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Review Article

A REVIEW ON TYPES AND TECHNIQUES FOR THE PREPARATION OF NANOPARTICLES

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ABSTRACT
For the past few decades, there has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. Nanoparticles (NPs) are defined as particles with a diameter smaller than 100 nm, are increasingly used in different applications, including drug carrier systems and to pass organ barriers such as the blood-brain barrier. Via nanotechnology we can achieve better therapeutic action, better bioavailability and better patient compliance. As because of several advantages over to the conventional drug delivery Nanosparticulate drug delivery prepared in several means by several ways of methods have several applications in different discipline of Pharmaceutical science. Several techniques are used for preparation of nanoparticles like Solvent Evaporation, Nanoprecipitation , Salting Out Method, Dialysis and Supercritical fluid technology.

Keywords: *Nanocrystals, Nanotechnology, Dendrimers, Nanoprecipitation, Solvent Evaporation.*

INTRODUCTION
Nanoparticles (NPs) are defined as particulate dispersions or solid particles drug carrier that may or may not be biodegradable. Nanoparticles are sub -nanosized colloidal structures composed of synthetic or semi-synthetic polymer and the particle size ranges from 10-100 nm in diameter (N. K. Jain, 2001) .
The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Nanoparticles are solid core spherical particulates which are nanometric in size. The term nanoparticle is a combined name for both nanospheres and nanocapsules (N. K. Jain, 2001).
Nanospheres: Nanospheres contain drug embedded with the matrix (or) adsorbed on to the surface (Vyas S.P, Khar,2002) .Nanospheres are the spherical particles which have the size between 10-200 nm in diameter and that exhibit some new enhanced size dependent properties in comparison of larger spheres of the same material (N. K. Jain, 2001).
Nanocapsules: are vesicular system in which drug is essentially encapsulated with in the central volume surrounded by an embryonic polymeric sheath (N. K. Jain, 2001).

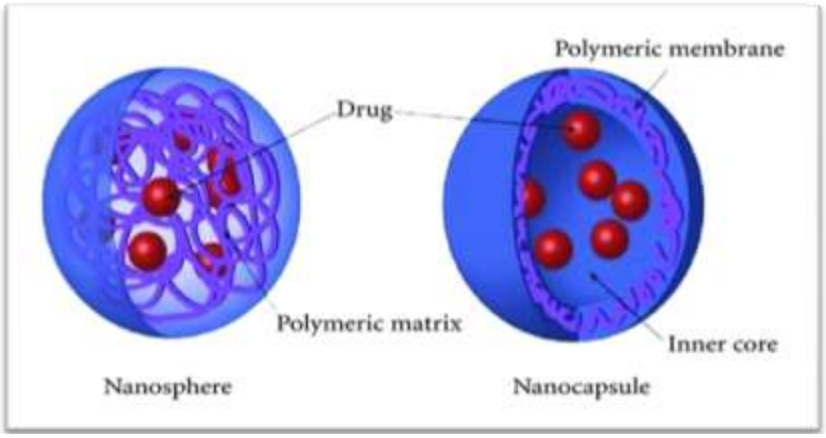

Figure 1: Nanoparticle system (Nanomedicine (2010) Future Medicine Ltd).

Advantages of Nanoparticles

Nanoparticles offers numerous advantages in drug delivery system. These advantages include :

- Nanoparticles have many significant advantages over conventional and traditional drug delivery system (Hemant K.S. Yadav *et al*, 2012).
- Nanoparticles enhance the aqueous solubility of poorly soluble drug, which improves bioavailability of drug (Hemant K.S. Yadav *et al*, 2012).
- Nanoparticles reduce drug toxicity and enhance efficient drug distribution. (Vyas S.P, Khar,2002)
- Nanoparticles shows better drug delivery as compare to other dosage forms and target to a particular cell or receptor (Hemant K.S. Yadav *et al* , 2012).
- Nanoparticles delivers a higher concentration of pharmaceutical agent to a desired location (Hemant K.S. Yadav *et al*, 2012).
- Nanoparticles are used to diagnose various diseases (Renu tiruwa, 2015).
- Decreased fed/fasted variability (Renu tiruwa, 2015).
- Decreased patient-to-patient variability (Renu tiruwa, 2015).
- Less amount of dose required (Renu tiruwa, 2015).
- More rapid onset of therapeutic action (Renu tiruwa, 2015).
- Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance (Hemant K.S. Yadav *et al* ,2012).
- The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc (Hemant K.S. Yadav *et al* ,2012).

Disadvantages of Nanoparticles

In spite of these advantages, Nanoparticles have some disadvantages:

- It can lead to particle-particle aggregation, making physical handling of nanoparticles , difficult in liquid and dry forms (Hemant K.S. Yadav *et al* ,2012).
- Small particle size results in limited drug loading and burst release (Renu tiruwa , 2015).
- On repeated administration, toxic metabolites may be formed during the biotransformation of polymeric carriers (Renu tiruwa,2015).
- Polymeric nanoparticles are slowly biodegradable which might cause systemic toxicity. (Renu tiruwa, 2015).

Polymers for Preparation of Nanoparticles

The polymers should be compatible with the body in the terms of adaptability and should be biodegradable and biocompatible (Hemant K.S. Yadav *et al* , 2012).

The polymers used for the preparation of nanoparticles are as follows:

- Natural polymers.
- Synthetic polymers.

Natural polymers: The most commonly used natural polymers in preparation of polymeric nanoparticles are: (Hemant K.S. Yadav *et al* ,2012).

- Chitosan .
- Gelatin.
- Sodium alginate.

Synthetic polymers: The most commonly used synthetic polymers in preparation of polymeric nanoparticles are: (Hemant K.S. Yadav *et al*, 2012).

- Polyorthoesters.
- Polyanhydrides.
- Polyglycolides.
- Poly(lactide co-glycolides) (PLGA) .

Applications of Nanoparticles

Different applications of nanoparticles are listed below:

- Used in targeted drug delivery (therapy) to brain and cancer therapy. (M. Anto Godwin *et al* ,2015).
- Drug and gene delivery (Saba Hasan *et al* ,2015).
- Detection of proteins (M. Anto Godwin *et al* ,2015).
- Biomarker mapping (Saba Hasan *et al* ,2015).
- Probing of DNA structure and also used in tissue engineering (M. Anto Godwin *et al* ,2015).
- Bio detection of pathogens (M. Anto Godwin *et al* , 2015).
- Separation and purification of biological molecules and cells (P.amareshwar *et al*, 2011).
- MRI contrast enhancement (M. Anto Godwin *et al* , 2015).
- Used in ocular delivery (P. amareshwar *et al*, 2011).
- Nanotechnology in Diabetes (M. Anto Godwin *et al* , 2015).
- Nanotechnology in CVS Disorders (M. Anto Godwin *et al* , 2015.

Types of Nanoparticles

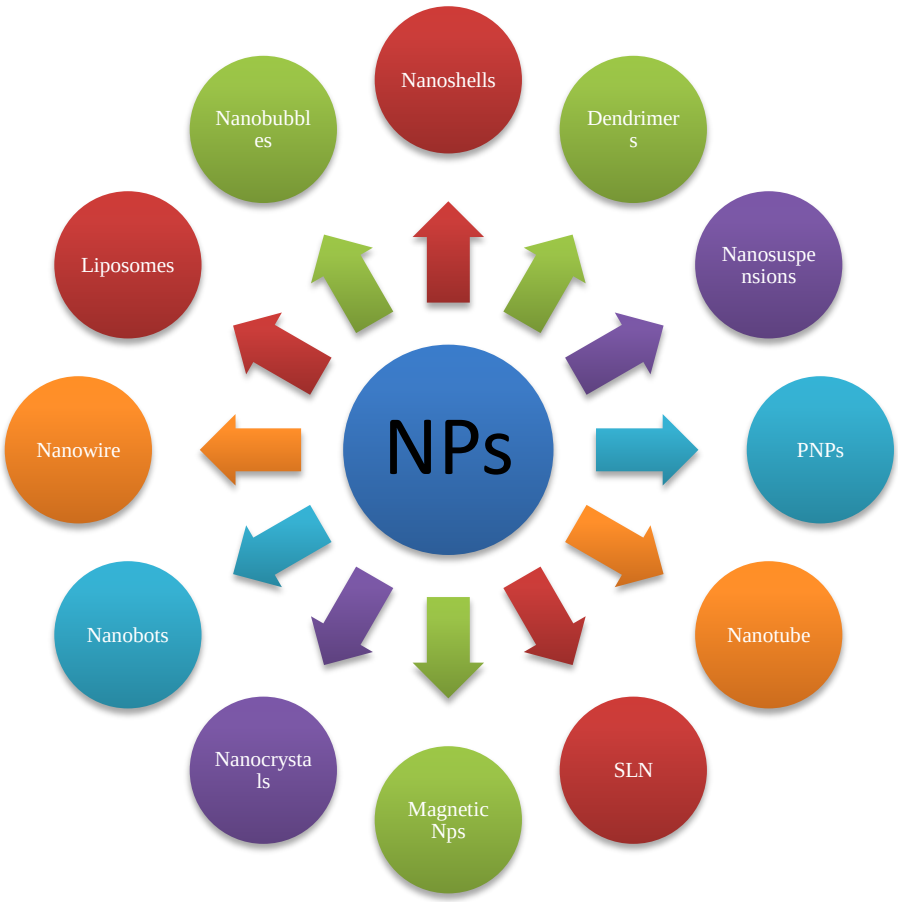

Figure 2: Types of Nanoparticles

Nanosuspensions

The suspension of nanoparticles prepared in a liquid is known as nanosuspenion. The size of nanoparticle ranges from 200 to 500 nm and incredible character of nanosuspension is the enhanced saturation, solubility and dissolution rate of the compound (P.Velavan *et al* ,2015). The saturation and solubility of compound increases below a particle size of 1 mcm. An outstanding character of nanosuspension is that they can produce variations in the crystalline structure such as they increase the amorphous fraction in particle. Nanosuspensions show an increased adherence to tissue (P.Velavan *et al* ,2015).

For instance: Nanosuspension of ibuprofen is formulated by emulsion solvent diffusion method for improving ocular availability. The need for nanosuspensions as a dosage form was recognized as a means to administer therapeutic quantities of water-insoluble dosage forms (P.Velavan *et al* ,2015).

Nanocrystal

Nanocrystal is any nanomaterial with at least one dimension ≤ 100nm and that is single crystalline (P.Velavan *et al* , 2015). More properly, any material with a dimension of less than 1 micrometre, i.e., 1000 nanometers, should be referred to as a nanoparticle, not a nanocrystal (P.Velavan *et al* ,2015). For example, any particle which exhibits regions of crystallinity should be termed nanoparticle or nanocluster based on dimensions. (P.Velavan *et al* ,2015). These materials are of huge technological interest since many of their electrical and thermodynamic properties show strong size dependence and can therefore be controlled through careful manufacturing processes (P.Velavan *et al,* 2015).

Drug nanocrystals have to be distinguished from polymeric nanoparticles, which consist of a polymeric matrix and an incorporated drug. Drug nanocrystals do not consist of any matrix material (Hemant K.S. Yadav *et al* , 2012).

Magnetic Nanoparticles

Magnetic nanoparticles are strong and adaptable diagnostic tool in the field of medicine. Magnetic immunoassay methods have been established in which the main field generated by the magnetically labelled target detected directly with sensitive magnetometer (P.Velavan *et al* ,2015). Super magnetic nanoparticles are used as adverse agents in magnetic resonance imaging. (Hemant K.S. Yadav *et al* , 2012).

Magnetic nanoparticles. Indomethacin established selective targeting under magnetic field of 8000 oe-strength, following normal administration, the concentration of the drug was higher in liver and spleen where the process of phagocytosis and endocytosis might occur (P.Velavan *et al,* 2015).

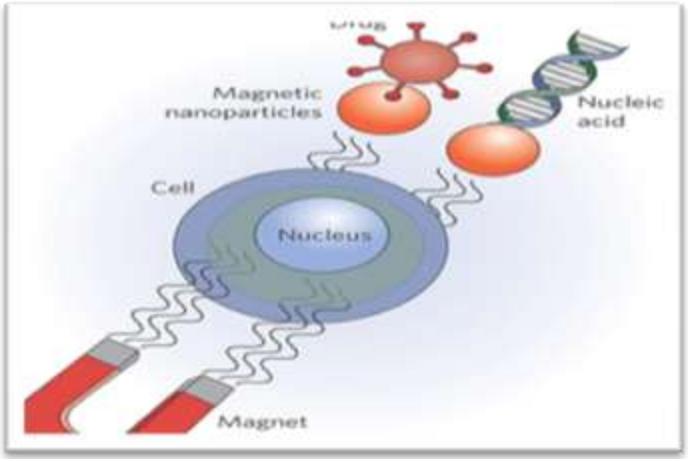

Figure 3: Magnetic Nanoparticles (Plank, *et al*).

The above Figure indicates that magnetic nanoparticles (orange circles) carrying nucleic acids or drugs can be magnetically guided into cells (blue circle) using n external magnet. Nucleic acids such as short interfering RNA can turn off certain genes that cause diseases (P.Velavan *et al,* 2015).

The advantages of magnetic nanoparticles drug delivery sytems include:

- The ability to target specific locations in the body (P.Velavan *et al*, 2015).
- The reduction of the quantity of drug needed to attain a particular concentration in the vicinity of the target (P.Velavan *et al*, 2015).
- The reduction of the concentration of the drug at non target sites minimizing severe side effects (P.Velavan *et al*, 2015).
- Magnetic nanoparticles can attach to cancer cells in the blood stream. These nanoparticles may allow doctors to remove cancer cells before they can establish new tumors (P.Velavan *et al*, 2015).
- Many types of magnetic nanoparticles-based biosensors have been surface functionalized to recognize specific molecular targets, due to their unique magnetic properties which are not found in biological systems (P.Velavan *et al*, 2015).

Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to tradition colloidal carriers such as - emulsions, liposomes and polymeric micro and nanoparticles. (P.Velavan *et al*, 2015). Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system . (Vyas S.P, Khar, 2002).

SLN are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals (Hemant K.S. Yadav *et al* , 2012).

In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by a solid lipid, which eventually transformed into solid lipid nanoparticles (P.Velavan *et al*, 2015).

The reasons for the increasing interest in lipid based system are many – fold and include. (Vyas S.P, Khar 2002).

- Lipids enhance oral bioavailability and reduce plasma profile variability.
- Better characterization of lipoid excipients.
- An improved ability to address the key issues of technology transfer and manufacture scale-up.

Solid lipid nanoparticles are one of the novel potential colloidal carrier systems as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid (Vyas S.P, Khar ,2002). They have many advantages such as good biocompatibility, low toxicity and lipophilic drugs are better delivered by solid lipid nanoparticles and the system is physically stable (Vyas S.P, Khar ,2002).

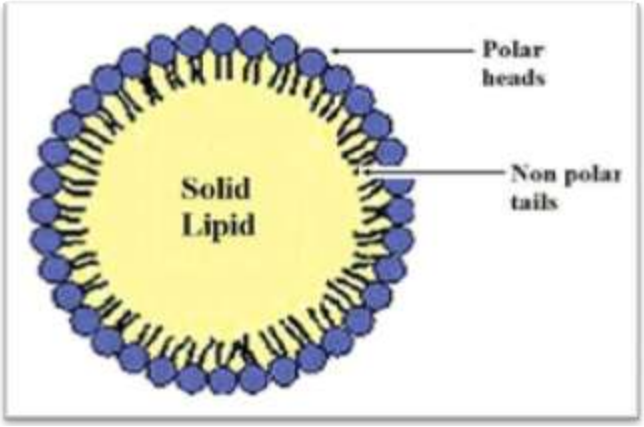

Figure 4: Solid Lipid NPs (Vyas S.P, Khar, 2002)

Nanotubes

Nanotubes are self-accumulating sheets of atoms organized into tubes (P.Velavan *et al*, 2015). They may be organic or inorganic in their constitution, and can be formulated as single or multi walled structures, carbon nanotubes have recently been introduced to this category (P.Velavan *et al*, 2015).

Carbon nanotubes (CNT) have shown substantial potential in a variety of biological applications including use as DNA and protein biosensors, ion channel blockers, bio-separators, and biocatalysts (Bianco *et al*,2005). Nanotubes have been constructed with length-to-diameter ratio of up to 132,000,000:1, which is significantly larger than any other material (P.Velavan *et al*, 2015). These cylindrical carbon molecules have novel properties which make them potentially useful in many applications in nanotechnology, electronics, optics, and other fields of materials science, as well as potential uses in architectural fields (Vyas S.P, Khar, 2002).

The ends of a nanotube may be capped with a hemisphere of the bucky ball structure (Vyas S.P, Khar,2002) .Their name is derived from their size, since the diameter of a nanotube is on the order of a few nanometers (approximately 1/50,000th of the width of a human hair), while they can be up to 18 centimeters in length (as of 2010). Nanotubes are categorized as single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs) (Vyas S.P, Khar, 2002).

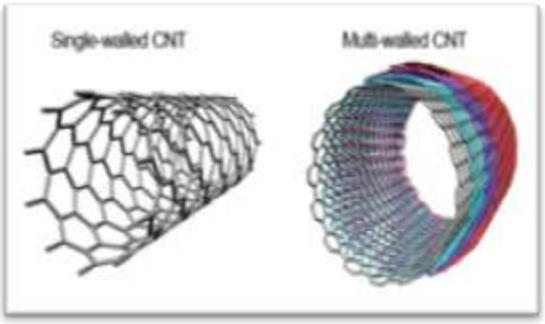

Figure 5: Nanotubes (P.Velavan *et al,* 2015).

Polymeric nanoparticles

Polymeric nanoparticles (PNPs) consists of a biodegradable polymer (Mahmoud Elsabahy, 2012). The advantages of using PNPs in drug delivery are many, being the most important that they generally increase the stability of any volatile pharmaceutical agents and that they are easily and cheaply fabricated in large quantities by a multitude of methods (P.Velavan *et al*, 2015).

Also, polymeric nanoparticles may have engineered specificity, allowing them to deliver a higher concentration of pharmaceutical agent to a desired location (Vyas S.P, Khar, 2002).The solid structure of polymeric nanoparticles gives them higher stability, uniform size distribution, and more sustained drug release profiles. It involves biodegradable synthetic polymers like polylactic co-glycolic acid (PLGA) and polycaprolactone (PCL) and natural polymers like poly peptides and polysaccharides (Mahmoud Elsabahy, 2012).

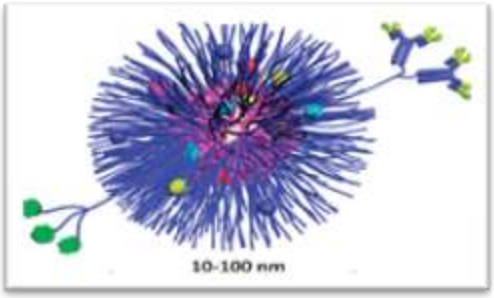

Figure 6: Polymeric nanoparticles (Mahmoud Elsabahy 2012)

Dendrimers

Dendrimers, a unique class of polymers, that presents the polymers in nanometric dimensions and are highly branched macromolecules whose size and shape can be precisely controlled (Urvashi Singh *et al* 2014). Dendrimers are fabricated from monomers using either convergent or divergent step growth polymerization. The well-defined structure, mono dispersity of size, surface functionalization capability, and stability are properties of dendrimers that make them attractive drug carrier candidates (P.Velavan *et al,* 2015). Dendrimers offer enormous capacity for solubilization of hydrophobic compounds, and can be modified with guest molecules (Urvashi Singh *et al* 2014).

Dendrimers that are involved in drug delivery and imaging are basically 10-100 nm in diameter having multiple functional groups on their surface, interpretating them ideal carriers for site specific drug delivery (V. J. Mohanraj *et al* , 2006). Studies of biomedical application of dendrimers are becoming more and more attractive especially in the field of non viral gene vector. (Urvashi Singh *et al* 2014).

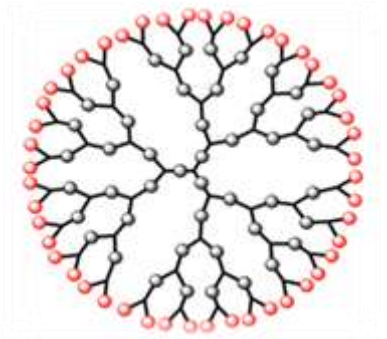

Figure 7: Dendrimers (Urvashi Singh *et al* 2014).

Nanoshells

Nanoshells are the new modified forms of targeted therapy, having core of silica and a metallic outer layer. These thin coated core particles of different material have gained considerable attention now days. The properties of nanoshells can be altered by simply tuning the core to shell ratio. (V. J. Mohanraj *et al* , 2006).

With the recent advancement in new techniques it is now possible to synthesize these nanostructures in desired shape, size and morphology (V. J. Mohanraj *et al* , 2006) . Nanoshells are synthesized to create novel structures with different morphologies, since not possible to synthesize all the materials in desired morphologies (V. J. Mohanraj *et al* , 2006). For obtaining desirable morphology core particles of different morphologies such as rods, wires, tubes, rings, cubes, etc can be coated with thin shell in core shell structures (P.Velavan *et al,* 2015). Therefore while synthesizing nanoshells expensive material is required in lesser amount than usual (P.Velavan *et al,* 2015). Targeting of nanoshells can be achieved by using immunological methods (P.Velavan *et al,* 2015). Nanoshells occupies variety of applications in diverse areas such as providing chemical stability to colloids, enhancing luminescence properties, engineering band structures, biosensors, drug delivery, etc (P.Velavan *et al,* 2015).

Nanobubbles

Nanobubbles (NBs) are nanoscaled bubble like structures that are generated in the interface of hydrophobic surfaces in liquids (P.Velavan *et al,* 2015). These nanobubbles remain stable at room temperature and when heated to physiological temperature within the body coalesce to form microbubbles (P.Velavan *et al,* 2015). The mechanism of NB formation is based on the nucleation of gas at the hydrophobic surface from a supersaturated solution, leading to trap atmospheric gases (P.Velavan *et al,* 2015).There are four types of nanobubbles: bulk, interfacial, plasmonic and oscillating nanobubbles (V. J. Mohanraj *et al* , 2006). Nanobubbles potentially exhibit advantages in targeting the tumor tissue and delivering the drug selectively under the influence of ultrasound exposure(V. J. Mohanraj *et al* , 2006).

Nanowire

A nanowire is a nanostructure, with the diameter of 10−9 meters (P.Velavan *et al*, 2015).Alternatively, nanowires can be defined as structures that have a thickness or diameter constrained to tens of nanometers or less and an unconstrained length (P.Velavan *et al*, 2015). Many different types of nanowires exist, including metallic e.g., Ni, Pt, Au, semiconducting e.g., Si, InP, GaN, etc., and insulating e.g., SiO2, TiO2 (P.Velavan *et al*, 2015).

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 (P.Velavan *et al*, 2015). Liposomes are characterized in terms of size, surface charge and number of bilayers (N. K. Jain, 2001). It exhibits number of advantages in terms of amphiphilic character, biocompatibility, and ease of surface modification rendering it a suitable candidate delivery system for biotech drugs (Vyas S.P, Khar, 2002). Liposomes have been used successfully in the field of biology, biochemistry and medicine since its origin (Vyas S.P, Khar, 2002).

Liposomes were the first nanoparticle platform applied in medicine since Bangham described them in 1961 (N. K. Jain ,2001).liposomes are nanometric (30–100 nm) versions of liposomes formed by spontaneous self-organization of phospholipids such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol and phosphatidylserine, and other molecules such as cholesterol (Vyas S.P, Khar, 2002).

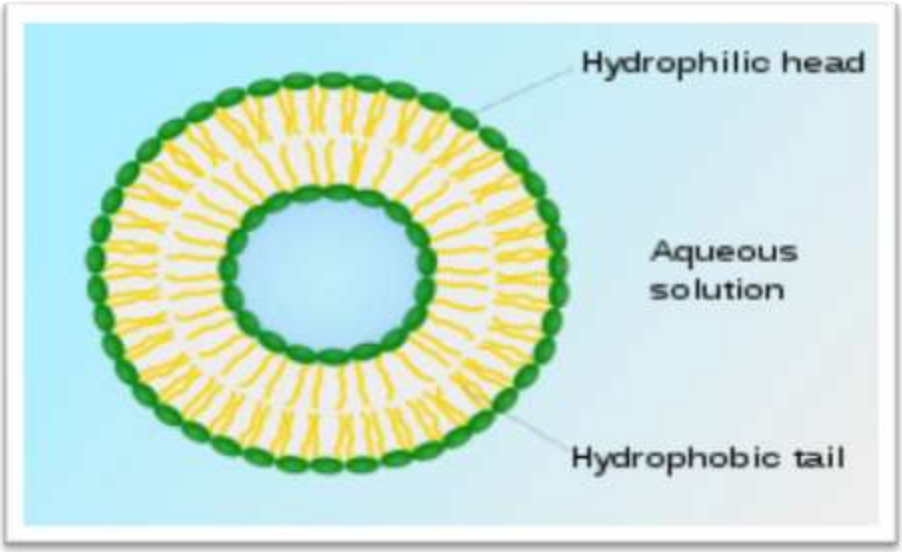

Figure 8: Liposomes ((N. K. Jain ,2001).

Nanobots

Nanorobotics is the technology of creating machines or robots at or close to the microscopic scale of a nanometer 10−9 meters (Deepak N. Kapoor, 2012) . Nanorobots are essentially nanoelectromechanical devices (NEMS) (Deepak N.Kapoor, 2012).

These nanorobotic devices are comparable to biological cells and organelles in size (Deepak N.Kapoor, 2012). It is a multidisciplinary field requiring advanced level input from different areas of science and technology including, physics, chemistry, biology, medicine, pharmaceutical sciences, engineering, biotechnology and other biomedical sciences (Deepak N.Kapoor, 2012).

Applications for nanorobotics in medicine include early diagnosis and targeted drug-delivery for cancer, biomedical instrumentation surgery, pharmacokinetics monitoring of diabetes, and health care (Deepak N.Kapoor, 2012).

Techniques for the preparation of nanoparticles

The appropriate method for the preparation of nanoparticles depends on the characteristics of polymer and the drug that is to be used in Nano preparations therefore in order to achieve the properties of interest the mode of preparation plays a vital role (Swati Tyagi *et al* ,2016).

Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection of matrix materials is dependent on factors like: (Swati Tyagi *et al*, 2016).

- Size of nanoparticles required.
- Degree of biodegradability,
- Biocompatibility and toxicity.
- Drug release profile desired.

❖ ***Nanoparticles can be prepared by following methods:***

- Emulsion Polymerization Method
- Interfacial polymerization
- Desolvation Technique
- Emulsion interfacial reaction method
- Solvent Evaporation Method
- Emulsification Or Solvent Diffusion Method
- Ionic Gelation Or Coacervation Method
- Salting out method
- Nanoprecipitation Method
- Spray drying method
- Dialysis
- Supercritical Fluid Technology

Emulsion Polymerization Method:

Emulsion polymerization is one of the fastest methods for nanoparticle preparation and is readily scalable. The method is classified into two categories, based on the use of an organic or aqueous continuous phase (Hemant K.S. Yadav *et al* ,2012). The continuous organic phase methodology involves the dispersion of monomer into an emulsion or inverse microemulsion, or into a material in which the monomer is not soluble (nonsolvent) (Hemant K.S. Yadav *et al* ,2012). Polyacrylamide nanospheres were produced by this method (Hemant K.S. Yadav *et al* , 2012). As one of the first methods for production of nanoparticles, surfactants or protective soluble polymers were used to prevent aggregation in the early stages of polymerization (Hemant K.S. Yadav *et al* ,2012). In the aqueous continuous phase the monomer is dissolved in a continuous phase that is usually an aqueous solution, and the surfactants or emulsifiers are not needed (Hemant K.S. Yadav *et al* , 2012).

The polymerization process can be initiated by different mechanisms. Initiation occurs when a monomer molecule dissolved in the continuous phase collides with an initiator molecule that might be an ion or a free radical (Swati Tyagi *et al* 2016). Alternatively, the monomer molecule can be transformed into an initiating radical by high-energy radiation, including g-radiation, or ultraviolet or strong visible light (Swati Tyagi *et al* 2016). Chain growth starts when initiated monomer ions or monomer radicals collide with other monomer molecules according to an anionic polymerization mechanism (Swati Tyagi *et al* 2016). Phase separation and formation of solid particles can take place before or after termination of the polymerization reaction (Hemant K.S. Yadav *et al* ,2012).

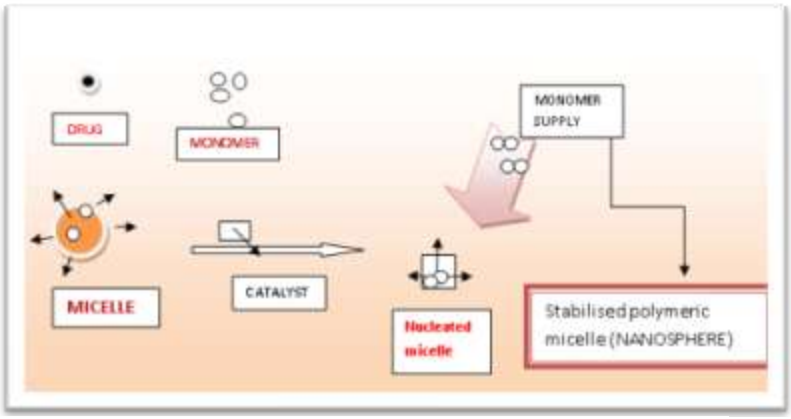

Figure 9: Poymerization Method (Niba Ibrahim *et al* 2018)

Interfacial Polymerization:

It is one of the well-established methods used for the preparation of polymer nanoparticles (Hemant K.S. Yadav *et al* , 2012). It involves step polymerization of two reactive monomers or agents, which are dissolved respectively in two phases (i.e., continuous- and dispersed-phase), and the reaction takes place at the interface of the two liquids (Hemant K.S. Yadav *et al*, 2012). Nanometer-sized hollow polymer particles were synthesized by employing interfacial cross-linking reactions as polyaddition and polycondensation or radical polymerization. Oil-containing nanocapsules were obtained by the polymerization of monomers at the oil/water interface of a very fine oil-in-water micro- emulsion (Hemant K.S. Yadav *et al* ,2012). The organic solvent, which was completely miscible with water, served as a monomer vehicle and the interfacial polymerization of the monomer was believed to occur at the surface of the oil droplets that formed during emulsification (Hemant K.S. Yadav *et al* , 2012). To promote nanocapsule formation, the use of aprotic solvents, such as acetone and acetonitrile was recommended (Hemant K.S. Yadav *et al*, 2012).

Desolvation Technique:

The protein or polysaccharide from an aqueous phase can be desolvated by P^H changes or change in temperature or by adding some appropriate counter ions **(** P.amareshwar *et al*, 2011).Aqueous drug polymer dispersion was prepared and pH was optimized to 7 . **(**P.amareshwar *et al* ,2011). The desolvating agent was added under continuous mechanical stirring.It is added intermittent or by continuous method till the solution become turbid. Appearance of turbidity in the solution indicates the end point of the process. **(** P.amareshwar *et al* ,2011).Then add 2 drops of glutaraldehyde , a cross - linking agent & allowed by continuous stirring for the next 12 hours at 700 rpm **(** P.amareshwar *et al* ,2011).The residual solvent was removed by rota evaporation. Free flowing nanoparticles were obtained are kept for air drying. **(** P.amareshwar *et al* ,2011).

- **Desolvation Technique:** Is prepared by two methods: **(** P.amareshwar *et al* ,2011).

- **Continuous method:** In this method solvent was added continuously 1ml/1 minute till the turbidity appears.
- **Intermittent method:** In this method solvent was added intermittently 1ml/5 minute till the turbidity appears.

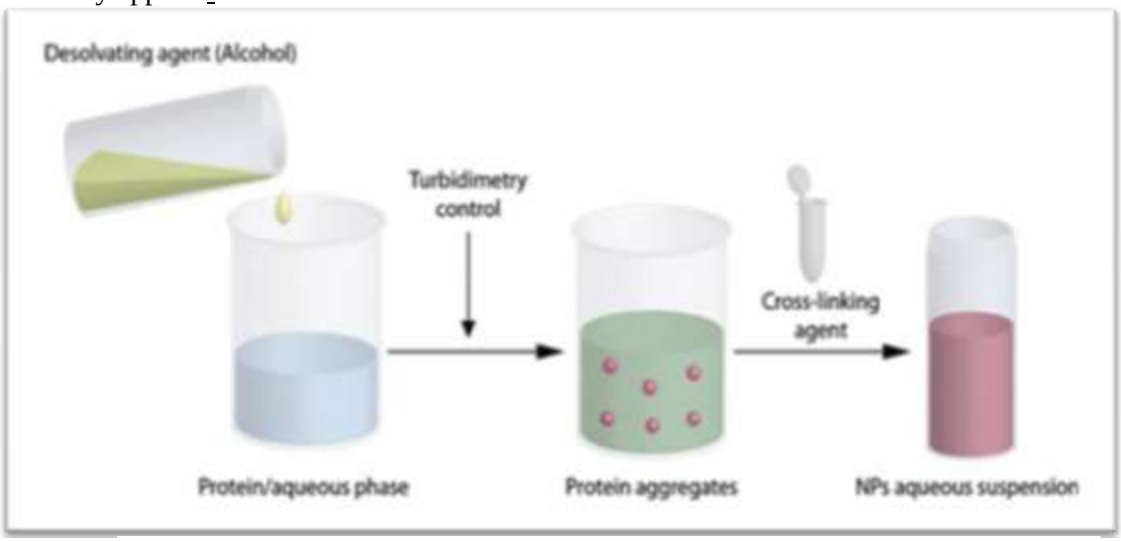

Figure 10: Desolvation Technique (Amrit Rai *et al*, 2017).

Emulsion interfacial reaction method:

For the preparation of nanoparticles by emulsion interfacial reaction method, following procedure was adopted. According to this technique (Vyas S.P, Khar, 2002).

Emulsion A: *1% (polymer) solution and 5% span 80 solution was prepared, then in a beaker 100 mg of* drug in 1 ml of methanol was taken. To this add 4 ml of polymer solution add 0.5ml of span 80 solution. It was kept for stirring at 2000 rpm for 5 mins (Vyas S.P, Khar, 2002).

Emulsion B: 0.25 ml of 2% Glutraldehyde was taken. To this 0.5 ml of span80 solution was added. Then kept for stirring at 3000 rpm for 5 mins. Then Emulsion A&B was mixed and kept for stirring at 5000 rpm for 10 mins. Finally the solution was filtered by vacuum filtration and kept for drying (Vyas S.P, Khar, 2002).

Solvent Evaporation Method:

Solvent evaporation was the first method that was developed for the preparation of nanoparticles, in this technique the polymer solutions were prepared in volatile solvents and emulsions were formulated by employing dichloromethane and chloroform, but now it is replaced with ethyl acetate that shows a much better toxicological profile to obtain polymeric particles less than 500 nm in size (Hemant K.S. Yadav *et al* , 2012). In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform or ethyl acetate, which is also used as the solvent for dissolving the hydrophobic drug (Hemant K.S. Yadav *et al* ,2012). The mixture of polymer and drug solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent to form oil in water (o/w) emulsion (Hemant K.S. Yadav *et al* ,2012). After the formation of stable emulsion, the organic solvent is evaporated either by reducing the pressure or by continuous stirring (Swati Tyagi *et al* 2016). Particle size was found to be influenced by the type and concentrations of stabilizer, homogenizer speed and polymer concentration (Swati Tyagi *et al* 2016). In order to produce small particle size, often a high-speed

homogenization or ultrasonication may be employed, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature or under reduced pressure resulting in the formation of solidified nanosized particles, collected by ultracentrifugation followed by washing to remove surfactants and at last the product is lyophilized (Swati Tyagi *et al* 2016).

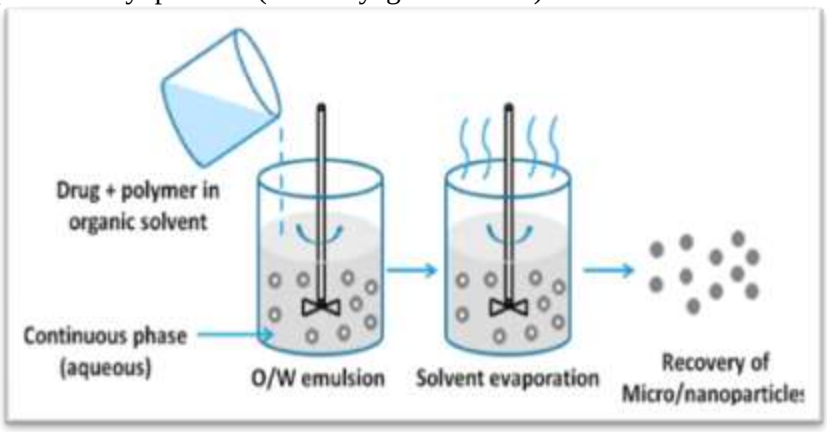

Figure 11: Solvent evaporation method (Swati Tyagi *et al* 2016).

Emulsification Or Solvent Diffusion Method:

This is a modified version of solvent evaporation method. In this method, the water miscible solvent like acetone along with a small amount of the water immiscible organic solvent like chloroform is used as an oil phase (Hemant K.S. Yadav *et al*, 2012). Due to the spontaneous diffusion of solvents an interfacial turbulence is created between the two phases leading to the formation of small particles (Hemant K.S. Yadav *et al*, 2012). As the concentration of water miscible solvent increases, a decrease in the size of particle can be achieved (Hemant K.S. Yadav *et al* ,2012). Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. (Hemant K.S. Yadav *et al*, 2012). In the case of hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved n the internal aqueous phase (Hemant K.S. Yadav *et al*, 2012).

As with some of the other techniques, this one is efficient in encapsulating lipophilic drugs (Hemant K.S. Yadav *et al* ,2012). Several drug-loaded nanoparticles were produced by this technique, including mesotetra (hydroxyphenyl) porphyrin-loaded PLGA (p-THPP) nanoparticles, doxorubicin-loaded PLGA nanoparticles, plasmid DNA-loaded PLA nanoparticles, coumarin-loaded PLA nanoparticles, indocyanine ,cyclosporine (Cy-A)-loaded gelatin and cyclosporin (Cy-A)-loaded sodium glycolate nanoparticles (Hemant K.S. Yadav *et al*. 2012).

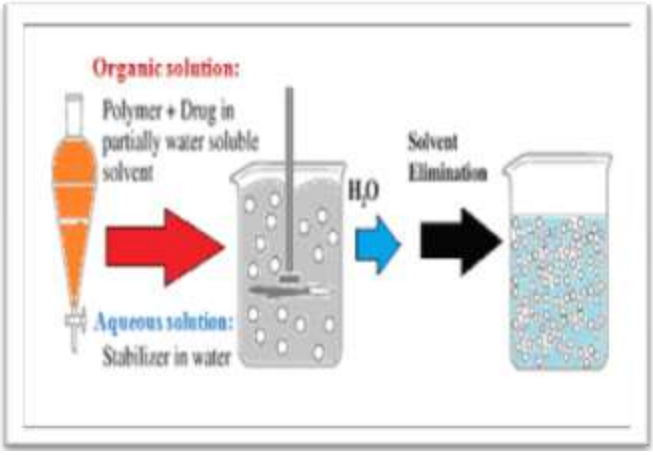

Figure 12: Emulsification Or Solvent Diffusion Method (Hemant K.S. Yadav 2012).

Ionic Gelation Or Coacervation Method:

Ionic gelation technique, also known as ion induced gelation. (Swati Tyagi *et al* 2016).By using biodegradable hydrophilic polymers (such as chitosan, gelatin and sodium alginate etc) nanoparticle prepared by Coacervation method. (*Calvo et al)*prepared nanoparticles by ionic gelation method which involves two aqeous phases. (Swati Tyagi *et al,* 2016).

First phase contain polymer like chitosan, a di-block co-polymer like ethylene oxide or propylene oxide (PEO-PPO). Second phase contain polyanion sodium tripolyphosphate. Between these two phases electrostatic interaction occurs which forms coacervates. coacervates are formed with a size in the range of nanometer(Renu tiruwa ,2015). Coacervates are formed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature (Renu tiruwa ,2015).

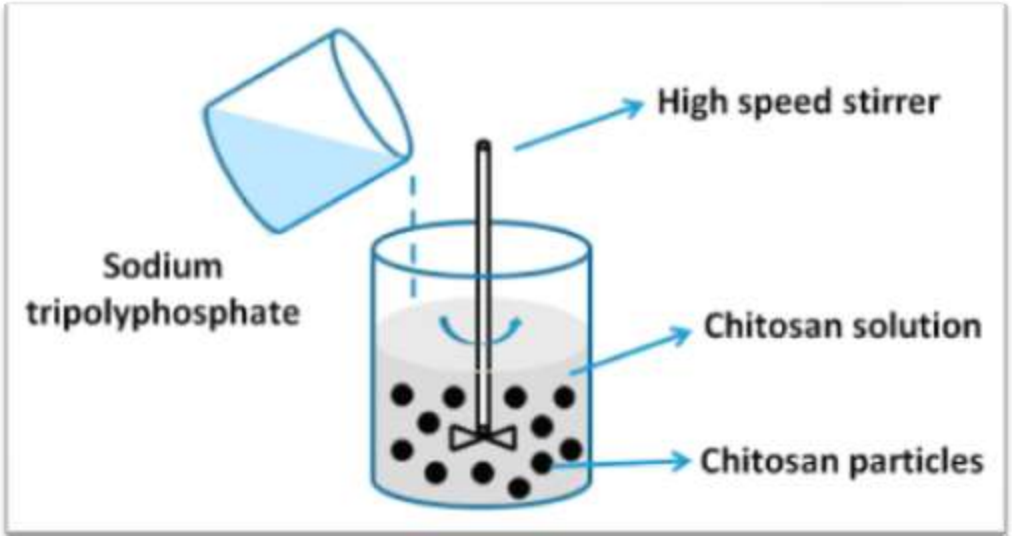

Figure 13: Ionic gelation method (Swati Tyagi *et al,* 2016).

Salting out method:

This technique was introduced and patented by *Bindschaedler et al. and Ibrahim et al.* Salting out method is very close to solvent-diffusion method (Swati Tyagi *et al,* 2016). This technique based on the separation of water-miscible solvent from aqueous solution by salting out effect. (Swati Tyagi *et al,* 2016). In this method toxic solvents are not used. (Swati Tyagi *et al,* 2016).

Generally acetone is used because it is totally miscible with water and easily removed. initially polymer and drug are dissolved in a solvent such as acetone, then it emulsifies into an aqueous gel consisting a salting-out agent in it as electrolytes such as magnesium chloride, calcium chloride, and magnesium acetate, or non- electrolytes such as sucrose (Hemant K.S. Yadav *et al,* 2012). Importance of technique depends upon the type of salting out agent used, as it play an important property of encapsulating efficiency of the drugs because the solvent and the salting out agent are then eliminated by cross-flow filtration (Hemant K.S. Yadav *et al,* 2012). This technique does not require an increase in temperature and stirring energy required for lower particle size. This technique used in the preparation of PLA, poly (methacrylic) acid, nanospheres leads to high efficiency and is easily scaled up (Hemant K.S. Yadav *et al,* 2012).

The main advantage of salting out is that it minimizes stress to protein encapsulants. Salting out does not require an increase of temperature and therefore, may be useful when heat sensitive substances have to be processed (Hemant K.S. Yadav *et al,* 2012).

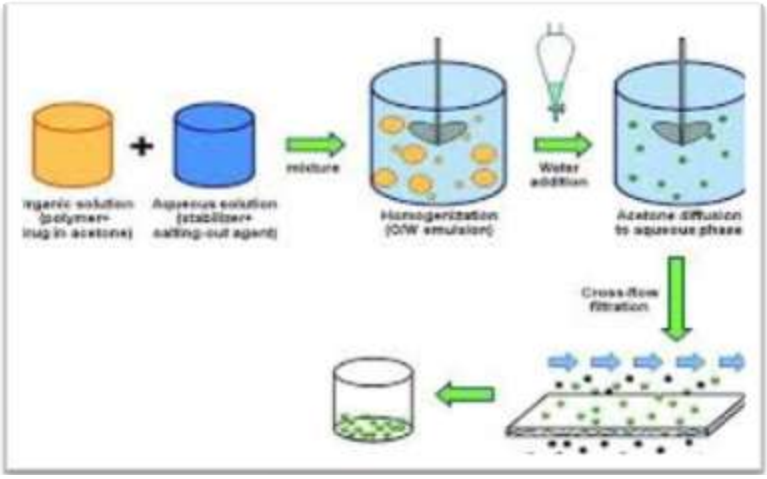

Figure 14: Salting out technique (Swati Tyagi *et al* 2016).

Nanoprecipitation method

This method is widely used for the preparation of nanoparticles, which is also called solvent displacement method (Hemant K.S. Yadav *et al*, 2012).

Nanoprecipitation is a facile, mild, and low energy input process to carry out polymeric nanoparticles synthesis which is also termed as solvent displacement method. (Hemant K.S. Yadav *et al*, 2012). The process of preparing involves preformed polymer of organic solution (acetone, ethanol, or methanol) and then in the presence or absence of surfactant the organic solvent is allowed to diffuse generally using polymer Poly-Lactic Acid (PLA) (Hemant K.S. Yadav *et al*, 2012).

The polymer PLA of intermediate polarity is allowed to dissolved in a water-miscible solvent, resulting in formation of nanospheres and the solution is injected into an aqueous solution containing stabilizer as a surfactant as to result the formation of nanoparticles due to interaction between the water and the organic solvent (Renu tiruwa ,2015).The nanoparticles synthesized through the process are of submicron size (<210 nm) with of low polydispersity. Biodegradable nanocarriers such as lipid or polymer based nanoparticles that were designed to enhance the efficacy of nanoparticles and reduce the toxic effects of drugs that results from therapeutic delivery of drugs for treatment of diseases. (Renu tiruwa ,2015).

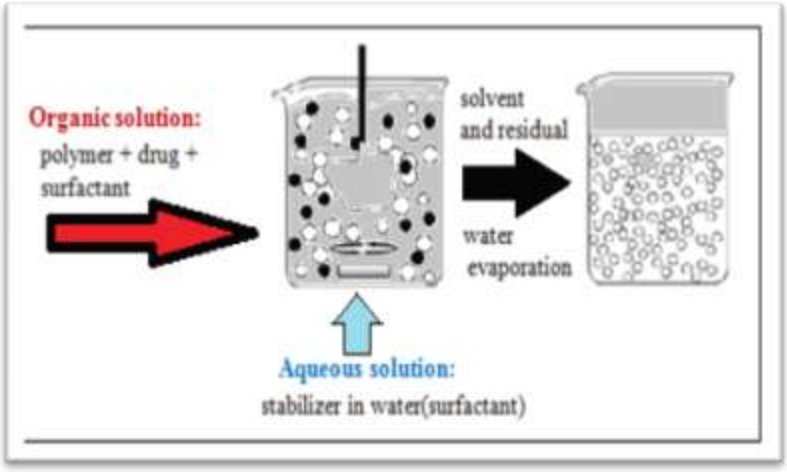

Figure 15: Nanoprecipitation method (Hemant K.S. Yadav 2012)

Spray drying method

In this method, chitosan is first dissolved in acetic acid; the drug is dissolved or dispersed in the solution and then a suitable cross-linking agent is added; this solution or dispersion is then atomised in a stream of hot air (Vyas S.P, Khar ,2002). Atomization leads to the formation of small droplets, from which the solvent evaporates, leading to the formation of free-flowing powders[1]. Particle size depends upon size of the nozzle, spray flow rate, atomisation pressure and inlet air temperature, and extent of cross-linking (Vyas S.P, Khar, 2002).

Dialysis

Dialysis is a simple and effective method for the preparation of small, narrow-distributed nanoparticles synthesis in which polymer is dissolved in an organic solvent and placed inside a dialysis tube with proper molecular weight cut off and the displacement of solvent inside the membrane is followed by the progressive aggregation of polymer due to a loss of solubility and the formation of homogeneous suspensions of nanoparticles (Swati Tyagi *et al* ,2016). whereas, it is based on the use of a physical barrier, specifically dialysis membrane or common semi permeable membranes that allow the passive transport of solvents to slow down the mixing of the polymer solution with a non-solvent; the dialysis membrane contains the solution of the polymer (Swati Tyagi *et al* ,2016).

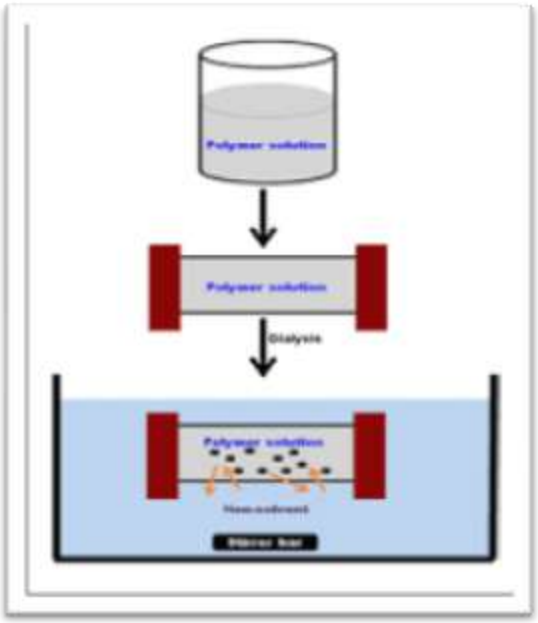

Figure 16: Dialysis (Swati Tyagi *et al* 2016)

Supercritical fluid technology

Supercritical fluid is defined as a solvent at a temperature above its critical temperature, at which the single phase regardless of pressure moreover , the technology has been used as an alternative to prepare biodegradable micro and nanoparticles because supercritical fluids are environmentally safe (Swati Tyagi *et al* 2016). The need to develop environmentally safer methods for the production of nanoparticles has motivated research on the utility of supercritical fluids as more environmental friendly solvents, with the potential to produce nanoparticles with high purity and without any trace of organic solvent (Swati Tyagi *et al* 2016).

Two principles have been developed for the production of nanoparticles using supercritical fluids: (Hemant K.S. Yadav 2012).

1. Rapid expansion of supercritical solution (RESS) (Hemant K.S. Yadav 2012).
2. Rapid expansion of supercritical solution into liquid solvent (RESOLV) (Hemant K.S. Yadav 2012).

CO2 is most widely used as supercritical fluid because of its mild conditions, non-toxicity, non-flammability where this fluid along with dense gas technology are expected to offer an interesting and effective technique of particle production , avoiding most of the drawbacks of the traditional methods . This technique is environmentally friendly, suitable for mass production and is more expensive (Swati Tyagi *et al* 2016).

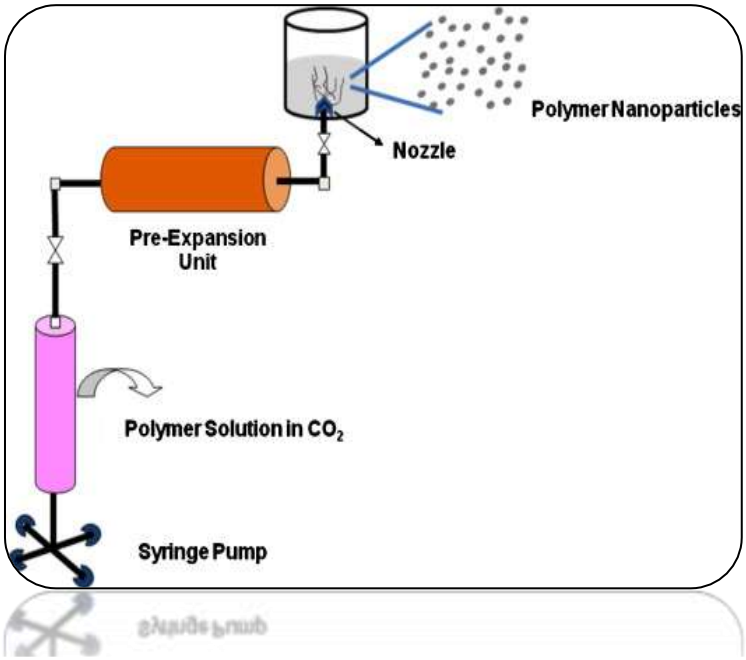

Figure 17: Supercritical fluid technology (Swati Tyagi *et al* 2016).

CONCULSION

The main aim of this study is to describe the different preparation techniques available for production of nanoparticles. Nanoparticles became very popular drug delivery system as it increases the stability and protects drug molecules from rapid degradation. The drug-loaded nanospheres or nanocapsules now can be produced by simple, safe, and reproducible techniques available. The technique for the preparation of NP's are more challenging as an important challenge is to obtain materials with well-defined structures and morphologies including wide range of physical, chemical, biological, physiological factors and conditions that must be taken into account for successful preparation and bio- fictionalization of nanoparticles for a given biomedical application.

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