Chapter-03

TECHNIQUES USED FOR POLYMERIC NANOPARTICLES

[1]Dr. NARENDER YADAV

[1]Assistant Professor, School of Pharmaceutical Sciences,
Apeejay Stya University, Gurugram

[2]Prof. ANUPAMA DIWAN

[2]Professor, School of Pharmaceutical Sciences,
Apeejay Stya University, Gurugram

Ch. Id:-ASU/GRF/EB/NDDS/2022/Ch.03
DOI: https://doi.org/10.52458/9789391842871.2022.eb.grf.asu.ch.03

INTRODUCTION

Polymeric nanoparticles (PNPs) are characterized as particulate dispersions or solid particles with a size in the range of 10-1000nm. There has been great scientific interest in the area of drug delivery, using particle delivery methods as carriers for small and large molecules. Particulate systems such as nanoparticles have been employed as a physical technique to alter and improve the pharmacokinetic and pharmacodynamic aspects of numerous types of medicinal molecules. Polymeric nanoparticles have been intensively explored as particulate carriers in in pharmaceutical and medical, industries because they show promise as drug delivery systems as a result of their controlled and sustained release capabilities, subcellular size, and biocompatibility with tissue and cells. Several methods to manufacture polymeric nanoparticles have been established and these strategies are classed according to whether particle creation needs a polymerization reaction or whether nanoparticles form directly from a macromolecule or premade polymer. Polymeric nanoparticles (PNPs) are made from biocompatible and biodegradable polymers in size between 10-1000 nm where the drug is dissolved, entrapped, encapsulated, or linked to a nanoparticle matrix. Depending upon the method of preparation nanoparticles, nanospheres or nanocapsules can be generated. Nanocapsules are systems in which the drug is confined to a cavity enclosed by a unique polymer membrane, while nanospheres are matrix systems in which the medication is physically and uniformly spread. The field of polymer nanoparticles (PNPs) is quickly increasing and playing a significant role in a wide range of sectors spanning from electronics, photonics, conducting materials, sensors, medicine, biotechnology, pollution control, and environmental technology. PNPs are potential vehicles for drug delivery by easy manipulation to prepare carriers with the purpose of delivering the pharmaceuticals to specific target, such an advantage enhances the drug safety. Polymer-based nanoparticles successfully deliver drugs, proteins, and DNA to target cells and organs. Their nanometer size improves effective penetration across cell membranes and stability in the bloodstream. Polymers are particularly convenient materials for the fabrication of endless molecular patterns that can be incorporated into unique nanoparticle constructions with many potential medical uses. Several ways have been established during the last two decades for manufacture of PNPs, these strategies are classed according to whether the particle formation involves a polymerization reaction or nanoparticles form directly from a macromolecule or premade polymer or ionic gelation method.

Advantages of polymeric nanoparticles

Enhances the stability of any volatile pharmaceutical ingredient in a manner that is simple, economical, and scalable for large-scale production

- They are far more efficient and effective than traditional oral and intravenous methods of drug administration.
- Delivers a medicinal agent in a more concentrated form to the location of your choice.
- The choice of polymer and the ability to change how drugs are released from polymeric nanoparticles make them ideal for cancer therapy, the delivery of vaccines, contraceptives, and targeted antibiotics.
- Polymeric nanoparticles can be easily integrated into various drug delivery-related operations, including tissue engineering.

Polymers used in preparation of nanoparticles:

- Polymers must be compatible with the body in terms of adaptability (non-toxicity) and antigenicity (non-antigenicity), as well as biodegradable and biocompatible.
- Natural polymers: Chitosan, Gelatin, Sodium alginate, and Albumin are the most often used natural polymers for creating polymeric nanoparticles.
- Numerous synthetic polymers exist, such as
  - Polylactides (PLA)
  - Polyglycolides (PGA)
  - Poly(lactide co-glycolides) (PLGA)
  - Polyanhydrides
  - Polyorthoesters
  - Polycyanoacrylates
  - Polycaprolactone
  - Poly glutamic acid
  - Poly malic acid
  - Poly(N-vinyl pyrrolidone)
  - Poly(methyl methacrylate)
  - Poly(vinyl alcohol)
  - Poly(acrylic acid)
  - Poly acrylamide
  - Poly(ethylene glycol)

- Poly(methacrylic acid)

MECHANISMS OF DRUG RELEASE

The polymeric drug carriers transfer the drug to the target tissue via either of three general physicochemical methods.

- By hydration-induced swelling of the polymer nanoparticles, followed by diffusion-mediated release.
- By an enzymatic response that results in rupture, cleavage, or degradation of the polymer at the site of administration, where the medication is released from the imprisoned inner core.
- Dissociation of the drug from the polymer and sorption/release of the drug from the swollen nanoparticles.

TECHNIQUES CAN BE USED TO ATTAINED POLYMERIC NANOPARTICLES

The properties of PNPs must be optimised based on the application in question. In order to attain the desired qualities, the method of preparation is crucial. In order to get PNPs with the appropriate properties for a certain application, it is incredibly advantageous to possess the requisite preparation processes. Various processes, including polymerization, premade polymers, and ionic gelation, are employed. Methods for preparing nanoparticles from premade polymer dispersion. Preparing biodegradable nanoparticles from poly (lactic acid) (PLA), poly (D, L-glycolide) (PLG), poly (D, L-lactide-coglycolide) (PLGA), and poly (cyanoacrylate) often involves dispersing the medication in premade polymers (PCA). Various techniques can be used to attained PNP are outlined **Figure 3.1**.

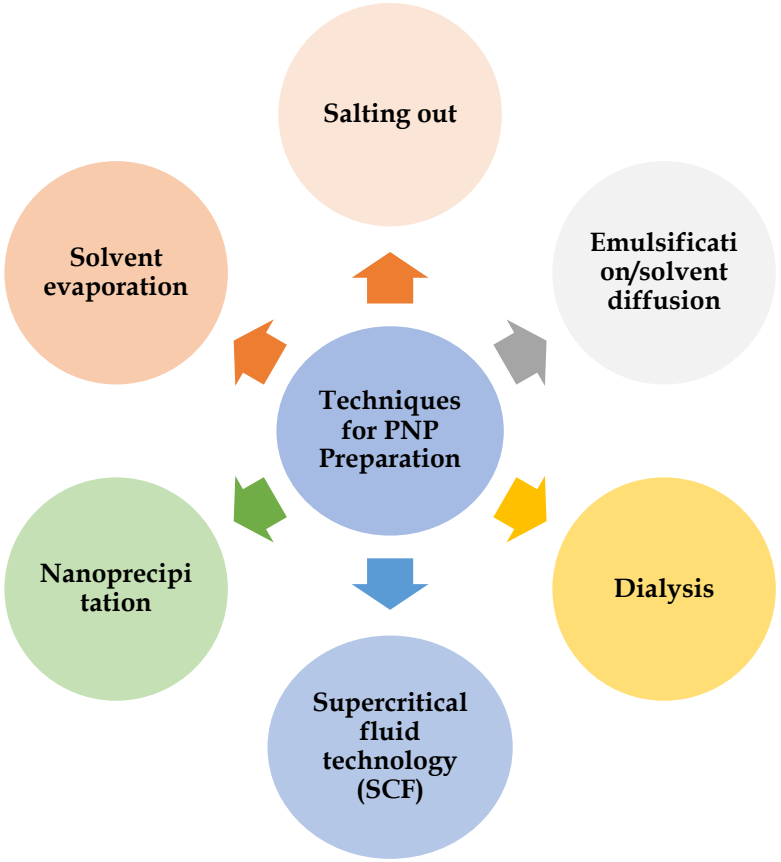

Figure 3.1: Different Techniques for PNP Preparation

Solvent Evaporation

The initial approach devised for preparing PNPs was solvent evaporation. **Figure 3.2** illustrates the technique. In this procedure, polymer solutions are formed in volatile solvents, and emulsions are formulated. Dichloromethane and chloroform-preformed polymers were commonly utilised in the past, but have been supplanted by ethyl acetate, which has a more favourable toxicological profile. The emulsion is transformed into a nanoparticle suspension upon the evaporation of the polymer's solvent, which is permitted to diffuse through the emulsion's continuous phase. For the development of emulsions, typical procedures employ either the preparation of single-emulsions, such as oil-in-water (o/w), or double-emulsions, such as (water-in-oil)-in-water (w/o)/w. These procedures involve high-velocity homogenization or ultrasonication, followed by evaporation of the solvent via continuous magnetic stirring at ambient temperature or at decreased pressure. Once the nanoparticles have solidified,

they can be collected by ultracentrifugation and cleaned with distilled water to remove additives such as surfactants. Finally, PLGA nanoparticles of approximately 200nm are lyophilized using dichloromethane 1.0 percent (w/v) as the solvent and PVA or Span 40 as the stabilising agent. PLGA produced nanoparticles with a typical particle size of 60 to 200 nm using dichloromethane and acetone (8:2, v/v) as the solvent system and PVA as the stabilising agent. Frequently, homogenization at high speed or ultrasonication is applied to achieve small particle size.

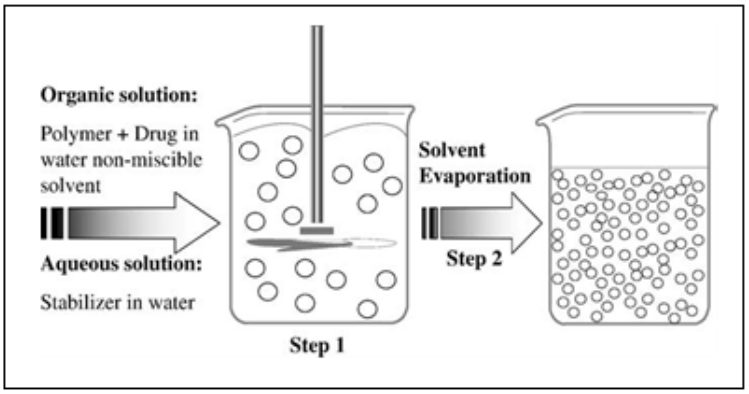

Figure 3.2: Schematic Representation of Solvent Evaporation Technique

Nanoprecipitation:

Nanoprecipitation is sometimes referred to as the solvent displacement technique. **Figure 3.3** llustrates the technique. It involves the precipitation of a preformed polymer from an organic solution and the diffusion of an organic solvent in an aqueous medium, with or without a surfactant. The polymer, typically PLA, is dissolved in a water-miscible solvent of intermediate polarity, resulting in nanosphere precipitation. This phase is injected into a surfactant-stabilized aqueous solution that has been agitated. Instantaneous production of a colloidal suspension is the result of polymer deposition at the interface between water and organic solvent produced by rapid diffusion of the solvent. To aid the creation of colloidal polymer particles in the first step of the technique, phase separation is carried out with a completely miscible solvent that is also insoluble in the polymer. The solvent displacement technique enables the production of nanocapsules by incorporating a little amount of non-toxic oil into the organic phase. When preparing nanocapsules, high loading efficiencies for lipophilic medicines are typically observed when considering the oil-based central chambers of the nanocapsules. This straightforward procedure is only applicable to water-miscible solvents in which the diffusion rate is sufficient to generate spontaneous emulsification.

Therefore, spontaneous emulsification is not observed if the coalescence rate of the produced droplets is sufficiently high, despite the fact that some water-miscible solvents cause a degree of instability when mixed with water. Although acetone/dichloromethane (ICH, class 2) are used to dissolve and increase the trapping of pharmaceuticals, the dichloromethane increases the average particle size and is hazardous. Due to the miscibility of the solvent with the aqueous phase, this approach is primarily relevant to lipophilic medicines and is ineffective for encapsulating water-soluble pharmaceuticals. Numerous polymeric polymers, including PLGA, PLA, PCL, and poly (methyl vinyl ether-comaleic anhydride) (PVM/MA), have been processed using this approach. This approach proved well-suited for the inclusion of cyclosporin A, since entrapment efficiencies as high as 98% were achieved. Using the solvent displacement approach, highly loaded nanoparticulate systems based on amphiphilic h-cyclodextrins were produced.

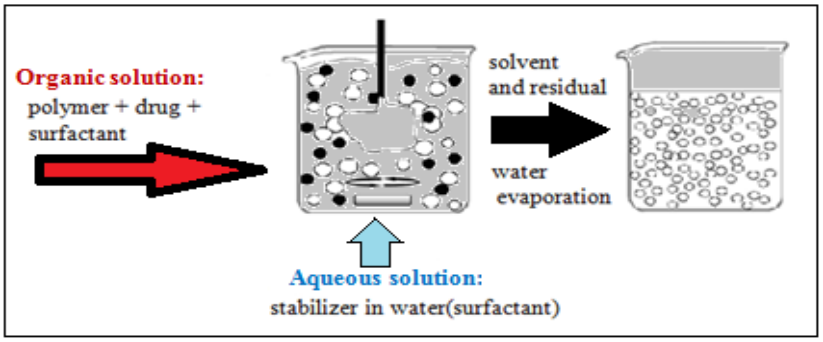

Figure 3.3: Schematic Representation of the Nanoprecipitation Technique

Emulsification/Solvent Diffusion (ESD)

This method modifies the solvent evaporation technique. The encapsulating polymer is dissolved in a solvent that is somewhat water-soluble, such as propylene carbonate, and saturated with water to guarantee initial thermodynamic equilibrium between the two liquids. To produce the precipitation of the polymer and the subsequent formation of nanoparticles, it is necessary to promote the diffusion of the solvent of the dispersed phase by dilution with an excess of water when the organic solvent is partially miscible with water or with a different organic solvent in the opposite case. Subsequently, the polymer-water saturated solvent phase is emulsified in an aqueous solution containing a stabiliser, resulting in the diffusion of solvent to the exterior phase and the creation of nanospheres or nanocapsules based on the oil-to-polymer ratio. **Figure 3.4** illustrates the technique. This approach has various advantages, including high encapsulation efficiency (usually greater than 70 percent),

minimal need for homogenization, excellent batch-to-batch reproducibility, simplicity, ease of scaling up, and a limited size distribution. High volumes of water must be removed from the suspension, and the water-soluble drug may leak into the saturated-aqueous exterior phase during emulsification, lowering encapsulation efficiency. As with previous procedures, this one is effective for encapsulating lipophilic medicines. ESD was used to produce a number of drug-loaded nanoparticles, 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.

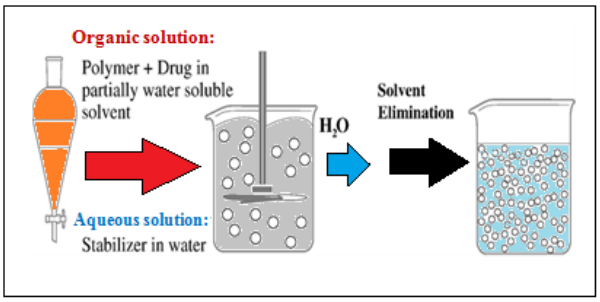

Figure 3.4: Schematic Representation of the Emulsification/Solvent Diffusion Technique

Salting Out:

Salting out relies on the salting out effect to separate a water-miscible solvent from an aqueous solution. The salting-out process is a variation of the emulsification/solvent diffusion process. Polymer and drug are first dissolved in a solvent such as acetone, which is then emulsified into an aqueous gel containing the salting-out agent (electrolytes such as magnesium chloride, calcium chloride, and magnesium acetate, or non-electrolytes such as sucrose) and a colloidal stabiliser such as polyvinylpyrrolidone or hydroxyethylcellulose. The selection of the salting-out agent is crucial, as it can have a significant impact on the efficacy of the drug's encapsulation. Via cross-flow filtration, both the solvent and the salting-out agent are then eliminated. This method for preparing poly (methacrylic) acid, poly (lactic acid), and nanospheres is highly efficient and scalable. The primary benefit of salting out is that it reduces the burden placed on protein encapsulants. Salting out does not necessitate an increase in temperature, therefore it may be effective for processing heat-sensitive compounds. The major disadvantages are limited use to lipophilic pharmaceuticals and extensive nanoparticle cleaning procedures. **Figure 3.5** illustrates the technique.

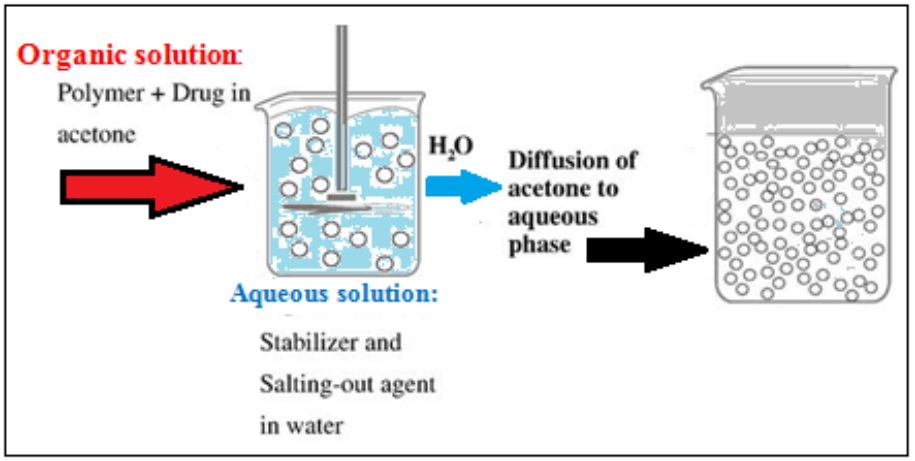

Figure 3.5: Schematic Representation of the Salting Out Technique

Dialysis:

Dialysis is a simple and effective way to make PN that is small and has a narrow distribution. Polymer is dissolved in an organic solvent and put in a dialysis tube with the right molecular weight cut off. Dialysis is done with a non-solvent that doesn't mix with the solvent. When the solvent moves out of the membrane, the polymer starts to stick together because it is no longer soluble. This leads to the formation of homogeneous suspensions of nanoparticles. At the moment, we don't fully understand how PNP is made by the dialysis method. It may work in a way similar to how nanoprecipitation works, which was proposed by Fessi et al. Through this method, a number of polymer and copolymer nanoparticles were made. DMF was used as the solvent to make nanoparticles of poly (benzyl-l-glutamate)-b-poly(ethylene oxide) and poly (lactide)-b-poly(ethylene oxide). The shape and size distribution of the nanoparticles are affected by the solvent used to make the polymer solution. Chronopoulou et al. wrote about a new method (**Figure 3.6**) that uses osmosis to make both natural and artificial PNP. It works by using a physical barrier, like a dialysis membrane or other semipermeable membranes, to slow down the mixing of the polymer solution with a non-solvent. The dialysis membrane holds the polymer solution.

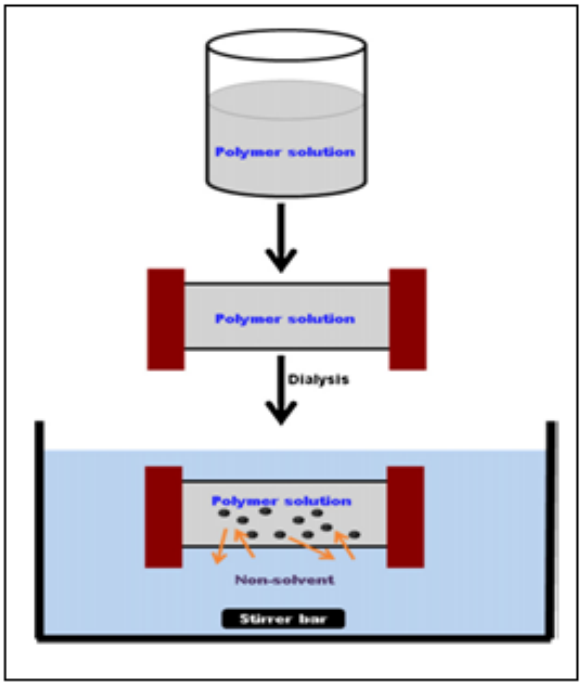

Figure 3.6: Schematic Representation of Osmosis based Method for Preparation of Polymer Nanoparticles

Supercritical Fluid Technology

The need to find ways to make PNP that are safer for the environment has led to research on the use of supercritical fluids as more environmentally friendly solvents. These fluids could be used to make PNPs that are very pure and have no trace of organic solvent. Supercritical fluid and dense gas technology are thought to offer a way to make particles that is interesting and effective, while avoiding most of the problems with traditional methods. Using supercritical fluids to make nanoparticles has led to the development of two main ideas:

- Rapid expansion of the supercritical solution (RESS)
- Rapid expansion of the supercritical solution into a liquid solvent (RESOLV).

Rapid expansion of supercritical solution

In traditional RESS, the solute is mixed with a supercritical fluid to make a solution. The solution is then quickly spread out into ambient air through an orifice or capillary nozzle. The high level of supersaturation and the rapid drop in pressure

during expansion lead to homogeneous nucleation and the formation of particles that are spread out evenly. Mechanistic studies of different model solutes for the RESS process show that the expansion jet has particles that are both nanometer- and micrometer-sized. Using RESS to make PNPs was the subject of some research. Poly droplets, made of perfluoropolyetherdiamide, are made when CO2 solutions grow quickly. The main parts of the RESS experimental equipment are a high-pressure mixing cell made of stainless steel, a syringe pump, and a pre-expansion unit. At room temperature, a polymer solution in CO2 is made. Before the solution leaves the nozzle, it is pumped to the preexpansion unit and heated isobarically to the preexpansion temperature. The supercritical solution is then allowed to expand through the nozzle at normal pressure. The polymer's concentration and degree of saturation have a big effect on the size and shape of the particles in RESS. **Figure 3.7** illustrates the technique.

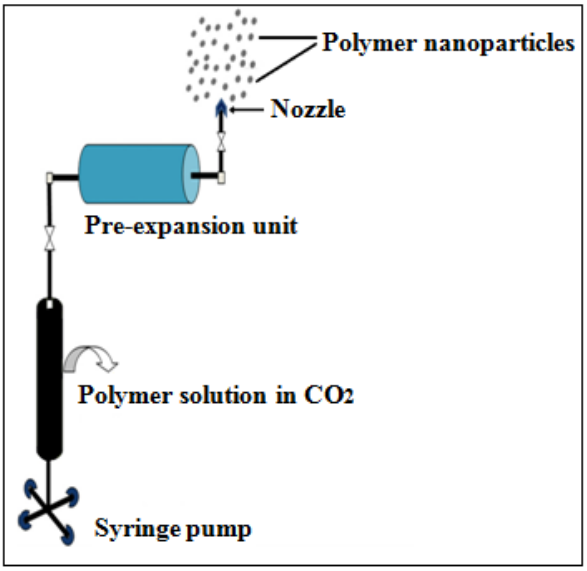

Figure 3.7: Schematic Representation for Preparation of Polymer Nanoparticles by Rapid Expansion of Supercritical Fluid Solution

Rapid expansion of supercritical solution into liquid solvent

A simple but important change to RESS is to let the supercritical solution expand into a liquid solvent instead of the surrounding air. This is called RESOLV. The average size of heptadecafluorodecyl acrylate poly nanoparticles is less than 50 nm. In the RESS method, no organic solvents are used to make PNPs. However, the main products made with this method are not nanoscale, but rather microscale. This is the biggest problem with RESS. In order to get around this problem, RESOLV, a new

supercritical fluid technology, has been made. In RESOLV, the liquid solvent seems to stop the particles from growing in the expansion jet, so mostly nanosized particles can be made. **Figure 3.9** illustrates the technique.

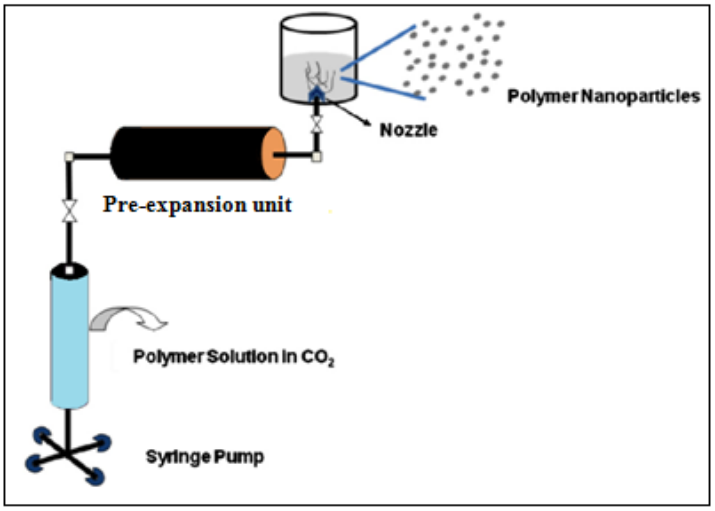

Figure 3.9: Schematic Representation for Rapid Expansion of Supercritical Fluid Solution into The Liquid Solvent Process

CONCULSION

The main purpose of this chapter was to talk about the different ways that polymeric nanoparticles can be made. It was seen that making PNPs is a cutting-edge technology that needs the right method from the many that are available. Nanospheres or nanocapsules that are filled with drugs can now be made using simple, safe, and repeatable methods. Depending on the physical and chemical properties of a drug, you can choose the best way to prepare it and the polymer to make nanoparticles with the size range you want and a good ability to trap the drug.