Antisolvent Crystallization of Poorly Water Soluble Drugs

Abhijit A. Lonare and Sanjaykumar R. Patel

***Abstract*—The enhancement in bioavailability of the drugs is one of the most important concerning aspects of the pharmaceutical industries. Preparation of nanoparticles or microparticles of these drugs is the newest formulation strategies. The size and morphology of a drug are affecting several essential pharmaceutical properties. In general, the drug delivery system needs narrow particle size distribution with regular particle shape, particularly, an engineered drug particles to meet biopharmaceutical and processing needs. An antisolvent crystallization technique is being used to prepare nanoparticles or microparticles for poorly water soluble drugs at research scale. This method has an ability to change the solid-state properties of pharmaceutical substances including the modification of crystal formation and particle size distributions. Therefore, various operating variables and their effect on the particle size of poorly water soluble drugs in an anti-solvent crystallization have been reviewed.**

***Index Terms*—Antisolvent, crystallization, poorly water soluble drugs, ultrasound.**

I. Introduction

Approximately 40% of drugs in the industry are falling in the category of low solubility–high permeability (Class II), and low solubility–low permeability (Class IV). These classes have the limited bioavailability of drugs due to their low solubility and dissolution rate [1]. The bioavailability is defined as the percentage of the quantity of the drug absorbed compared to its initial quantity of dosage, which can be improved by a decrease in their particle size [2]. The dissolution rate of the active pharmaceutical ingredient (API) is proportional to the available surface area for dissolution as described by the Noyes–Whitney equation and, in addition, by an increasing the solubility of nanosized API is also expected to enhance the dissolution rate as described by the Ostwald–Freundlich equation [3].

Nanoparticles can be obtained either by top-down approach or bottom-up approach [4]. The top down approach involve the mechanically reduction of previously formed larger particles by the technologies available like; jet milling, pearl mill, spiral media milling technology, and high pressure homogenization. However, these techniques are not efficient due to high energy input and denaturation during the milling process [5]. In contrast, the approach known as ‘‘bottom up’’ which includes antisolvent precipitation technology is rarely applied. As compared to milling and high pressure homogenization (top-down approach), antisolvent precipitation (‘‘bottom up’’ approach) is simple, cost effective, and easy to scale-up [6]. Also, Anti-solvent crystallization can be used as a substitute for cooling or evaporation crystallization. An anti-solvent crystallization can alter the physical properties of pharmaceutical substances including the modification of crystal formation and particle size distributions. In addition, water can be used as an anti-solvent as it has a low solubility toward most drug compounds and the relatively high miscibility with few of polar solvents. Therefore, additional experimental parameters like; ultrasonic waves can be applied through the crystallization process. The use of ultrasound during the crystallization process is known to affect the rate of nucleation and crystal growth and, also, it can alter the physical properties of the resulting particles. Primarily, it is applied to reduce the particle size of the crystals [7]. Hence, in the present paper, effect of operating variables on anti-solvent crystallization of poorly water soluble drugs have been surveyed relating to crystal size distribution and their morphology.

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II. Antisolvent Crystallization Process

Anti-solvent crystallization is the separation and purification method which is used as an effective way to prepare micro to nano-size drug particles [3]. This technique produces crystals from solutions and controls the crystalline properties such as particle size and their morphology [8]. The use of the antisolvent in crystallization reduces the solubility of a solute in the solution and to induce rapid crystallization. The physical and chemical properties of the antisolvent can alter the rate of mixing with the solutions and thereby affect the rate of nucleation and crystal growth of the crystallizing compounds. Additionally, parameters of crystallization experiments strongly influence the mechanism of particle formation and govern the form of crystal size and its distribution [9]. Generally, the antisolvent contains hydrophilic stabilizer (i.e. Surfactants) which is absorbed on the crystal surface to inhibit crystal growth. Hydroxypropyl methylcellulose (HPMC) is a non-toxic in nature and has good hydrophilic property which is widely used as thickening, emulsifying and stabilizing agent in food and pharmaceutical formulations [10]. However, this technique involves some basic problems, i.e. Difficulty in maintaining the size of the particles produced after precipitation, usually with a rapid growth rate which leads to a broad particle size distribution (PSD). The technique involves dissolution, followed by precipitation and then drying. Thus, the mechanical energy input is minimized but the resulting nanoparticles might be crystalline or amorphous and also depending on the process conditions. Even if the particles are crystalline, the crystal growth rate must be controlled to limit the particle size [11]. Also, Poor micromixing during anti-solvent process leads to accidental zones of local

supersaturation and, therefore, aggregation of particles. In contrast, ultrasound proves to be a feasible mixing method to provide uniform conditions throughout the vessel during antisolvent process.

III. Ultrasound Assisted Antisolvent Crystallization

Now a day, ultrasound has received much attention to be used as an effective measure to influence the nucleation in crystallization processes. The use of ultrasonic waves in crystallization has been increased at laboratory scale because; (i) rapid and uniform nucleation throughout the sonicated volume leads to smaller and uniform-sized particles, and (ii) reduction of agglomeration of particles and controlling the number of nuclei [11]. The mean particle size and its distribution can be effectively controlled by adjusting ultrasound variables such as the power intensity and ultrasonic time during crystallization. Sonocrytallization can also be used for the high energy materials which are sensitive to friction and impact during size reduction by mechanical means [12].

When ultrasound waves propagate through a liquid medium, its power will initiate an important phenomenon known as cavitation. The formations of cavitational bubbles are occurring during the negative pressure period of the sound wave. These bubbles will grow up to their resonance size and then they implode, generating a localized hot spot with a high temperature and pressure including the release of powerful shock waves. The power of ultrasound and cavitation phenomena will initiate the nucleation and thereby crystal growth in a crystallization process. The use of ultrasound may also influence the solubility and thereby the supersolubility. It can also alter the crystal habit as the ultrasound can increase or decrease the growth rate of certain crystal faces. Localized hot spots may influence the crystal lattice and have some effect on the crystal habit change due to abrasion [13].

IV. Effect of Operating Variables

A. Effect of Drug Concentration

The drug concentration and the size of the precipitated particles are inversely proportional to each other. The size of precipitated drug particles decreases with an increase in the drug concentration. This proportion is interpreting the dependency of the nucleation rate on the concentration of the drug in their solutions from which the drug is crystallized. Degree of supersaturation can alter the rate of nucleation and it depends on the concentration of drug solution. The high rate of nucleation is responsible for the creation of a large number of nuclei, which leads to the increase in the number of crystals and hence, it could make the size of each crystal smaller. Park and Yeo [9] have observed that the crystal habit of Roxithromycin was not influenced by concentration of the drug solution up to some level. But, further increase in the concentration at a higher level, the resultant particles tend to agglomerate together during the course of the precipitation, which lead to a poor distribution in both size and shape of the final product. This phenomenon observed might be due to the formation of the number of nuclei at the solvent/antisolvent interface and the influence on the viscosity by drug concentration. Large number of nuclei decreases the diffusion from solvent to antisolvent and lead to particle aggregation [6], [14], [15]. An increase in the viscosity of the drug solution hinders the drug diffusion between solution and antisolvent and results in non-uniform supersaturation and agglomeration. Kakran *et al.* [15] observed reverse trend at the higher stirring speed (1000 rpm) that the size of particles decreased as the concentration was increased from 5 to 15 mg/ml. From this observation, this can be interpreted that as mixing increases; the supersaturation effect dominates the agglomeration effect of drug concentration. Therefore, the smaller particles are produced at the higher stirring speed at even at higher drug concentrations.

B. Effect of Drug Solution Flow Rate

The rate of mixing between the solution and the antisolvent (injection rate) controls the particle size. The faster and slower mixing of the two liquid media produces smaller and the larger crystals, respectively. At a low flow rate, mixing efficiency of solvent/antisolvent becomes lower which increase the prolonged crystal growth process and results in the formation of larger crystals. In contrast, increasing the flow rate increases the mixing of the amount of solvent/anti-solvent per unit time results in the shortest of time for allowing the crystal growth and forms smaller crystals. On the other hand, Kakran *et al.* [6] observed that there was no significant decrease in the diameter of the curcumin particle with an increase in the flow rate due to the fact that the crystal growth of curcumin occurs in one direction leads to needle-shape crystals [6], [15], [16].

C. Effect of Temperature

Theory of crystallization suggests that the rate of nucleation is inversely proportional to temperature. So, the temperature is considered as an important governing factor which can control the final particle size and its distribution. When the crystallization occurs at higher temperatures, general observation indicates that the larger crystals are produced. Zhang *et al.*, [4] observed that the precipitated particles have a mean size of about 2 μm at 30 ℃ with an irregular flake like morphology; while the particles obtained at 3 ℃ presented rod like morphology with size around 240nm. At low temperature, the solubility of the drug in the solvent-antisolvent mixture decreases which results in the higher supersaturation condition. Therefore, Low temper-ature would decrease the diffusion and growth kinetics at the crystal boundary layer interface. As a result, smaller drug particles are obtained at low temperature [4], [6], [17], [18].

D. Effect of the Solvent to Antisolvent (SAS) Volume Ratio

A solvent to antisolvent volume ratio is an important parameter which affects the particle size. As the ratio increases the particle size decreases drastically. When the drug solution is added to the antisolvent, rapid reduction in the drug concentration occurs with an increase in the amount of antisolvent leading to rapid precipitation of the drug into

nanoparticles. Furthermore, a greater amount of antisolvent lead to a greater nucleation rate and produces smaller nuclei and simultaneously the growth occurs. In the subsequent growth, the higher antisolvent amount increases the diffusion distance for growing species and consequent diffusion becomes the limiting step for the growth nuclei [6], [15]. The nucleation rate is more dependent on supersaturation in comparison with the crystal growth rate and greatly affects the final particle size distribution. There is an inversely proportionality between the critical size and the logarithm of the supersaturation ratio. Therefore, high supersaturation condition results in small particles due to the formation of large number of nuclei [17].

E. Effect of Stirring Speed

The stirring speed is an important parameter because it affects on the mixing phenomena between solvent to ant solvent leading to a reduction in the solubility of solute in a solvent. An overall phenomenon is that increasing the stirring speed decreases the size of the particles due to the intensification of the micromixing (i.e. Mixing on the molecular level) between the multi-phases. Increasing the micromixing efficiency increases the mass transfer and the rate of diffusion between the multiphases and generates a high homogenous supersaturation, which induces the rapid nucleation to produce smaller drug particles. When the stirring speed goes higher up, the high intense speed produces a large amount of heat energy which enhances the temperature leading to increase in the nanoparticle size [4], [6], [15]-[19].

F. Effect of Ultrasound

Now a day, the use of ultrasound wave in the antisolvent crystallization has been increased drastically to produce the smaller size crystals with uniform in morphology. The influence of an ultrasonic wave on particle size can be studied by changing three basic parameters: ultrasound addition time, ultrasonic power intensity, and the time at which the sonication is applied. The particle size is mostly observed as to decrease with the increase in ultrasonic power input. This phenomenon is attributed to the increase in erosion effect on the surface of large crystals with an increase in ultrasonic power and hence, crystal can agglomerate. The other parameter, sonication time is also responsible to decrease the particle size to a certain extent. Prolong sonication time provides more persisting cavitation bubbles and increases the probability of collision between the particles. When the collision occurs, it generates the large number of nuclei and causes the subsequent reduction in particle size. Ultrasound can also cause the reduction of the particle size when the sonication is applied to the solution at the initial stage of crystallization where the crystal growth is about to start. The most important effect of the presence of an ultrasonic wave during crystallization is that it reduces both the nucleation induction time and the metastable zone width. Hence, the ultrasound may control the rate of nucleation and crystal growth and thereby affect the resulting size of each particle [3], [8], [9].

V. Antisolvent Crystallization of Poorly Water Soluble Drugs

Many researchers have produced microparticles to nanoparticles of different active pharmaceutical ingredients (APIs) using an antisolvent crystallization with water as an antisolvent has been shown in Table I.

TABLE I: Details of Antisolvent Crystallization of Different APIS

API	Parameters	Particle Size (μm)	Ref.
Artemisinin	Temperature:10-25 ℃ SAS volume ratio:1:10-1:20 Drug concentration:5-15mg/ml Stirring speed:200-1000 rpm Flow rate: 2-10 ml/min Solvent: ethanol	Diameter: 1.5 Length: 3.8	[15]
Beclometha-sone Dipro-pionate	Solvent: methanol Solution:antisolvent:1:20 Drug concentration:30mg/ml Temperature: 4-40 ℃ Stirring speed: 500-2000 rpm Stirring time: 10s-240s	0.2-1.2	[17]
Bicalutamide	Temperature: 3-30 ℃ Stirring speed: 1000-15000 rpm	0.326-0.334	[18]
Carbamaze-pine	Temperature: 25-45 ℃ Drug concentration :10-40 mg/ml Flow rate: 1.4-10 ml/min Sonication time: 30-90s	13.9-112.3	[8]
Celecoxib	Solvent: acetone Drug concentration: 60 mg/ml Temperature: 4 ℃	0.144-0.174	[20]
Curcumin	Drug concentration: 5-15 mg/ml Flowrate: 2-10 ml/min Solvent: ethanol Stirring speed: 200-1000 rpm SAS volume ratio: 1:10-1:20 Temperature: 5-25 ℃	Diameter: 0.155-0.300, Length: 0.920-1.680	[6]
Deflazacort	Solvent: methanol SAS volume ratio:1:1-1:6	3.3-561.0	[21]
Fenofibrate	Solvent: ethanol Drug concentration: 50 mg/ml Stirring speed:1000 rpm	0.299-0.337	[22]
Griseofulvin	Solvents: Acetone, Ethanol Temperature: 25 ℃	1.5	[23]
Ibuprofen	Solvent: isopropyl alcohol Stirring speed: 3000 rpm Surfactant concentration: 0.1-1 %w/v	0.2-0.4	[2]
Irbesartan	Solvent: methanol Drug concentration: 1 wt% Stirring speed: 2500 rpm Stirring time: 30s Concentration of PVP: 1.5g/1000ml Concentration of SDS: 0.25g/1000ml	0.055	[24]
Megestrol acetate	Solvent: Acetone Drug concentration: 30-120 mg/ml Concentration of Kollidon VA 64(surfactant): 0.2 %(w/v)	1.048-3.491	[5]
Meloxicam	Solvent: DMF Temperature: 8 ℃ Stabilizer concentration: 0.1-0.6%w/v Sonication: 300 W for 20 time length	0.183-0.750	[25]
Nitrendipine	Solvent: mixture of PEG 200 and acetone (1:1 v/v) Drug concentration: 30mg/ml Stabilizer (PVA) concentration:	0.2-0.218	[3]

	0.15%(w/v) Temperature: 3 ℃ Stirring speed: 400 rpm Sonication: 400 W, 15 min		
Norfloxacin	Solvent: dimethylsulfoxide SAS volume ratio: 1:3-1:10 Drug concentration: 5-20 mg/ml	0.170-0.350	[26]
Quercetin	Solvent: ethanol Drug concentration: 5-15 mg/ml Flow rate: 2-8ml/min Stirring speed: 300-1000 rpm SAS volume ratio: 1:10-1:25	0.17 ±0.03 -0.255 ± 0.025	[16]
Siramesine	Solvent: Ethanol Drug concentration:1%w/v, 50ml SAS volume ratio: 1:4 Excipient concentration: 0.025% w/v, 200ml	5 ±1-147 ± 28.5	[27]
Spironolact-one	Solvent: N-methyl-2-pyrrolidone Drug concentration: 10-100 mg/ml Stirring speed: 1000 rpm	0.2-0.3	[28]
trans-Resveratrol	Solvent: ethanol Drug concentration: 60 mg/ml Stabilizer concentration: 0.5 wt.% Stirring speed: 1000 rpm Temperature: 5-25 ℃ Stirring time: 5 min	0.232-0.560	[10]

VI. Conclusion

Various techniques have been employed to decrease the particle size of drugs to the nanoscale. Antisolvent crystallization is one of the most important crystallization process which is being used for the enhancement of the bioavailability of poorly water soluble drugs. Antisolvent crystallization has advantages like controlled particle size distribution, rapid and easy to perform. Various operation parameters like; concentration, temperature, solvent to antisolvent ratio, sonication power etc. have been explained in detail considering their effect on particle size and the morphology. All the parameters have a significant effect on the particle size but ultrasound power has a more influence on the particle size and morphology. Controlling the ultrasound variables one can control the particle size distribution. Therefore, in general, antisolvent crystallization is quite simple, cost effective and easy for scaling-up to produce nanoparticles of poorly water soluble drugs. Additional variable like ultrasound waves can easily be applied as water is used as an antisolvent.

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