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Drug particle engineering of poorly water soluble drugs

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Abstract

Poor aqueous solubility is a major issue in the pharmaceutical industries for dosage form development. A limiting factor for in vivo performance of these drugs after oral administration is their inadequate ability to be wetted by and dissolved into the fluid in the gastrointestinal tract. Particle engineering techniques are tools to modify the physicochemical, micromeritics and biopharmaceutical properties of the poorly soluble drug and hence solubility. In the present review different approaches of particle engineering technology like mechanical techniques, evaporative precipitation into aqueous solution, controlled precipitation, supercritical fluid technologies, freezing techniques, sonication technology etc. which improve the aqueous solubility of drugs are discussed.

INTRODUCTION

Many potentially bioactive molecules have been rejected during the early stages of development because of their poor water soluble and difficulty to wet. It has been reported that about 40% of compounds being developed by the pharmaceutical industries are poorly water soluble [1, 2]. The term "poorly soluble" is defined as requiring 1000 or more part water to dissolve 1 part solute [3]. The poorly water soluble and highly permeable drugs discussed in the Biopharmaceutical Classification System Class II (BSC II) are of particular interest [4, 5]. A limiting factor for *in vivo* performance of these drugs after oral administration is their inadequate ability to be wetted by and dissolved into the fluid in the gastrointestinal (GI) tract. Such drugs often demonstrate low bioavailability when administered orally. Therefore, increasing the dissolution rate of these drugs is an important and significant challenge to pharmaceutical scientists in order to maximize absorption.

Various formulation strategies have been investigated to improve solubility and dissolution rate of poorly water soluble drugs such as inclusion complexation with cyclodextrins, solid dispersion, salt formation, particle size reduction, use of surfactants, cosolvency etc.

The drug solubility and particle size can be correlated by the Ostwald–Freundlich equation which shows that solubility is inversely proportional to particle radius. So reducing the particle size and thus increasing the surface area will increase the dissolution rate of poorly water soluble drugs [6]. Particle engineering techniques are tools to modify the physicochemical, micromeritics and biopharmaceutical properties of the drug. In the present review different approaches of particle engineering technology which improve the aqueous solubility of drugs are discussed.

Particle size can be reduced by two approaches. In the first approach the particle is broken down to smaller size, whereas in the second approach the particle will be built up from molecules [7]. Schematic representation of two general particle size reduction techniques is as shown in Figure 1.

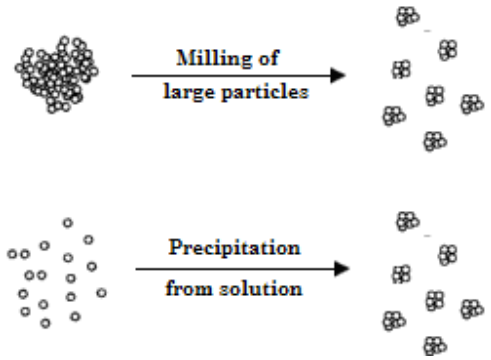

Figure 1: Schematic representation of two general particle size reduction techniques.

The various particle engineering techniques used to are as follows

A. Mechanical Techniques
   1. Wet Milling
   2. High-pressure homogenization

B. Precipitation Techniques
   1. Antisolvent precipitation
      a. Evaporative Precipitation into Aqueous Solution
      b. Controlled Precipitation.
   2. Supercritical fluid technologies
      a. Rapid Expansion from Supercritical Solutions (RESS)
      b. Gas Anti Solvent Recrystallization (GAS)
      c. Precipitation with Compressed Fluid Anti Solvents (PCA)
      d. Supercritical Anti Solvent (SAS)
   3. Freezing Techniques
      a. Spray freezing into liquid
      b. Ultra-Rapid freezing

C. SONICATION TECHNOLOGY
   1. Solution Atomization & Crystallization by Sonication (SAXS)

A. Mechanical Techniques

Particle size reduction by milling of poorly soluble drugs is a common approach used for many years in the pharmaceutical industry. Here the material is subjected to stress resulting in breakage of the particle [7]. The standard microparticles produced by milling have particle size about 5 µm. The formation of particles below 1µm is a challenge due to aggregation of high surface area materials. Until now, two such mechanical processes were commercialized. First, the wet milling technique, NanoCrystals technology, was developed and patented in 1992 by Liversidge et al and formerly owned by Sterling Drug Inc., later acquired by Elan Corporation [8-11]. The second process is a high pressure homogenization process, DissoCubes technology, which was developed and patented by Müller et al in 1994 and formerly owned by the Drug Delivery Services GmbH in Germany and now owned by SkyePharma PLC [8, 9].

A.1. Wet Milling

Wet milling is an attrition process in which large micron size drug crystals are wet milled in the presence of grinding media and a surface modifier. The rigid grinding media is typically spherical in form, having an average size less than about 3 mm. The grinding media used in the process include zirconium oxide, such as 95% ZrO stabilized with magnesia, zirconium silicate, and other media, such as glass grinding media stainless steel, titania, alumina, and 95% ZrO stabilized with yttrium [9, 10]. The surface modifiers include various polymers, low molecular weight oligomers, natural products and surfactants, such as polyvinyl pyrrolidone, pluronic F68, pluronic F108, and lecithin. High-energy-generated shear forces and the forces generated during impaction of the milling media with the solid drug provide the energy to fracture drug crystals into nanometer-sized particles [11].

A. 2. High Pressure Homogenization

High pressure homogenization is another mechanical process to prepare nanometer size particle in suspensions containing poorly water soluble drugs. Procedure involves dispersal of a drug powder in an aqueous surfactant solution and passing through a high-pressure homogenizer, producing nanosuspensions. The cavitation force generated is sufficient to disintegrate the drug from microparticles to nanoparticles. The particle size is dependent on the various factors like hardness of the drug substance, the processing pressure, and the number of cycles applied. A few points have to be considered, such as chemical instability of fragile drugs under harsh production conditions, Ostwald ripening in long-term storage, toxicity of surfactants and batch-to-batch variation in crystallinity level [12].

B. Precipitation Techniques

The various precipitation techniques involve the dissolution of a drug into a solvent and then precipitation in an antisolvent or evaporation of the solvent. The processes differ by the type of solvent/antisolvent and the temperature and pressure at which the technique is carried out. Surfactants and stabilizers typically are incorporated into either or both the antisolvent and the solvent [13].

B. 1. Antisolvent precipitation

B.1.a. Controlled Precipitation

Controlled precipitation process involves dissolution of drug and stabilizers within a water-miscible solvent, which is then dispersed within an aqueous solution in a controlled manner.

Upon introduction into the aqueous solution, solvent power of the organic solution is lost which leads to nucleation and precipitation of the dissolved drug. Stabilizers and crystal growth inhibitors can be added in both the organic and the aqueous phase. Adsorption of the stabilizers to the particle surface prevents particle growth. Solvent can be removed by any desirable means including evaporation, dialysis and distillation [13-15]. Schematic representation of controlled precipitation is as shown in Figure 2.

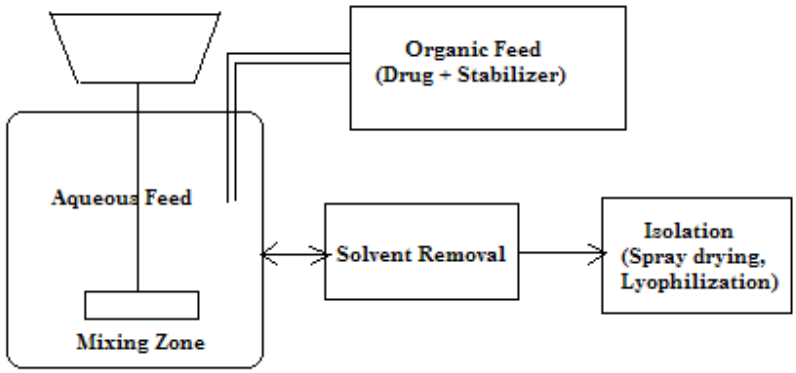

Figure 2: Schematic Representation of Controlled Precipitation.

B.1.b. Evaporative precipitation into aqueous solution (EPAS)

In the evaporative precipitation into aqueous solution (EPAS) process, the poorly soluble drug precipitates owing to evaporation of the organic solvent near or above the boiling point and contact with an aqueous solution. The drug is dissolved in low boiling organic solvents including diethyl ether, methylene chloride, ethyl acetate, dimethyl ether. This solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's normal boiling point. The pressure should be sufficient enough to maintain a liquid phase. The solution is sprayed through a fine atomizing nozzle into a heated aqueous solution. The upper temperature limit will depend upon the operating pressure, but is probably low enough so as not to degrade the drug but high enough to evaporate the solvent but not evaporate too much of the water. Rapid evaporation of the organic solvents produces large supersaturation of the drugs and rapid precipitation of the drug to produce amorphous particles. A particle stabilizer is added to the organic solution, the aqueous solution or both to optimize particle formation and stabilization. The stabilizers adsorb on to the newly formed drug particle surface, consequently decreasing the surface energy and providing steric and/or electrostatic repulsion between particles. The drug particles are recovered by removing the water from the particles. Removing the water can be performed using any technique including spray drying, lyophilization, drying with cold air and filtration [16, 17]. Schematic representation of EPAS is as shown in Figure 3.

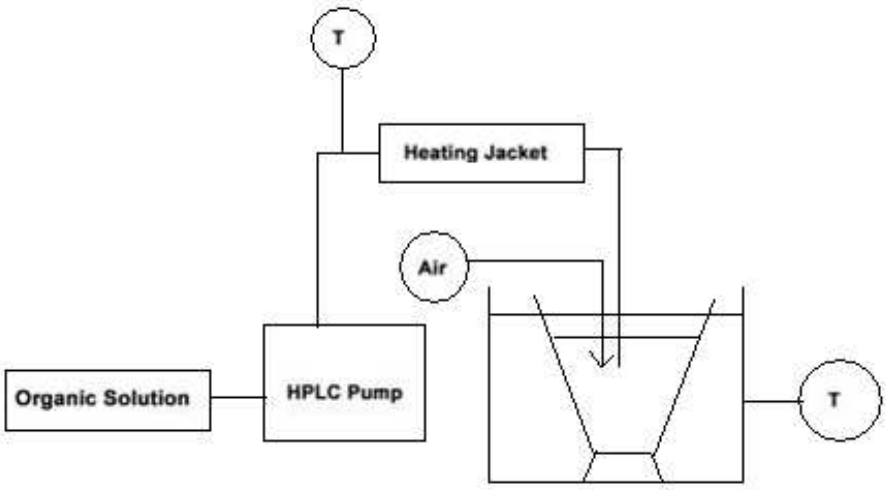

Figure 3: Schematic representation of EPAS

B. 2. Supercritical fluid technologies

A supercritical fluid (SCF) can be defined as a dense noncondensable fluid. A fluid reaches the supercritical status when its temperature and pressure exceed the relevant critical temperature and pressure. At the critical point only a single phase exist which has some properties typical of liquids (density) and some of gases (viscosity, compressibility, and mass diffusion coefficient). Therefore, a SCF can behave as a solvent, since the solvent power is proportional to density. A SCF is dense but compressible and any change of pressure alters its density and consequently the solvent power. For pharmaceutical applications, the most widely used SCF is carbon dioxide (more than 98% of the applications have been developed using this fluid) because of its low and easily accessible critical temperature (31.2 $^{\circ}$C) and pressure (7.4MPa), non-flammability, non-toxicity and inexpensiveness [18].

B. 2. a. Rapid Expansion from Supercritical Solutions (RESS)

In RESS process, the solute is first dissolved in a supercritical fluid, then the solution is rapidly expanded (decompression) by passing through a heated nozzle at supersonic speed. During the rapid expansion of the supercritical solution, the density and solvent power decrease dramatically, leading to a supersaturation of the solution and subsequent precipitation of solute particles. Sufficient solubility of the material to be processed in the SCF is the major prerequisite for the use of RESS process and the particle sizes achieved by this process are influenced by various factors like the temperature, pressure, nozzle geometry, and solution concentration. But drawback of this technique is that of low solubility of some drugs and surfactants in supercritical CO_2. However, this process is advantageous due to the absence of organic solvent and the uniform condition of particle formation [18, 19]. Schematic representation of the RESS process is as shown in Figure 4.

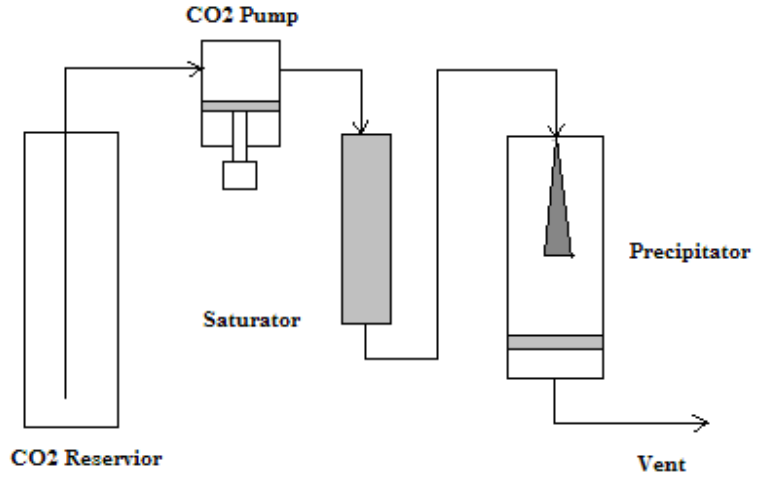

Figure 4: Schematic representation of the RESS process.

B. 2. b. Gas Anti Solvent Recrystallization (GAS)

In the GAS technique, first solute is dissolved in a good solvent followed by the introduction of supercritical fluid in the gaseous state (anti solvent gas) into that solution which results in precipitation of the solute. In this process, the size distribution of precipitate depends on the rate of addition of the supercritical fluid. The most important requirement for this technique is that the carrier solvent and the supercritical fluid anti solvent must be at least partially miscible [20-22]. Schematic representation of the GAS process is as shown in Figure 5.

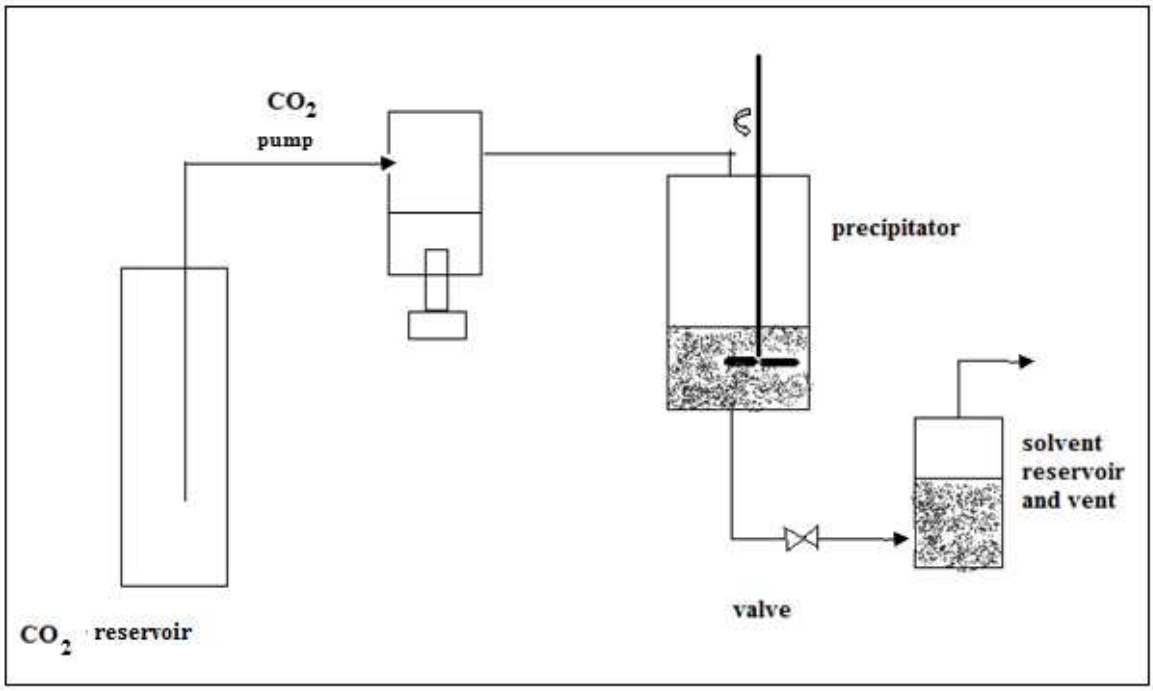

Figure 5: Schematic representation of the GAS process.

B. 2.c. Supercritical Anti Solvent Technique (SAS)

In this technique, first solute is dissolved in a good solvent then the solution is fed into a pressure vessel under supercritical conditions, through a nozzle (i.e. sprayed into supercritical fluid anti solvent). When the solution is sprayed in to supercritical fluid anti solvent, the anti solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses in to the anti solvent. Because the supercritical fluid expanded solvent has lower solvent power than the pure solvent, the mixture becomes supersaturated resulting in the precipitation of the solute and the solvent is carried away with the supercritical fluid flow [23]. Schematic representation of SAS technique is as shown in Figure 6.

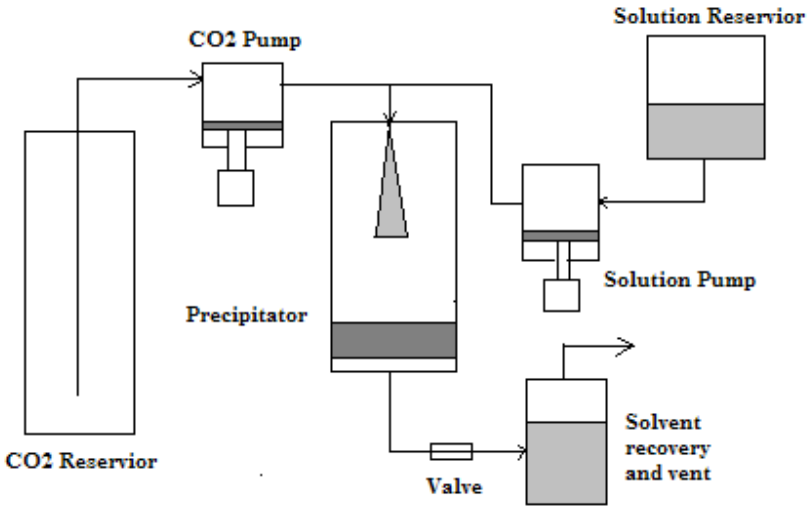

Figure 6: Schematic representation of SAS technique.

B.2.d. Precipitation with Compressed Fluid Anti Solvents (PCA)

In this process, the drug is first dissolved in an organic solvent and then the solution is sprayed into a liquid or supercritical CO_2 where the two liquids collide and intense atomization into micronized droplets occurs. Microparticles or nanoparticles of drugs are formed by two way mass transfers: extraction of the organic solvent into CO_2 and CO_2 diffusion into the droplets [23]. Schematic representation of PCA process is as shown in Figure 7.

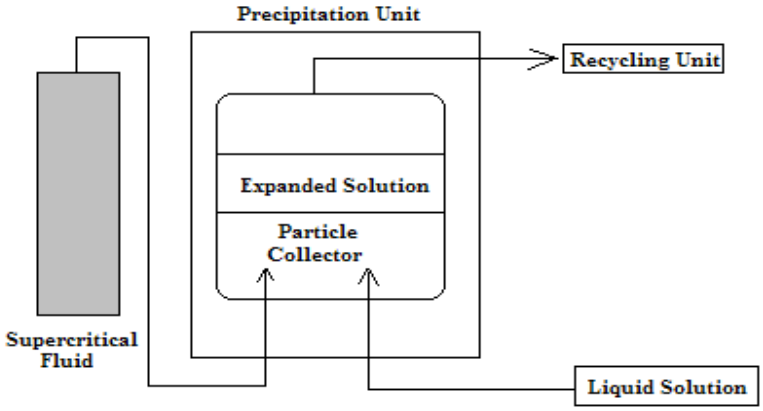

Figure 7: Schematic representation of PCA process.

B.**3 Cryogenic technologies**

Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low temperature conditions. After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze drying, atmospheric freeze drying, vacuum freeze drying and lyophilisation [24].

B.3.a. Spray freezing into liquid (SFL)

When an organic or aqueous-organic co-solvent solution of drug and pharmaceutical excipient(s) is pumped into a cryogenic liquid such as compressed CO_2, helium, propane, ethane or the cryogenic liquids including nitrogen, argon or hydro fluroetheres through an insulating nozzle results in intense atomization of the droplets. Rapid freezing of these droplets causes large super saturation and rapid nucleation rates of dissolved substance which leads to small primary particles on the order of 10nm to 10 micron after drying. The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders. The amorphous structure, high surface area, and enhanced wetability of the SFL nanostructured particles were the predominant characteristics of the poorly water soluble drug that enhanced dissolution [3, 25]. Schematic representation of SFL process is as shown in Figure 8.

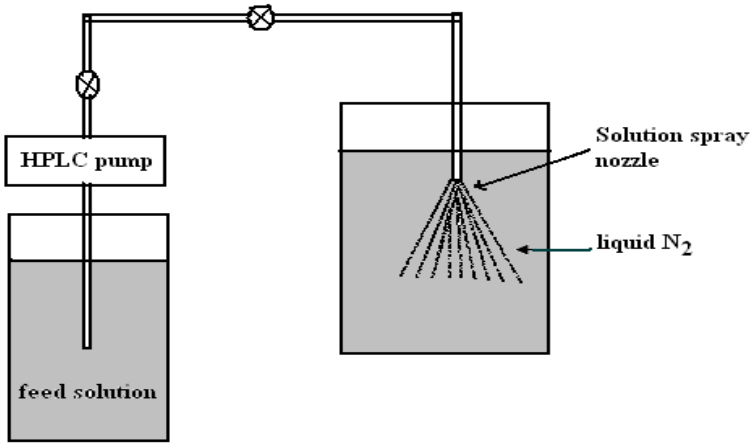

Figure 8: Schematic representation of SFL process.

B.3.b. Ultra Rapid Freezing (URF)

Ultra-rapid freezing (URF) technology involves the use of a solid cryogenic substrate with a thermal conductivity between 10 and 20 W/m degrees K. A solution of the drug is applied to the solid surface of the substrate, where instantaneous freezing takes place. Brownian motion of the particles in solution is slowed significantly, so reactive species have little time to react before being frozen into the solid state. Removal of the frozen particles and lyophilization of the solvent produces stable amorphous drug particles. URF technology has been shown to produce uniform, amorphous, drug particle/excipient aggregates. Additionally, the process is continuous, allowing for improved scale-up applications [26, 27]. Schematic representation of URF process is as shown in Figure 9.

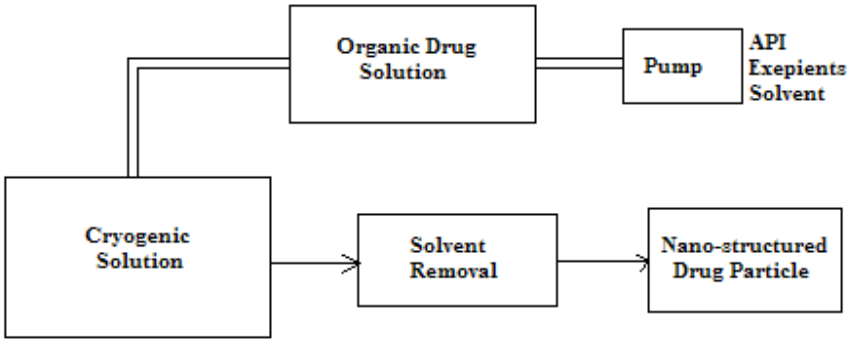

Figure 9: Schematic representation of URF process.

C. Sonication technology

C.1. Solution Atomization & Crystallization by Sonication (SAXS)

This is a single-stage processing technique that uses ultrasonic waves to produce increased sphericity in crystalline particles within a well-defined particle size range. The SAXS process consists of three interdependent processes:

i. The production of aerosol droplets of the solute from a carrier solvent using a suitable aerosol generator to produce highly supersaturated spherical constructs of the drug within a well-defined particle size for controlled crystallization. Although not limited to any particular atomization system, but use of an electrohydrodynamic (EHD) atomization system and a conventional air pressure atomizer is reported in literature.

ii. The collection of the highly supersaturated droplets in a crystallization vessel containing a nonsolvent of the drug. A common nonsolvent used was Cyclohexane (surface tension 24.98 mu/m).

iii. The application of ultrasonic waves to a crystallization vessel to control and induce homogeneous nucleation and crystal growth. The ultrasonic frequency is continually swept at a frequency of between 35 KHz and 45 KHz.

By combining these processes and controlling relevant parameters, high-purity micron-size, sphere-like crystalline particles could be readily produced in a single-step (solution to particle) operation [28].

The applications of various particle engineering techniques are shown in Table 1.

Table 1: Applications of Various Particle Engineering Techniques

Sr. No.	Technique	Drugs Studied	Reference
1.	Wet milling	Naproxen	11
2.	High Pressure Homogenization	Atovaquone	13
3.	Controlled precipitation	Gemfibrozil Rifabutin	29 30
4.	EPAS	Carbamazepine Cyclosporine	31 32

5.	RESS	Salicylic acid	33
6.	GAS	Theophylline	34
7.	PCA	Soy lecithin	35
8.	SAS	Camptothesin	36
9.	SFL	Danazol	37
10.	URF	Repaglanide	26
11.	SAXC	Paracetamol	38

CONCLUSION

Drug particle engineering techniques for poorly water soluble drugs including wet milling, high pressure homogenization, controlled precipitation , EPAS, RESS, SAS, GAS, PCA, SFL, URF and SAXS techniques have been discussed. These techniques have successfully incorporated poorly water soluble drugs alone or with excipients into the microparticles or nanoparticles with significantly improved *in vitro* dissolution rate and *in vivo* bioavailability. In conclusion, particle engineering technologies for poorly soluble drugs is a promising area for continued research with the aim of improving their bioavailability and therapeutic effectiveness.

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