ejbps, 2016, Volume 3, Issue 3, 230-234. ***Review Article*** **SJIF Impact Factor 3.881**

EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 3
230-234
Year: 2016

"ANTISOLVENT CRYSTALLIZATION: A NOVEL APPROACH TO BIOAVAILABILITY ENHANCEMENT"

Meena Kurup* and Arun Raj R.

Department of Pharmaceutical Science, Mahatma Gandhi University RIMSR, Kottayam-9, Kerala, India.

***Author for Correspondence: Meena Kurup**

Department of Pharmaceutical Science, Mahatma Gandhi University RIMSR, Kottayam-9, Kerala, India.

Article Received on 20/12/2015 **Article Revised on 10/01/2016** **Article Accepted on 03/02/2016**

ABSTRACT

Pharmaceutical particle technology is employed to improve poor aqueous solubility of drug compounds that limits in vivo bioavailability owing to their low dissolution rate in the gastrointestinal fluids following oral administration. The particle technology involves several approaches from the conventional size reduction processes to the Novel particle technology that modify the solubility properties of the drugs and produce solid, powdered form of the drugs that are readily soluble in water and can be easily formulated into various dosage forms. This review highlights the advantages of anti-solvent crystallization for improving solubility, dissolution and bioavailability of drugs with poor aqueous solubility. An anti-solvent crystallization technique is being used to prepare nanoparticles or micro particles 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, their effect on the particle size of poorly water soluble drugs in an anti-solvent crystallization and problems related to anti-solvent crystallization have been reviewed.

KEYWORDS: Anti-solvent crystallization, Problems, Oil out, Operation variables.

1. INTRODUCTION

The water solubility of a drug is a fundamental property that plays an important role in the absorption of the drug after oral administration. It also governs the possibility of parenteral administration of a drug and is useful in manipulating and testing of drug properties during the drug design and development process. The drug solubility is an equilibrium measure but also the dissolution rate at which the solid drug or drug from the dosage form passes into solution is critically important when the dissolution time is limited [1]. Poorly water-soluble drugs after oral administration often require high doses in order to reach therapeutic plasma concentrations. The bioavailability of an orally administered drug depends on its solubility in aqueous media over different pH ranges. Various techniques are used for the improvement of the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, Micellar solubilization, hydrotropy etc.

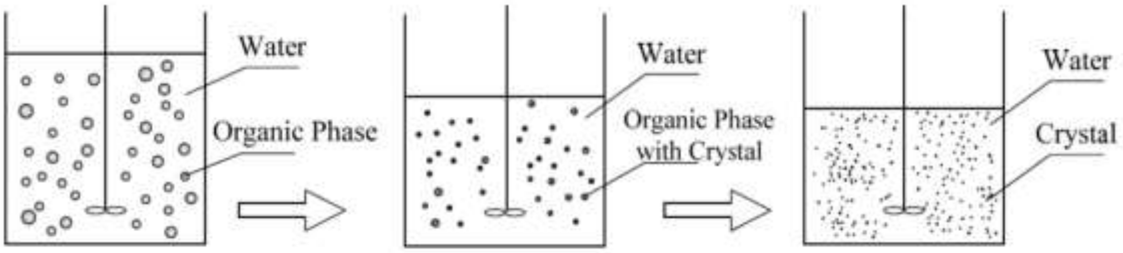
The bioavailability is defined as the percentage of the quantity of the drug absorbed compared to its initial quantity of dosage, which can be improved by a decrease in their particle size [2]. The dissolution rate of the active pharmaceutical ingredient (API) is proportional to the available surface 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 anti solvent precipitation technology is rarely applied. As compared to milling and high pressure homogenization (top-down approach), anti-solvent precipitation ("bottom up" approach) is simple, cost effective, and easy to scale-up.[6]

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. Anti-solvent crystallization can be used in the production of submicronic particles of pharmaceutical compounds as well as in the manufacture of crystals that require an enhanced drug release rate. Indeed, the polycrystalline drug particles with higher amorphous portions exhibit a faster dissolution rate in solutions. In general, three types of fluids: gas, liquid, and supercritical fluids can be employed as anti-solvents. 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. Crystallization processes that use gas- or supercritical fluid as anti-solvents have been studied widely to produce particles of polymers and pharmaceuticals.

In these processes, different methods of mixing and flow configurations of solutions and anti-solvents have been adopted to optimize the properties of the resulting crystals. The operations were performed in either a batch- or continuous-type, and sometimes the anti-solvent acted as a dispersion media to improve the micronization of the precipitated particles. The use of a gas- or supercritical fluid anti-solvent eliminates the concerns regarding residual anti-solvent remaining on the crystal surface and the anti-solvent can be separated easily from the solution. In fact, the residues of solvent used as an anti-solvent could be not only found on the crystal surface, but also entrapped inside the crystals, it is even more difficult to remove them. In addition, gas- or supercritical fluid anti-solvent process, however, the crystallization process should be performed in a high pressure apparatus to maintain the anti-solvents under a high pressure or in a supercritical state.

2. ANTI-SOLVENT CRYSTALLIZATION

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 [7]. The use of the anti-solvent in crystallization reduces the solubility of a solute in the solution and to induce rapid crystallization. The physical and chemical properties of the anti-solvent 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 [8]. 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 [9].



3. EFFECT OF OPERATING VARIABLES

3.1 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 super saturation 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 anti-solvent and lead to particle aggregation [6], [14], [15]. An increase in the viscosity of the drug solution hinders the drug diffusion between solution and anti-solvent and results in non-uniform super saturation 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 super saturation 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.

3.2 Effect of Stirring Speed

The stirring speed is an important parameter because it effects on the mixing phenomena between solvent to anti-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 super saturation, 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].

3.3 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].

3.4 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 °C with an irregular flake like morphology; while the particles obtained at 3 °C 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 temperature would decrease the diffusion and growth kinetics at the crystal boundary layer interface. As a result, smaller drug particles are obtained at low temperature.

3.5 Effect of the Solvent to Anti solvent (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 anti-solvent, rapid reduction in the drug concentration occurs with an increase in the amount of anti-solvent leading to rapid precipitation of the drug into nanoparticles. Furthermore, a greater amount of anti-solvent lead to a greater nucleation rate and produces smaller nuclei and simultaneously the growth occurs. In the subsequent growth, the higher anti-solvent 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 super saturation 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 super saturation ratio. Therefore, high super saturation condition results in small particles due to the formation of large number of nuclei [17].

4. ADVANTAGE

1) The process of crystallization is quiet easy
2) Anti-solvent crystallization is that the process can be carried out at temperatures near the ambient temperature. It is quite convenient for heat-sensitive substances.
3) The process demand less energy than a solvent evaporation process.
4) The solvent-anti-solvent mixture can be separated in order to recover and recycle one or both solvents.
5) Change in solvent composition may favor change in crystalline phases

5. DISADVANTAGE

A potential problem for anti-solvent crystallization methods is the tendency for organic compounds to oil out or agglomerate as fine particles into amorphous undefined structures. One possible cause of oiling out is that drops of the product solution are surrounded by the anti-solvent, in which the solubility is very low, and this low solubility creates localized regions with very high super saturation ratios. Before mixing to the molecular level is achieved, the localized high super saturation forces the product out of solution without allowing sufficient time for ordering of molecules to enable crystal development. The resulting oily particles have a tendency to clump together before the occluded solvent migrates throughout the solution. As the mixture is aged, the oiled-out particles may transform into amorphous solids or become crystalline. Solids developed in this manner will likely have poor lattice structure.

6. REMEDY

Unfortunately, many industrial anti-solvent crystallization operations are far from optimum. To minimize the above disadvantage, the process took place in a fully baffled crystallizer with a 1.6-ft.-dia. 4-blade PBT operating at 90 rpm. The API was dissolved in isopropanol (IP) and crystallized by subsurface linear addition of isopropyl acetate (IPAc) for 1 hr. via a 2-in.-dia. pipe near a baffle. This led to a volume increase to approximately 1,000 gal from the original 500 gal. No seeding was used. The slurry was aged at 20°C and cooled to 10°C.

7. CONCLUSION

Various techniques have been employed to decrease the particle size of drugs to the nanoscale. Anti-solvent crystallization is one of the most important crystallization process which is being used for the enhancement of the bioavailability of poorly water soluble drugs. Anti-solvent crystallization has advantages like controlled particle size distribution, rapid and easy to perform. Various operation parameters like; concentration, temperature, solvent to anti-solvent ratio etc. have been explained in detail considering their effect on particle size and the morphology. Oil out is the one of the major drawback of anti-solvent crystallization, which can be overcome by the above remedies. Therefore, in general, anti-solvent crystallization is quite simple, cost effective and easy for scaling-up to produce nanoparticles of poorly water soluble drugs , Only if oil out is avoided.

8. REFERENCE

1. A. A. Thorat and S. V. Dalvi, “Liquid antisolvent precipitation and stabilization of nanoparticles of poorly water soluble drugs in aqueous suspensions: Recent developments and future perspective,” Chemical Engineering Journal, 2012; 181-182: 1-34.
2. M. Mansouri, H. R. Pouretedal, and V. Vosough, “Preparation and characterization of ibuprofen nanoparticle by using solvent/antisolvent precipitation,” The Open Conference Proceeding Journal, 2011; 2: 88-94.
3. D. Xia, P. Quan, H. Piao, S. Sun, Y. Yin, and F. Cui, “Preparation of stable nitrendipine nanosuspensions using the precipitation–ultrasonication method for enhancement of dissolution and oral bioavailability,” European Journal of Pharmaceutical Sciences, 2010; 40: 325-334.
4. Z. Zhang, Z. Shen, J. Wang, H. Zhao, J. Chen, and J. Yun, “Nanonization of Megestrol Acetate by Liquid Precipitation,” Industrial and Engineering Chemistry Research, 2009; 48: 8493-8499.
5. E. Cho, W. Cho, K. Cha, J. Park, M. Kim, J. Kim, H. J. Park, and S. Hwang, “Enhanced dissolution of megestrol acetate microcrystals prepared by antisolvent precipitation process using hydrophilic additives,” International Journal of Pharmaceutics, 2010; 396: 91-98.
6. M. Kakran, N. G. Sahoo, I. L. Tan, and L. Li, “Preparation of nanoparticles of poorly water-soluble antioxidant curcumin by antisolvent precipitation methods,” Journal of Nanoparlicle Research, 2012; 14: 757.
7. M. W. Park and S. D. Yeo, “Antisolvent crystallization of carbamazepine from organic solutions,” Chemical Engineering Research and Design, 2012; 90: 2202-2208.
8. M. W. Park and S. D. Yeo, “Antisolvent Crystallization of Roxithromycin and the Effect of Ultrasound,” Separation Science and Technology, 2010; 45: 1402-1410.
9. S. Kim, W. K. Ng, Y. Dong, S. Das, and R. B. H. Tan, “Preparation and physicochemical characterization of trans-resveratrol nanoparticles by temperature-controlled antisolvent precipitation,” Journal of Food Engineering, 2012; 108: 37-42.
10. H. Chan and P. C. L. Kwok, “Production methods for Nano drug particles using the bottom-up approach,” Advanced Drug Delivery Reviews, 2011; 63: 406–416.
11. U. N. Hatkar and P. R. Gogate, “Process intensification of anti-solvent crystallization of salicylic acid using ultrasonic irradiations,” Chemical Engineering and Processing, 2012; 57-58: 16-24.
12. H. Zhang, J. Wang, Z. Zhang, Y. Le, Z. Shen, and J. Chen, “Micronization of atorvastatin calcium by antisolvent precipitation process,” International Journal of Pharmaceutics, 2009; 374: 106-113,.
13. M. Kakran, N. G. Sahoo, L. Li, and Z. Judeh, “Fabrication of quercetin nanoparticles by anti-solvent precipitation method for enhanced dissolution,” Powder Technology, 2012; 223: 59-64.
14. Z. Wang, J. Chen, Y. Le, and Z. Shen, “Preparation of Ultrafine Beclomethasone Dipropionate Drug Powder by Antisolvent Precipitation,” Industrial and Engineering Chemistry Research, 2007; 46: 4839-4845.
15. C. Li, C. Li, Y. Le, and J. Chen, “Formation of bicalutamide nanodispersion for dissolution rate enhancement,” International Journal of Pharmaceutics, 2011; 404: 257-263.
16. Y. Liu, C. Sun, Y. Hao, T. Jiang, L. Zheng, and S. Wang, “ Mechanism of Dissolution Enhancement and Bioavailability of Poorly Water Soluble Celecoxib by Preparing Stable Amorphous Nanoparticles,” Journal of Pharmacy and Pharmaceutical Sciences, 2010; 13(4): 589-606.
17. A. S. Paulino, G. Rauber, C. E. M. Campos, M. H. P. Mauricio, R. R. deAvillez, G. Capobianco, S. G. Cardoso, and S. L. Cuffini, “Dissolution enhancement of Deflazacort using hollow crystals prepared by antisolvent crystallization process,” European Journal of Pharmaceutical Sciences, 2013; 49: 294-301.
18. J. Hu, W. K. Ng, Y. Dong, S. Shen, and R. B. H. Tan, “Continuous and scalable process for water-redispersible nanoformulation of poorly aqueous soluble APIs by antisolvent precipitation and spray-drying,” International Journal of Pharmaceutics, 2011; 404: 198-204.
19. C. Desai, X. Meng, D. Yang, X. Wang, V. Akkunuru, and S. Mitra,“Effect of solvents on stabilization of micro drug particles,” Journal of Crystal Growth, 2011; 314: 353-358.
20. Z. Zhang, Y. Le, J. Wang, H. Zhao, and J. Chen, “Irbesartan drug formulated as nanocomposite particles for the enhancement of the dissolution rate,” Particuology, 2012; 10: 462-467.
21. A. J. Raval and M. M. Patel, “Preparation and Characterization of Nanoparticles for Solubility and

Dissolution Rate Enhancement of Meloxicam," International Research Journal of Pharmaceutical, 2011; 01(02): 42-49.

22. T. Panagiotou, S. V. Mesite, and R. J. Fisher, "Production of Norfloxacin Nanosuspensions Using Microfluidics Reaction Technology through Solvent/Antisolvent Crystallization," Industrial and Engineering Chemistry Research, 2009; 48: 1761-1771.
23. A. Zimmermann, A. M. Fureby, M. R. Elema, T. Hansen, A. Mullertz, and L. Hovgaard, "Adsorption of pharmaceutical excipients onto microcrystals of siramesine hydrochloride: Effects on physicochemical properties," European Journal of Pharmaceutics and Biopharmaceutics, 2009; 71: 109–116.
24. P. Barrett, B. Smith, J. Worlitschek, V. Bracken, B. O'Sullivan, D. O'Grady, A review of the use of process analytical technology for the understanding and optimization of production batch crystallization processes, Organic Process Research and Development 2005; 9: 348–355.
25. M. Birch, S.J. Fussell, P.D. Higginson, N. McDowall, I. Marziano, Towards a PATBased strategy for crystallization development, Organic Process Research and Development 2005; 9: 360–364.
26. R.D. Braatz, Advanced control of crystallization processes, Annual Reviews in Control 2002; 26: 87–99.
27. A.J. Mahajan, D.J. Kirwan, Nucleation and growth kinetics of biochemical measured at high supersaturations, Journal of Crystal Growth 1994; 144: 281– 290.
28. X.Y. Woo, R.B.H. Tan, P.S. Chow, R.D. Braatz, Simulation of mixing effects in antisolvent crystallisation using a coupled CFD-PDF-PBE approach, Crystal Growth and Design 2006; 6: 1291–1303.
29. L.X. Yu, R.A. Lionberger, A.S. Raw, R. D'Costa, H.Q. Wu, A.S. Hussain, Applications of process analytical technology to crystallization processes, Advanced Drug Delivery Reviews 2004; 56: 349–369.
30. G.X. Zhou, M. Fujiwara, X.Y. Woo, E. Rusli, H.H. Tung, C. Starbuck, O. Davidson, Z.H. Ge, R.D. Braatz, Direct design of pharmaceutical antisolvent crystallization through concentration control, Crystal Growth and Design 2006; 6: 892– 898.