Original Article

Recent Advances In The Development Of Nanoparticles In Enhancement Of Solubility Of Poorly Soluble Drugs

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Abstract

The formulation of poorly soluble drugs is one of the most difficult tasks for pharmaceutical formulators. Conventional techniques for increasing the solubility of these drugs have had limited success. This is especially true when dealing with drugs that have low aqueous and organic solubility. Solubility is an important determinant of drug liberation and thus drug absorption, and it plays an important role in formulation oral bioavailability. A drug solubility directly influences its dissolution rate. Most New drugs have low water solubility, making them difficult to formulate into drug delivery systems. As a result, improving the solubility of poorly water soluble drugs is one of the necessary preformulation steps in pharmaceutical product development research. The use of nanoparticles in the formulation of hydrophobic drugs improves their solubility and efficacy. Emulsion-solvent evaporation method, Double Emulsion and Evaporation method, Salting out method, Emulsions diffusion method, Antisolvent Precipitation Method, Polymerization method, and Coacervation or Ionic Gelation method can all be used to make nanoparticles. Bottom-up methods such as Antisolvent precipitation are the most efficient and cost effective in the preparation of nanoparticles.

Key words: Solubility enhancement, Nanoparticles, Antisolvent Precipitation method.

1.INTRODUCTION:

More than 40% of drugs fall into the BCS Class II (low solubility high permeability) and class IV (low solubility low permeability) categories, according to the Biopharmaceutics classification system (BCS). A growing interest has been focused on nano science and nanotechnology in medicine, with nanocarriers loaded with APIs in a scale range of upto 1000nm being viewed as nanodrug delivery systems. Excipients were used to stabilize the API, resulting in drug nanoparticles such as micelles, polymeric nanoparticles, nanocrystals, nanoemulsion, liposomes, and mesoporous silica nanoparticles. These nanoparticle formulations offered several advantages for the delivery of insoluble drugs, including: [1] increasing the surface area to volume ratio, which generally improves the dissolution rate and solubility of poorly water soluble drugs, enhancing specific interactions with cells and tissues, promoting absorption and increasing bioavailability for BCS class II drug. [2] Forming some drugs as nanodrugs will improve their chemical stability and control their release profile in the gastrointestinal tract; [3] the drug nanoparticles could be tailored via surface functionality to achieve long circulation and targeted delivery. The primary goals of nanoparticle delivery system design are to control particle size, surface properties, and the release of pharmacologically active substances in order to achieve drug specific effects at optimal therapeutic levels and dosage regimen [4, 5]. A Significant proportion of the drugs on the market are thought to be poorly soluble in water [6, 7]. Poor water soluble drug formulation is a challenge in the pharmaceutical industry because the typical issues with this class of compounds are low oral bioavailability and erratic absorption [81]. Among the many factors influencing drug absorption, water solubility, physiological environment, and intestinal permeability are critical in determining the fraction of a dose absorbed. For some poorly soluble drugs, particularly those with high intestinal permeability, dissolution is considered a rate limiting step. To increase solubility kinetics, reduce particle size to increase area [11], and coat drug particles with hydrophilic surfactants to improve wetting and solvation by intestinal juices. [12-14], the formation of solid dispersions [15,16] and the transformation of crystalline drugs to amorphous states [17]. Size reduction can improve dissolution and dissolution properties in the Noyes-Whitney and Ostwald Freundlich equations [18]. Many methods for reducing particle size have been attempted, including micromechanics [19], supercritical fluid engineering [20], and antisolvent precipitation method [21]. Micromechanical methods require a large amount of energy and have several drawbacks in practice, including electrostatic effects, a wide particle size distribution, and thermal degradation, contamination, and reproducibility issues between batches [22].

1.1. ADVANTAGES:

- Nanoparticles' particle size and surface can be easily manipulated; they control and maintain drug release during transport and localization, and they regulate drug distribution.
- Increase the therapeutic effect of the drug while decreasing side effects.
- The controlled release and decomposition properties of the particles can be easily adjusted by changing the substrate composition.
- Site-specific targeting is possible.
- This system can be used for a variety of administration routes.

1.2. Limitations:

- Their small particle size and large surface area can cause particle aggregation, making it difficult to physically handle liquid and dry nanoparticles.
- Furthermore, their small particle size and large surface area can easily lead to limited drug delivery.

2. TECHNIQUES FOR SOLUBILITY ENHANCEMENT:

Physical modifications, chemical modifications of the drug substance, and other techniques such as Physical Modifications, Chemical Modifications and Miscellaneous Methods are all examples improvement techniques.

2.1. Particle Size Reduction:

Micronization reduces drug particle size while increasing drug dissolution rate due to increased surface area. Milling techniques such as jet mills and rotor stator colloid mills are used to micronize drugs [23]. These methods were used to synthesize griseofulvin, progesterone, spironolactone diosmin, and fenofibrate. Micronized fenofibrate increased dissolution by more than tenfold (1.3% to 20%) in 30 minutes [24, 25].

2.2. Solid Dispersion:

Sekiguchi and Obi first proposed the concept of solid dispersions in the early 1960s, when they investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water soluble carrier [26]. A solid dispersion is a type of solid product that consists of at least two different components, typically a hydrophilic matrix and a hydrophobic drug. Polyvinylpyrrolidine, polyethylene glycols, and Plasdone S630 are the most commonly used hydrophilic carriers for solid dispersions. Solid dispersion using suitable hydrophilic carriers can improve the solubility of celecoxib, halofantrine, and ritonavir [27].

2.3. Hot-Melt Method (Fusion method):

The physical mixture of a drug and a water soluble carrier is heated directly until the two melts in this method. The melted mixture is then rapidly cooled and solidified in a nice bath while being vigorously stirred. The fine solid mass is crushed, pulverized, and sieved before being compressed into tablets using tableting agents [28].

2.4. Solvent Evaporation Method:

Tachibana and Nakamura [29] were the first to dissolve the drug and the carrier in the same solvent and then evaporate the solvent under vacuum to produce a solid solution. The main advantage of the solvent evaporation method is that thermal decomposition of drugs or carriers can be avoided due to low temperature required for organic solvent evaporation. The disadvantages are the higher preparation cost, the difficulty in completely removing the organic solvent, the use of a common volatile solvent, and the difficulty in reproducing crystal forms [30].

2.5. Hot-Melt Extrusion:

Hot melt extrusion is essentially the same as fusion, except that the extruder causes intense mixing of the components. Miscibility of the drug and the matrix, as in the traditional fusion process, could be an issue. High shear forces in the extruder cause a high local temperature, which is a problem for heat sensitive materials. This technique allows for continuous production, making it suitable for large-scale production.

2.6. Nanosuspensions:

Nanosuspensions are colloidal dispersions of nano sized drug particles stabilized by surfactants that are submicron in size. Nanosuspensions are made up of poorly water suspended in a dispersion of matrix material. There are several methods for preparing nano suspensions.

2.6.1. Precipitation Technique:

The drug is dissolved in a solvent, which is then added to an antisolvent to precipitate the crystals in the precipitation technique. Solid particle size distribution in nanosuspensions is typically less than one micron, with an average particle size ranging between 200 and 600 nm [31,32].The primary benefit of the precipitation technique is the use of simple and low cost equipment. The drug must be soluble in at least one solvent and this solvent must be miscible with the antisolvent for this technique to work [33].

2.6.2. Media Milling:

High shear media mills are used to create the nanosuspensions. For several days, the milling chamber is filled with milling media, water, drug, and stabilizer and rotated at a high shear rate at a high shear rate at controlled temperatures (at least 2-7 days). The impaction of the milling media with the drug generates high energy shear forces, resulting in the breaking of microparticulate drug to nanosized particles.

2.6.3. High pressure Homogenization:

A drug and surfactant suspension forced under pressure through a nanosized aperture valve of a high pressure homogenizer in this method. The principle of this method is based on aqueous cavitation. The cavitation forces within the particles are strong enough to transform the drug microparticles into nanoparticles. Poorly soluble drugs such as spironolactone, budesonide, and omeprazole have had their dissolution rate and bioavailability improved [34-35].

2.6.4. Combined Precipitation and Homogenization:

Precipitated drug nanoparticles tend to form crystals as small as micro crystals. They must be dealt with using high energy forces (homogenization). The precipitated particle suspension is then homogenized while retaining the particle size obtained during the precipitation step.

2.6.5. Super critical fluid (SCF) process:

Supercritical fluids have temperatures and pressures that are higher than their critical temperature (Tc) and critical pressure (Tp), allowing them to have the properties of both a liquid and a gas. SCFs are highly compressible at near critical temperatures, allowing moderate pressure changes to significantly alter the density and mass transport characteristics of the fluid, which largely determine its solvent power. Once the drug particles have been solubilized in the SCF (typically carbon dioxide), they can be recrystallized at much smaller particle sizes [36, 37].

2.7. Cryogenic Techniques:

Cryogenic inventions are distinguished by the type of injection device (capillary, rotary, pneumatic, or ultrasonic nozzle), the location of the nozzle (above or below the liquid level), and the cryogenic liquid composition (hydrofluoro alkanes, N_2,Ar, O_2, and organic solvents). Dry powder can be obtained after cryogenic processing through a variety of drying processes such as spray freeze drying, atmospheric freeze drying, vacuum freeze drying and lyophilisation [38-40].

2.8. Spray Freeze onto Cryogenic Fluids:

Spray freezing onto cryogenic fluids was invented by Briggs and Maxvell. The drug and carrier (mannitol, maltose, lactose, inositol, or dextran) were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant in this technique. To improve aqueous solution dispersion, a sonication probe can be placed in the stirred refrigerant [41].

2.9. Spray Freezing into Cryogenic Liquids (SFL) :

Using SFL particle engineering technology, amorphous nano structured drug powder aggregates with a high surface area and good wettability were created. It achieves intense atomization into micro droplets and, as a result, significantly faster freezing rates by using direct liquid-liquid impingement between the automated feed solution and the cryogenic liquid. The particles are lyophilized after freezing to produce dry and free flowing micronized powders [43].

2.10.Spray Freezing into Vapor over Liquid(SFV/L):

The freezing of drug solution in cryogenic fluid vapours, followed by the removal of frozen solvent, results in fine drug particles with high wettability. Before contacting the cryogenic liquid the atomized droplets typically begin to freeze in the vapour phase during SFV/L. The drug becomes supersaturated in the unfrozen regions of the atomized droplet as the solvent freezes, allowing fine drug particles to nucleate and grow[43].

2.11. Ultra -Rapid Freezing (URF):

Using solid cryogenic substances, ultra rapid freezing creates nanostructured drug particles with greatly increased surface area and desired surface morphology. When a drug solution is applied to the solid surface of a cryogenic substrate, it instantly freezes, and subsequent lyophilization (to remove the solvent) results in micronized drug powder with improved solubility. The ultra-rapid freezing of pharmaceutical ingredients prevents phase separation and crystallization, resulting in intimately mixed, amorphous drug carrier solid dispersions and solid solutions [44].

2.12. INCLUSION COMPLEX

2.12.1. Formation-Based Techniques:

Inclusion complexes are formed when a nonpolar molecule or nonpolar region of one molecule (known as the guest) is inserted into the cavity of another molecule or group of molecules (known as host). Cyclodextrins are the most commonly used host molecules. [45,46]. The cyclodextrin molecules are water soluble due to their surface, but the hydrophobic cavity provides a micro environment for appropriately sized non-polar molecules.

2.12.2. Kneading Method:

The CDs are impregnated with a small amount of water or hydro alcoholic solutions to form a paste in this method. The drug is then mixed into the above paste and kneaded for a set amount of time. The kneaded mixture is then dried and, if necessary, passed through a sieve. In the laboratory, kneading can be accomplished with a mortar and pestle. This is the most common and straight forward method for producing inclusion complexes at a low cost [47,48].

2.12.3. Lyophilization/Freezing-Drying Technique:

The solvent system from the solution is removed using technique by first freezing and then drying the solution containing both drug and CD at low pressure. This method can successfully convert thermolabile substances into complex forms. Lyophilization/freeze drying is a technique that involves molecular mixing of drug and carrier in a common solvent as an alternative to solvent evaporation [49].

2.12.4. Microwave Irradiation Method:

The microwave irradiation reaction between the drug and the complexing agent is used in this technique. A definite molar ratio of the drug and CD is dissolved in a round bottom flask with a specified proportion of water and organic solvent. The mixture is reacted in the microwave oven for one to two minutes at 60 degrees Celsius. Following the completion of the reaction, an appropriate amount of solvent mixture is added to the above reaction mixture to remove the residual uncomplexed free drug and CD. The resulting precipitate is separated using whatman filter paper and dried in a vacuum oven at 40^0C [50].

2.13. Micellar Solubilization :

The use of surfactants to improve the dissolution performance of poorly soluble drug products is most likely the most fundamental and oldest method. Surfactants lower surface tension and improve lipophilic drug dissolution in aqueous medium. They are also used to keep drug suspensions stable. Surfactant also improves solid wetting and accelerates solid disintegration into finer particles. Non ionic surfactants that are commonly used include polysorbates, polyoxyethylated castor oil, polyoxyethylated glycerides, and lauryl macroglycerides [51-53]

2.14. Hydrotrophy:

Hydrotrophy is a solubilisation process in which a large amount of the second solute, the hydrotropic agent, is added, resulting in an increase in the aqueous solubility of the first solute. Hydrotropic agents are alkali metal salts of various organic acids that are ionic organic salts. Additives or salts that increase solubility in a given solvent are said to "salt in", while salts that decrease solubility are said to "salt out"[54,55].

2.15.Crystal Engineering :

It is possible to prepare crystals with different packing arrangements by using different solvents, changing the stirring, or adding other components to the crystallizing drug solution. As a result, physicochemical properties such as solubility, dissolution rate, melting point, and stability may differ between polymorphs of the same drug [56].

2.16. Pharmaceutical cocrystals :

Pharmaceutical cocrystals are formed under ambient conditions by combining a molecular or ionic drug with a solid cocrystal former. Slow evaporation from a drug solution containing stoichiometric amounts of the components (cocrystal formers) is used to make these; however, sublimation, melt growth, or grinding of two or more solid cocrystal formers in a ball mill are also viable methods. Another emerging technology is melt sonocrystallization, which uses ultrasonic energy to create porous fast dissolving particles for hydrophobic drug molecules [57-58].

3. TYPES OF NANOPARTICLES :

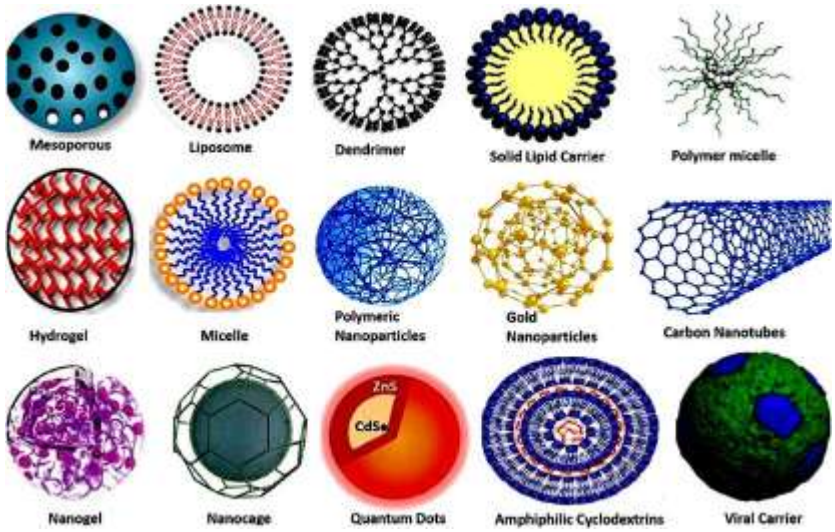

Figure 1: Types of Nanoparticles

3.1. Liposomes:

Liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Liposomes are characterized in terms of size, surface charge and number of bilayers. It exhibits number of advantages in terms of amphiphilic character, biocompatibility, and ease of surface modification rendering it a suitable candidate delivery system for drugs (Figure 2).

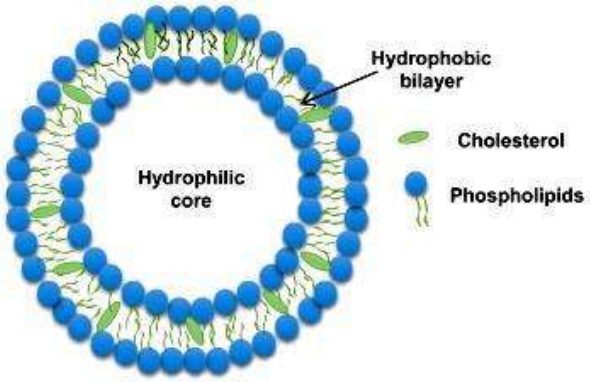

Figure 2: Liposomes

3.2. Solid lipid nanoparticles :

SLNs have been developed and studied for parenteral, pulmonary, and dermal administration routes. Solid Lipid Nanoparticles are made up of a solid lipid matrix, into which the drug is normally incorporated, and have an average diameter of less than 1m. (Figure 3). Different surfactants are used to prevent aggregation and stabilize the dispersion. SLN have been proposed as new transfection agents that use cationic lipids as matrix lipids. The same cationic lipids that are used to make liposomal transfection agents can be used to make cationic solid lipid nanoparticles (SLN) for gene transfer [59].

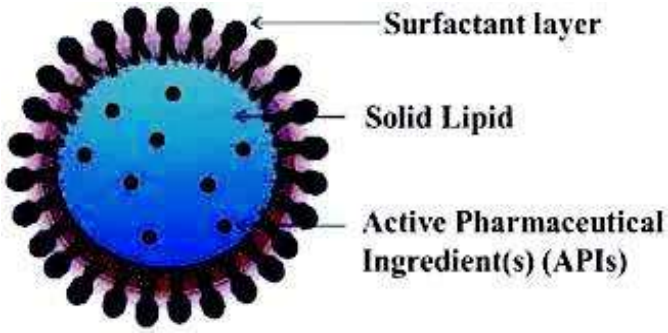

Figure 3 : Solid lipid nanoparticles

3.3.Polymeric nanoparticles :

Unlike SLN or nanosuspensions, polymeric nanoparticles (PNPs) are made of a biodegradable polymer (figure 4). The benefits of using PNPs in drug delivery are numerous, the most important of which is that they generally increase the stability of any volatile pharmaceutical agents and are easily and cheaply manufactured in large quantities using a variety of methods. Furthermore, polymeric nanoparticles with engineered specificity may be able to deliver a higher concentration of pharmaceutical agent to a desired location [60].

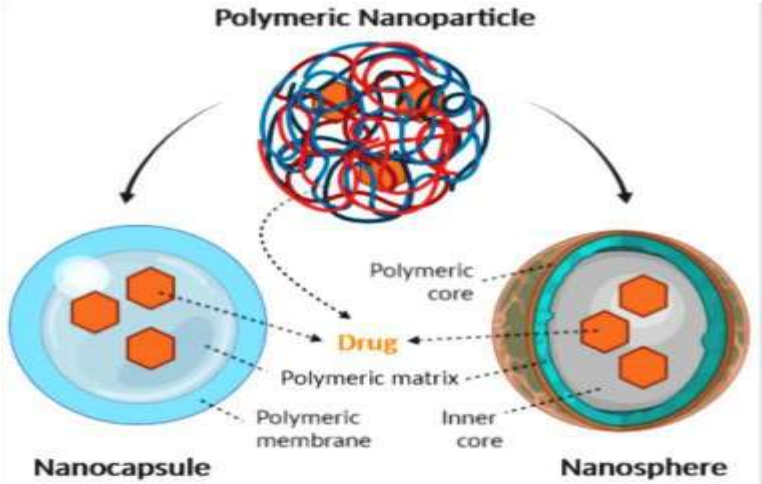

Figure 4: Polymeric Nanoparticles

3.4. Nanocapsules:

The drug in nanocapsules is confined to a cavity surrounded by a unique polymeric membrane, whereas the drug in nanospheres is dispersed throughout the polymer matrix. Throughout or within the polymeric shell/matrix, the candidate drug is dissolved, entrapped, attached or encapsulated. The release characteristics of the incorporated drug can be controlled depending on the method of preparation. Because of their small size and surface modification with a specific recognition ligand, nanoparticles can be directed to a specific location. Their surface is easily modifiable and functionalizable.

3.5Nanospheres:

Dendrimers, a distinct class of polymers, are highly branches macromolecules with precise control over size and shape (figure 5). Dendrimers are made from monomers via convergent or divergent step growth polymerization. Dendrimers are appealing drug carrier candidates due to their well-defined structure, monodispersity of size, surface functionalization capability, and stability. Drug molecules can enter dendrimers through complexation or encapsulation [61-62].

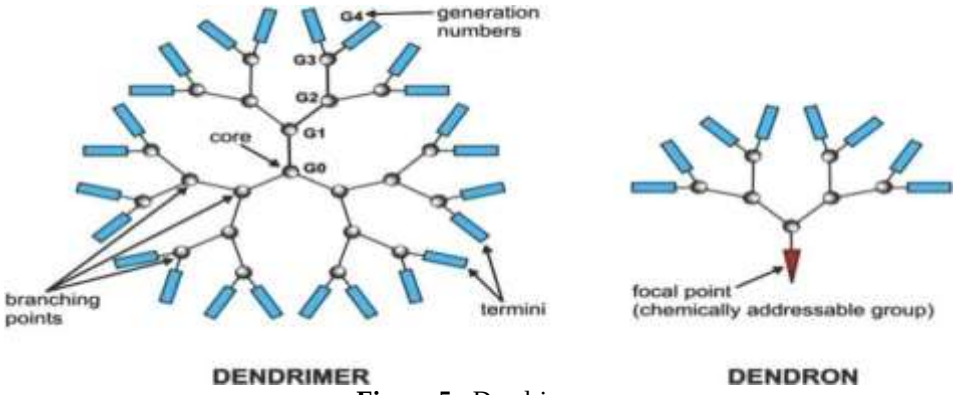

Figure 5 : Dendrimers

3.7.Drug Nanocrystals :

Pure solid drug particles with a mean diameter less than 1000nm are referred to as drug nanocrystals. The term "drug nanocrystals" implies that the discrete particles are crystalline, but depending on the manufacturing method, they can also be partially or completely amorphous. Drug nanocrystals must be up of a polymeric matrix and a drug. There is no matrix material in drug nanocrystals.

3.8. Nanotubes:

Carbon nanotubes (CNTs) have demonstrated significant potential in a wide range of biological applications, including DNA and protein biosensors, ion channel blockers, bioseparators, and biocatalysts. This potential stems from their unique surface or adaptable size-dependent properties, as well as their anisotropic is significant because it affects their electronic, photonic, mechanical, and chemical properties.(figure 6).

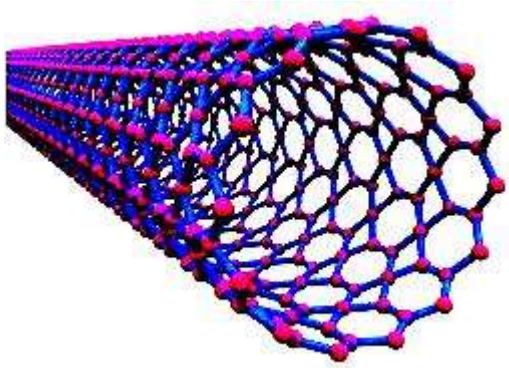

Figure 6 : Nanotubes

4. METHODS OF PREPARATION OF NANO PARTICLES:

4.1. Solvent evaporation method :

The preparation of an oil/water (o/w) emulsion is required first in this method [63], which leads to the production of nanospheres (figure 7). To begin, an organic phase is made up of a polar organic solvent in which the polymer is dissolved and the active ingredient (eg.,drug) is dissolved or dispersed. Dichloromethane and chloroform were widely used, but because of their toxicity, they were replaced by ethyl acetate, which has a better toxicological profile [64-65]. An aqueous phase containing a surfactant (eg., polyvinyl acetate;PVA) has also been frequently prepared, The organic solution is emulsified in the aqueous phase with a surfactant before being processed with high speed homogenization or ultrasonication to produce a nanodroplet dispersion. The solvent is evaporated either through continuous magnetic stirring

at room temperature or through a slow reduction process. The solidified nanoparticles can be washed and collected by centrifugation after the solvent has evaporated, followed by freeze-drying for long term storage.

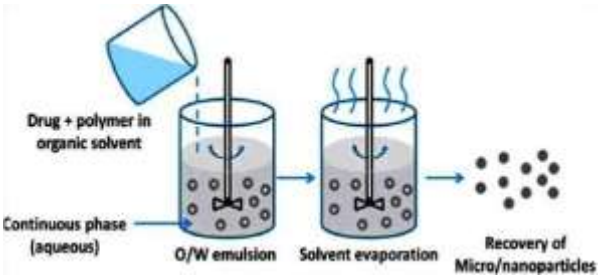

Figure 7: Schematic diagram of solvent evaporation method.

4.2. Emulsification/Solvent diffusion:

This method involves forming an o/w emulsion from a partially water miscible solvent containing polymer and drug and an aqueous solution containing a surfactant (figure 8) [66]. This emulsions internal phase is made up of a partially hydro miscible organic solvent, such as benzyl alcohol or ethyl acetate that has been previously saturated with water to ensure an initial thermodynamic balance of both phases at room temperature. Following dilution with a large amount of water, solvent diffusion from the dispersed droplets into the external phase occurs, resulting in colloidal particle formation. Finally depending on the boiling point of the organic solvent, this final stage can be removed by evaporation or filtration [67]. Despite the need for a large volume of aqueous phase to be removed from the colloidal dispersion and the risk of hydrophilic drug diffusion into the aqueous phase, this method is frequently used to produce polymeric NPs [68].

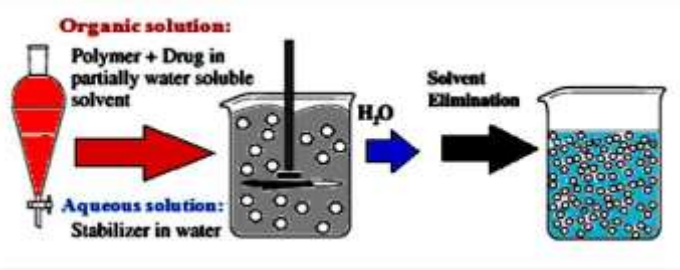

Figure 8 : Schematic diagram of emulsion-solvent diffusion method

4.3. Emulsification/Reverse salting-out:

The salting out method relies on the salting out effect, which may result in the formation of nanospheres, to separate an aqueous solution from a hydromiscible solvent (figure 9) [69].The main difference is that the o/w emulsion is made of a polymer solvent that dissolves in water, like acetone or ethanol. The aqueous phase also has a gel, a salting out agent, and a colloidal stabilizer. Non-electrolytes like sucrose and electrolytes like magnesium chloride, calcium chloride, and magnesium acetate are good salting out agents [70]. Saturating the aqueous phase reduces the miscibility of acetone and water, making it possible to create an o/w emulsion from other miscible phases [71,72]. At room temperature, the o/w emulsion is prepared by vigorous stirring. After that, an aqueous solution is used to dilute the emulsion so that the polymer precipitates, nanospheres are formed, and the organic solvent can diffuse to the external phase. Cross flow filtration removes the salting out agent and remaining solvent [73,74]. The preparation of ethyl cellulose, PLA, and poly (methacrylic) acid nanospheres can be quickly and easily scaled up using this method [75,76]. Since this method does not require an increase in temperature, salting out may be useful for heat sensitive substances.

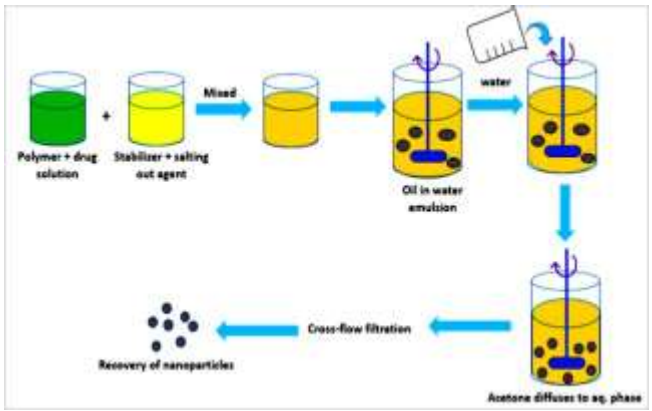

Figure 9 : Schematic diagram of reverse salting out method

4.4.Coacervation technique:

The polymer is dissolved in a organic solvent (such as dichloromethane,ethyl acetate or acetonitrile) in this method of synthesis. Centrifugation is used to collect the nanoparticles. It's a cost effective approach. This methods main drawback is that it requires a lot of solvent.

4.5. Nanoprecipitation

The interfacial deposition of a polymeric following the transition of the organic solvent from the lipophilic solution to the aqueous phase is the underlying principle of this method (figure 10) After the polymer has been dissolved in a solvent of intermediate polarity that is water- miscible, either a controlled addition rate or a stepwise addition of this solution in to a aqueous solution with stirring (in a dropwise manner) is done. The nanoparticles immediately form as a result of the rapid spontaneous diffusion molecules. The polymer precipitates in the form of nanoparticles or nanospheres as the solvent diffuses out of the nanodroplets. In most cases, the aqueous phase is mixed with the organic phase, but the procedure can also be reversed without affecting the formation of nanoparticles (77-83). Typically, surfactants can be added to the procedure to improve the colloidal suspensions stability (84). Nanoprecipitation is a technique that can be used to acquire nanospheres or nanocapsules in addition to polymeric NPs with dimensions of around 170nm (85-87).

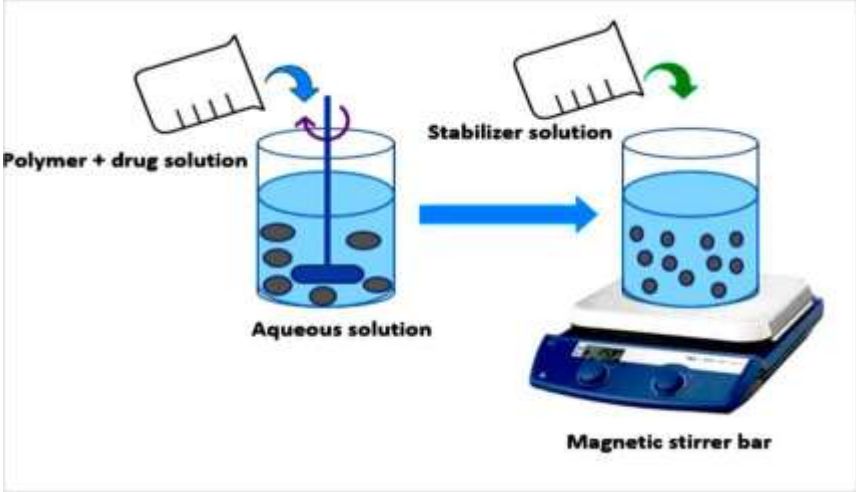

Figure 10: Schematic diagram of Nanoprecipitation method

4.6. Spray drying method:

The nanocrystals can be formulated by spray drying method. For that drug solutions with different concentrations are dried with mini spray dryer. The spray dried nanocrystals are directly collected after the process.

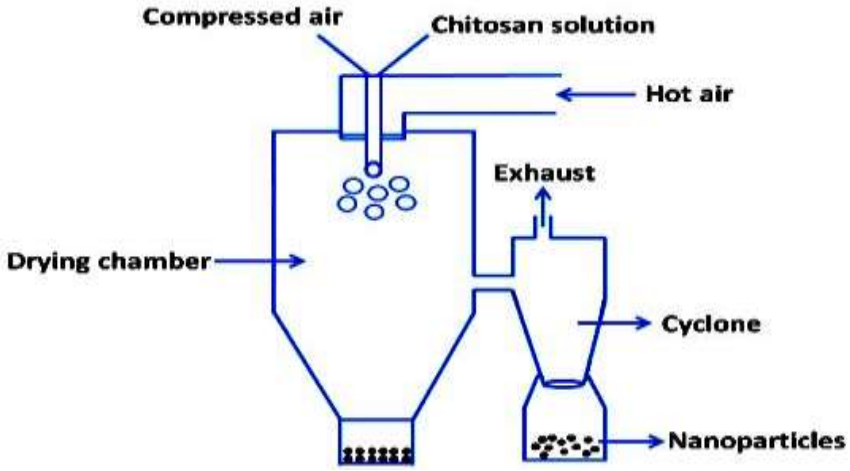

Figure 11: Schematic diagram of spray drying method

4.7. Microemulsions:

Microemulsion is considered as an ideal method for nanoparticles fabrication. The surfactants used in this method are hydrophobic in nature for water soluble drugs and hydrophilic in nature for oil soluble drugs .Microemulsion is formed when a small amount of surfactants is stirred and drug is added in it along with oil and water .It results in the formulation of turbid solution which generally appears like small droplets .Various types of surfactants are used to increase the surface stabilization of nanoparticles. This method is easy and can be effectively used for drug delivery with less energy expenditure. Microemulsion technique is affected by certain parameters like temperature and pH variation.

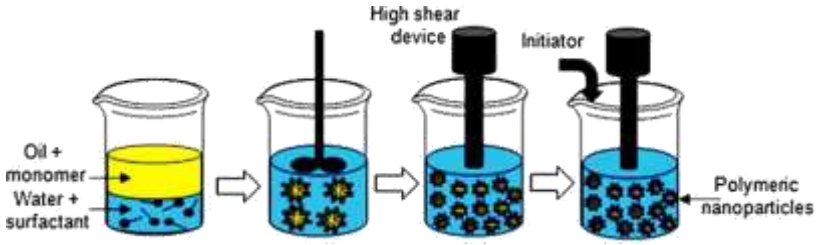

Figure 12: Schematic diagram of Microemulsion method

4.8. Wet milling method:

The nanoparticles can be synthesized from wet milling method. The drug is suspended in an appropriate dispersing solvent. The obtained solution is further agitated under ultrasonication method .Distilled water is used for the synthesis of nanoparticles. The obtained solution is then allowed to centrifuge and the formed nanoparticles are collected.

4.9. Thin film hydration method:

In this method of synthesis. Drug and surfactants are allowed to mix in a suitable organic solvent under sonication condition. Solvent is allowed to evaporate under certain pressure.

4.10. Solid dispersion method:

In this method, the matrix and hydrophobic drugs are mixed. Matrix can be in the amorphous or in crystalline form. This can be used to dissolve the insoluble hydrophobic drug.

4:11. Polymerization method:

In the method, monomers are polymerized to form nanoparticles in an aqueous solution. Drug is incorporated either by being dissolved in the polymerization medium or by adsorption onto the nanoparticles after polymerization completed (figure 10) . The nanoparticles suspension is then purified to remove various stabilizer and surfactants employed for polymerization by ultracentrifugation and resuspending the particle in an isotonic surfactants free medium.

This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles [88,89]. Nanocapsules formation and their particle size depends on the concentration of the surfactants and stabilizers used [90].

Advantages:

- The system is simple and requires thermal insulation .
- The polymer is obtained pure.
- Large casting may be prepared directly .
- Molecular weight distrubution can be easily changed with the use of a chain transfer agent.

Disadvantages:

- Heat transfer and mixing become difficult as the viscosity of reactions mass increases.
- Highly Exothermic.
- The polymerization is obtained with a broad molecular weight distribution due to the viscosity and lack of good heat transfer.
- Very low molecular weights are obtained.

Figure 13: Schematic diagram of polymerization method

4.12. Fessi method:

In this method of synthesis, drug is dissolved in suitable under sonication condition. The solution thus obtained is further added in pure water along with certain surfactant with constant stirring.

4.13: Ionic gelation method:

Much research has been focused on the preparation of nanoparticles using biodegradable hydrophilic polymers such as chitosan, gelation and sodium alginate.

Calvo and coworkers develops a method for preparing hydrophilic chitosan nanoparticles by ionic gelation (figure 14) [91,92]. The method involves a mixture of two aqueous phase,of which one is the polymer chitosan , a diblock copolymer ethylene oxide or propylene oxide (PEOPPO) and the other is a polyanion sodium tripolyphosphate . In this method, positively charged amino group of chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometer. Coacervates are formed as a result of electrostatic interaction between two aqueous phase, whereas, ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction condition at room temperature.

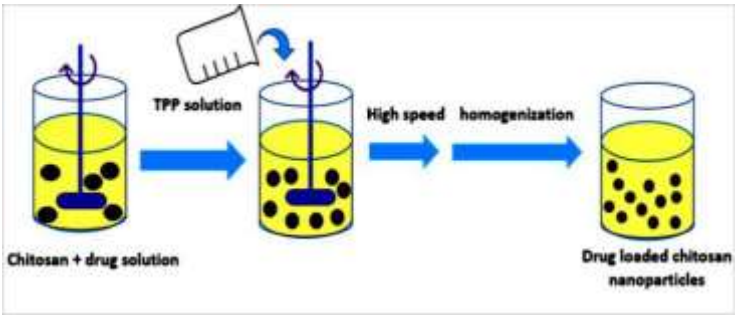

Figure 14: Schematic diagram of Coacervation or ionic gelation method

4.14. Ultrasonication :

This method is generally employed for the drugs which are less water soluble. By the technique, drug is first dissolved in an organic solvent and the resulting solution is then added into the polyelectrolyte solution under ultrasonication condition for several intervals of time and the formed nanoparticles are formed.

4.15. Double Emulsion and Evaporation method:

Poor entrapment of hydrophilic drugs is the main drawback of the method. Therefore to encapsulate hydrophilic drug the double emulsion technique is engaged, in which aqueous drug solutions is added to organic polymer solution with vigorous stirring to form mixed emulsion (w/o/w) , this w/o emulsion is added into another aqueous phase. Then by the evaporation solvent is removed by centrifugation at high speed nano particles can be isolated .Before lyophilisation the prepared Nanoparticles must be washed. [93] The variables used in this method are incorporated quantity of hydrophilic drug, the amount of polymer, the volume of aqueous phase and the stabilizer concentration [94]

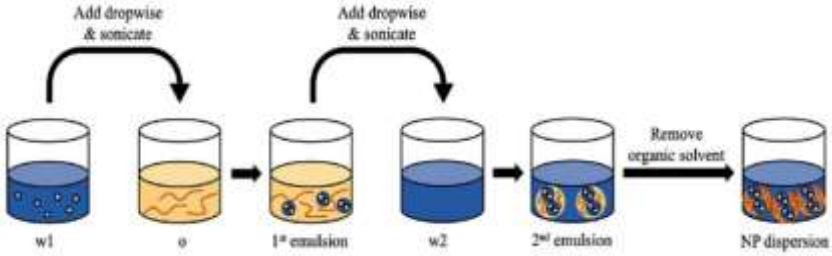

Figure15: Schematic diagram of Double Emulsion and Evaporation Method

Table 1: Comparison of Preparation method

5. ANTI-SOLVENT PRECIPITATION METHOD :

The antisolvent precipitation method for producing ultra fine drug particles is promising [25]. The drug is dissolved in a solvent, which is then mixed with an antisolvent (in which the drug is insoluble) . As a result of the super saturation change caused by mixing the solution and the anti solvents, the drug precipitate (figure 16). The key to producing ultra fine particles through anti solvent precipitation is to create conditions that allow for very rapid particle formation why allowing for little or no particle growth. The technique as the advantage of being a simple method that is quick and simple implement. Several drugs have been successfully prepared using it, including budesonide [96], danazol [97] ,beclomethasone dipropionate, prednisolone, atorvastatin, griseofulvin, and fenofibrate.

In general ,nontoxic class 3 organic solvents were widely used in the anti precipitation method; the organic solvents will be composed of one or more polar organic solvent such as tetrahydrofuran (THF), acetonitrile, dimethyl sulfoxide (DMSO), acetone, dimethyl formamide(DMF) ,and ethanol, and should freely miscible with antisolvent. Water or an aqueous buffer solution is commonly used as antisolvent.

To ensure high supersaturation degree of precipitation , the ideal organic solvent should have the highest capacity to dissolve the drugs and other hydrophobic excipients ,such as polymers ,lipids or surfactants .ASP is based on high super saturation condition of drug molecule to trigger nucleation and growth of nanoparticles under controlled solvent /antisolvents increases drug solubility in the mixed solution , a lower supersaturation level is created , which limits drug nucleation induction .Second ,the mixing rates of the relevant solvent and antisolvent influence the nucleation and growth of the solute. The organic solvent must be removed from the system because the formed nanoparticles were dispersed in aqueous and organic solvent mixtures. Meanwhile, the organic solvent in the mixed solvent will improve Ostwald ripening because the organic solvent from the drug nanoparticles formulation may decrease Ostwald ripening and thus improve physical stability .High boiling point solvents, such as DMSO and DMF, are removed by dialysis, whereas low boiling point solvents, such as THF, acetone, and ethanol, can be removed by vacuum evaporation. Furthermore, antisolvent precipitation is commonly used in conjunction with freeze drying or spray drying to remove the solvent and stabilize the drug nanoparticles for long term storage. Table 2 lists nanoparticles formulation reported by various researchers.

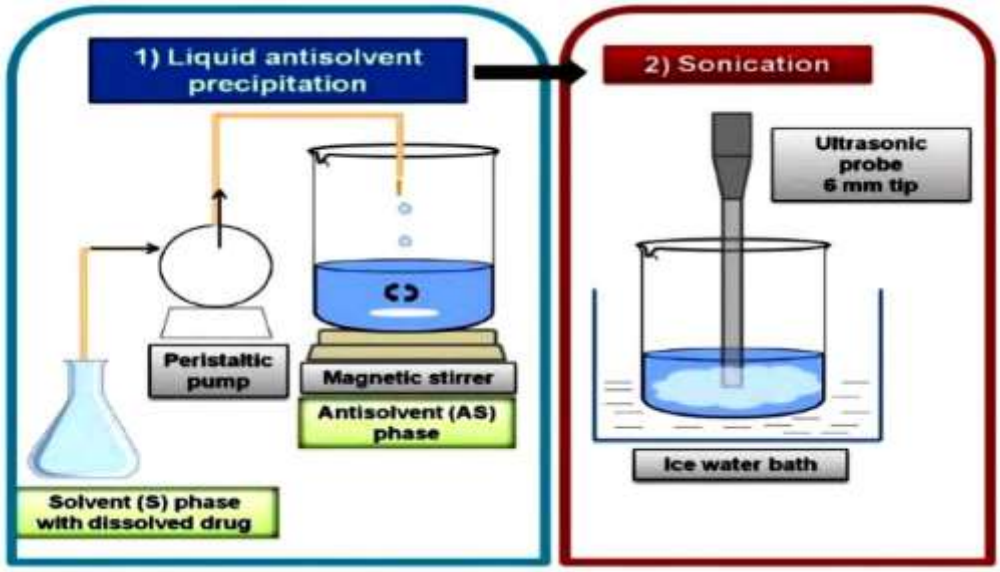

Figure 16: Schematic representation of Antisolvents technique in preparation of Nanoparticles.

5.1. Stabilizers:

For drug nanoparticles prepared by Antisolvent precipitation, the stabilizers have great influence on their formed particle size and long term stability during storage. The selection of the stabilizers and its concentration is crucial to stabile the drug nanoparticles with smaller size. The types of stabilizer used in ASP could be nonionic polymer (HPMC, PMMA, HPC, HPMCAS, CMCAB,), ionic polymer (NACMC, NaAlg, Chitosan, PEI , PAH, Chitosan,PPS) , linear polymer(PVP,PVA, PEG, PAA) ,hydrophobic polymer (PLGA, PLC, PLA), amphiphilic copolymer (poloxamer,PEG-PCL,PEG-PLA,PEG-PS,PEG-PLGA),surfactants of ionic type (SDS, CTACI sodium cholic acid , sodium deoxycholic acid) or nonionic type (Tween ,span, TPGS, lecithin, DSPE-PEG, Cremophor EL).

5.2. Temperature:

Temperature also influences particle size and particle size distribution during the Antisolvent precipitation process by controlling solubility, supersaturation, nucleation rate, and process kinetics. Antisolvents precipitation was typically carried out at room temperature.

Table 2: Nanoparticle formulations reported by different researchers

S. no	Drug	Chemicals	Characterization	References
1	Fluconazole	Dichloromethane, HPMC, Kollicoat IR . Pluronic F127, Xanthan gum (XG), Polyvinyl pyrrolidone, Carbopol 934, Sodium alginate , acetonitrile, Formic acid	Particle size and zeta potential, DSC, XRPD, Solubility study, TEM, drug release study, Ex vivo permeation study	98
2	Procyanidin	2,2-azino bis(3 hylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS),2,2-diphenyl-1 icrylhydrazyl (DPPH), 6-hydroxy 2,5,7,8 tetramethyl chroman-2 carboxylic acid (Trolox),2,4,6- tripyridyl-s-triazine (TPTZ)	FTIR, XRD, GC, TGA	99
3	Rifampicin	Ultrasonics Sonochemistry 43 (2018) 208 - 218, Sodium hydroxide (NaOH) and potassium dihydrogen phosphate (KH2PO4)	particle size and zeta potential, drug content, DSC, XRD SEM,,Solubility study, *In vitro* drug release study,.	100
4	Silibinin	HPMC, hydroxypropyl-b-cyclodextrin, ethanol, methanol and glacial acetic acid	FTIR, SEM, XRD, DSC,TG	101
5	Nifedipine, griseofulvin	Hydrogenated soybean phosphatidylcholine, dipalmitoyl phosphatidylglycerol , Ethanol, Gelatin powder	Particle size measurement, Thermal Analysis. XRD, DSC	102
6	Telmisartan	Poloxamer 188 and Tween 80, Urea and SLS	Particle size analysis, Zeta potential, DSC, SEM.	103
7	Dapsone	ethanol or methanol, Poloxamer, HPMC, Potassium dihydrogen orthophosphate, Disodium hydrogen phosphate	FTIR, DSC, SEM, XRD, AFM	104
8	Lovastatin, Atorvastatin	HPMC K15M, poly vinyl pyrrolidone K-30, N-carboxymethylchitosan, Tween 80, Ethanol and acetonitrile	DSC, FTIR, Saturation solubility	105
9	Lovastatin	HPMC K15M, Pluronic F68, Acetone, Chloroform, Methanol, Ethanol.	Particle Size Analysis, Polydispersity Index, TEM, Zeta potential	106
10	Ibuprofen	Sodium dodecyl sulfate polyvinyl pyrolidone, sodium lauryl sulfate, tween 80, triethanolamine, Isopropyl alcohol, acetonitrile, methanol, ortho-phosphoric acid	IR, DSC, SEM	107
11	Fenofibrate	Eudragit L-100, poly vinyl alcohol, methanol and acetone	SEM, PXRD, DSC, Particle size analysis	108
12	Piroxicam	Polyvinylpyrrolidone (PVP) K30 and Sodium tripoly phosphate. Acetate acid, dichloromethane, Acetone, methanol and ethyl acetate.	FTIR, XRD, DSC, Particle size analysis	109

6. CHARACTERIZATION OF NANOPARTICLES:

6.1. Yield of Nanoparticles [110]:

The yield of nanoparticles was dictated by looking at the entire load of nanoparticles framed against the combined load of the co polymer and drug.

$$\%yield=\frac{\text{Amount of Nanoparticles}}{\text{Amount of drug + polymer}}*100$$

6.2. Drug content / Surface entrapement / Drug entrapement [111] :

After centrifugation, the amount of medication in the supernatant (w) is measured using a UV spectrophotometer. Following that, the standard adjustment bend was plotted. At that point, the amount of medication present in the supernatant is subtracted from the total amount used in the design of nanoparticles (w). (w-w) is the medication entangled measurement. The percentage of tranquilize entanglement determined by

$$\%\text{Drug entrapment} = \frac{W-w}{W}*100$$

6.3. Polydispersity index [112] :

Polydispersity index of prepared nanoparticles was carried out by using Malvern Zetasizer.

6.4. Kinetic study [113] :

For estimation of the motor and system of medication discharge, the after effect of invitro medication discharge investigation of nanoparticles were fitted with different active condition like zero request (combined % discharge vs time), first request (log % tranquilize remaining versus time), Higuchi's model (aggregate % sedate discharge versus square base of time). R^2 and K esteems were determined for the direct bend got by relapse investigation of the above plots.

6.5. Stability of Nanoparticles [114]:

Stability studies of prepared nanoparticles were conducted by storing optimized formulations in a stability chamber at $4^0C\pm 1^0C$ and 30 $^0C\pm 2^0C$ for 90 days. The samples were analyzed after 0,1,2 and 3 months for drug content, drug release rate (t50%), and any changes in their physical appearance.

6.6. Particle size [115] :

The most important parameters of nanoparticles characterization are molecule size distribution and morphology. Electron microscopy is used to estimate morphology and size.

6.7. Dynamic light scattering (DLS) [116] :

It is also referred to as photon correlation spectroscopy (PCS). In colloidal suspensions, DLS is commonly used to determine the size of Brownian nanoparticles in the nano and submicron ranges.

6.8. Scanning electron microscopy [117] :

SEM (scanning electron microscopy) provides morphological assessment through direct perception. The sample surface attributes are obtained from the auxillary electrons transmitted from the sample surface.

6.9. Transmission electron microscope [118] :

The dispersion of nanoparticles is deposited on to support grids or films. Nanopartricles are fixed using either a negative staining material, such as Phosphotungstic acid or derivatives, uranyl acetate, etc., or by plastic embedding to make them withstand the instrument vacuum and facilitate handling. The surface characteristics of the sample are obtained by passing an electron beam through an ultra thin sample and interacting with it as it passes through it.

6.10. Atomic force microscopy [119] :

Atomic force microscopy (AFM) provides ultrahigh goals in molecule size estimation and is based on a physical examination of tests at the submicron level with a nuclear scale test tip. It reveals more morphological properties of nanoparticles then SEM analysis.

6.11. Surface charge [120] :

The zeta capability of nanoparticles is used to assess colloidal dependability. The zeta potential is estimated using expectations about the capacity soundness of colloidal scattering. Estimates of zeta potential would then be able to predict the degree of surface hydrophobicity.

6.12. Surface hydrophobicity [121] :

A number of systems, such as hydrophobic connection chromatography, biphasic parceling, test adsorption, contact angle estimations, and so on, can be used to control surface hydrophobicity. For the purpose of surface examination of nanoparticles, a small number of contemporary diagnostic tools have recently been documented. On the surface of nanoparticles, X-ray beam photon relationship spectroscopy makes it possible to identify specific chemical groups.

6.13. Drug release [122] :

USP type II dissolution assembly was used for *invitro* drug release at a speed of 50 rpm. The vessel was filled with 900 milliliters of dissolution medium and kept at 37^0C. In order to maintain a constant volume, the required quantity of the medium was collected, and a comparable volume of the dissolution medium was substituted. HPLC or UV spectrophotometers were used to analyze the examples that were collected.

7.CONCLUSION:

Nanotechnology is an innovative concept that can be used to solve problems associated with the solubility, stability, and bioavailability of poorly soluble drugs. In this review, various methods of nanoparticle preparation and their benefits and drawbacks are discussed, with an emphasis on the importance of antisolvent precipitation, which is an efficient and cost effective method. The administration of drugs via nanotechnologies opens up a promising future in the pharmaceutical field. The emergency of nanotechnology could have a significant impact on drug delivery, affecting all routes of drug delivery, from oral to parenteral.

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