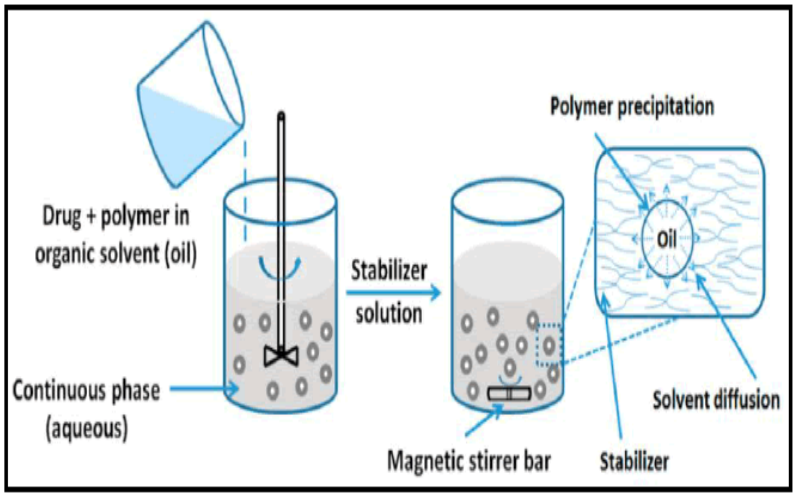


Fig No. 4: Nanoprecipitation Method.

5. Coacervation or Ionic Gelation Method

Recent exploration of biodegradable polymers such as gelatin and sodium alginate has been focused now to yield biodegradable nanoparticles having features like biocompatibility and low toxicity. Methods such as ionic gelation can be used for preparing hydrophilic polymer based nanoparticles. Calvo and co-workers developed method for preparing chitosan based nanoparticles by ionic gelation method.[22, 23]

In this method two different aqueous phases are prepared for polymer[chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO)] and the other is for polyanion sodium tripolyphosphate. This method is based on the strong electrostatic interaction between positively charged amino group of chitosan and negative charged tripolyphosphate to form coacervates with a size in the range of nanometer. Existence of strong electrostatic interaction between two aqueous phases leads to the formation of coacervates. In contrast ionic gelation

involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature.

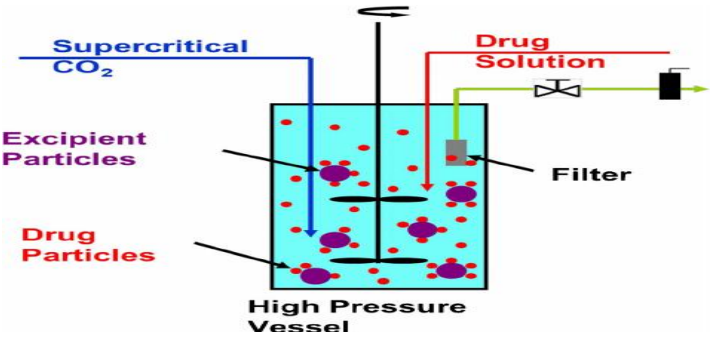
6. Salting out Method

The salting-out process is another method for the preparation of nanoparticles. This technique is based on the precipitation of a hydrophobic polymer, is useful for the encapsulation of either hydrophilic or hydrophobic drugs because a variety of solvents, including polar (e.g., acetone or methanol) and non-polar (methylene chloride or chloroform) solvents can be chosen for dissolving the drug.[7]

7. Supercritical Fluid Technology

Above mentioned conventional methods (such as solvent extraction-evaporation, solvent diffusion and organic phase separation methods) obligatory use organic solvents which are hazardous to the environment as well as to physiological systems. Therefore, there is an urgent requirement of suitable technology which avoid the usage of organic solvents or any other ingredient hazardous to health. Since supercritical fl uids are environmentally safe, therefore, the supercritical fl uid technology has been investigated as an alternative to prepare biodegradable micro- and nanoparticles.[25] Supercritical fl uid technology technique, although environmentally friendly and suitable for mass production, requires specially designed equipment and is more expensive. Supercritical fl uids are those fl uids which are at a temperature above its critical temperature remains in a single phase regardless of pressure.[25] CO 2 (SC CO 2) is the most widely used supercritical fl uid because of its mild critical conditions, non-fl ammability, low price and nontoxicity. Among the various processing techniques involving supercritical fl uids, supercritical anti-solvent (SAS) and rapid expansion of critical solution (RESS) are the most common one. In former process a liquid solvent (methanol) is selected on the basis of it's completely miscibility with the supercritical fluid. This is done to dissolve the solute to be micronized at the process conditions. Since the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fl uid leads to the instantaneous precipitation of the solute, results in the formation of nanoparticles. This process is reported for formation of hydrophilic drug dexamethasone phosphate drug nanoparticles for microencapsulation purpose. In later process called as RESS, solute is dissolved in a supercritical fl uid such as supercritical methanol and then the solution is rapidly expanded through a small nozzle into a region lower pressure.[25] This dramatically affects the solvent power of supercritical fluids which is

ultimately decreases and the solute eventually precipitates. RESS and its modifi ed process have been used for the product of polymeric nanoparticles.[26]



Polymeric Nanoparticles.

Polymers can be used as a controlled release system since they have unique physicochemical, synthetic, biocompatibility, and degradation properties. Additionally, polymeric nanoparticles also have advantages over lipidic carriers such as liposomes.[27]

Biodegradable polymers

Nanoparticles can be synthesized from the biodegradable as well as nonbiodegradable polymers. A wide range of the natural and the synthetic polymers can be used for the preparation. Today, the most commonly used polymers for controlled drug release applications include poly (D, Llactide-co-glycolide) (PLGA), poly(lactic acid) (PLA), poly (glutamic acid) (PGA), poly(caprolactone) (PCL), N-(2hydroxypropyl)-methacrylate copolymers (HPMA), and poly(amino acids). In particular, PLGA, PGA and PLA have been widely used in an impressive number of controlled release products, particularly due to their favourable biocompatibility and biodegradability properties.[5]

Evaluation of Nanoparticles

Drug loading Content / Surface entrapment / Drug entrapment

After centrifugation amount of drug present in supernatant determined by UV spectrophotometery. After that standard calibration curve plotted. Then amount of drug present in supernatant subtracted from the total amount used in the preparation of nanoparticles. % drug loading content calculated by[28]

$$\text{Drug loading content (\%)} = \frac{\text{Weight of the drug in nanoparticles}}{\text{Weight of the nanoparticles}} \times 100 \quad (1)$$

$$\text{Encapsulation efficiency (\%)} = \frac{\text{Weight of the drug in nanoparticles}}{\text{Weight of the feeding drugs}} \times 100 \quad (2)$$

Zeta potential[29]

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 insuspension, as the surface charge prevents aggregation of the particles.

Particle Shape[30]

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

Particle size[31]

Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the in vivo distribution, biological fate, and toxicity and targeting ability of nanoparticle system. In addition, they can also influence 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).

Drug Release[2]

It's very essential to determine extent of the drug release and in order to obtain such information most release methods require that the drug and its delivery vehicle be separated. drug loading capacity of the nanoparticles is defined as the amount of drug bound per mass of polymer or in another term it is the moles of drug per mg polymer or mg drug per mg polymer or it could also be given as percentage relative to the polymer. Various techniques

such as UV spectroscopy or high performance liquid chromatography (HPLC) after ultracentrifugation, ultra Filtration, gelfiltration, or centrifugal ultrafiltration are used to determine this parameter. Methods that are employed for drug release analysis are also similar to drug loading assay which is more often assessed for a period of time to evaluate the drug release mechanism.

Kinetic Study[34]

For estimation of the kinetic and mechanism of drug release, the result of in vitro drug release study of nanoparticles were fitted with various kinetic equation like zero order (cumulative % release vs. time), first order (log % drug remaining vs time), Higuchi‟s model (cumulative % drug release vs. square root of time). r^2 and k values were calculated for the linear curve obtained by regression analysis of the above plots.

Stability of Nanoparticles[34]

Stability studies of prepared nanoparticles determined by storing optimized formulation at 4°C ±1°C and 30°C ± 2°C in stability chamber for 90 days. The samples were analyzed after a time period like at 0, 1, 2, and 3 months for their drug content, drug release rate (t50%) as well as any changes in their physical appearance.

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