Spherical crystallization: A technique use to reform solubility and flow property of active pharmaceutical ingredients

Arindam Chatterjee[1], Madan Mohan Gupta[1,2], Birendra Srivastava[1]

[1]Department of Pharmaceutics, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India, [2]Department of Pharmaceutics, Laboratory of Pharmaceutical Formulation Design and Development, School of Pharmacy, Faculty of Medical Sciences, The University of the West Indies, St. Augustine, Trinidad and Tobago, West Indies

Abstract

Tablets have been choice of manufacturers over the years due to their comparatively low cost of manufacturing, packaging, shipping, and ease of administration; also have better stability and can be considered virtually tamper proof. A major challenge in formulation development of the tablets extends from lower solubility of the active agent to the elaborated manufacturing procedures for obtaining a compressible granular material. Moreover, the validation and documentation increases, as the numbers of steps increases for an industrially acceptable granulation process. Spherical crystallization (SC) is a promising technique, which encompass the crystallization, agglomeration, and spheronization phenomenon in a single step. Initially, two methods, spherical agglomeration, and emulsion solvent diffusion, were suggested to get a desired result. Later on, the introduction of modified methods such as crystallo-co-agglomeration, ammonia diffusion system, and neutralization techniques overcame the limitations of the older techniques. Under controlled conditions such as solvent composition, mixing rate and temperature, spherical dense agglomerates cluster from particles. Application of the SC technique includes production of compacted spherical particles of drug having improved uniformity in shape and size of particles, good bulk density, better flow properties as well as better solubility so SC when used on commercial scale will bring down the production costs of pharmaceutical tablet and will increase revenue for the pharmaceutical industries in the competitive market. This review summarizes the technologies available for SC and also suggests the parameters for evaluation of a viable product.

Keywords: Agglomeration, compressibility, granulation, powder flow, solubility enhancement, spherical crystallization

Address for correspondence: Dr. Madan Mohan Gupta, School of Pharmacy, Faculty of Medical Sciences, Building 39, Eric Willaims Medical Sciences Complex, Mount Hope, The University of the West Indies, Trinidad and Tobago, West Indies.
E-mail: mmingupta@gmail.com

INTRODUCTION

Direct tableting of active pharmaceutical ingredients (APIs) is possible when powders have a good flow property and compression characteristics, which is a problem for major of the active ingredients that have poor compressibility and flow. However, on addition of excess amount of diluents or by wet or dry granulation satisfactory results can be

Access this article online	
Quick Response Code:	Website: www.jpionline.org
	DOI: 10.4103/jphi.JPHI_36_16

How to cite this article: Chatterjee A, Gupta MM, Srivastava B. Spherical crystallization: A technique use to reform solubility and flow property of active pharmaceutical ingredients. Int J Pharma Investig 2017;7:4-9.

obtained.[1] The addition of excess amount of directly compressible diluents is not favored, as they may increase the compressibility but may not increase the flow property of powder blend while wet granulation is a process that consumes time, energy, and required maintenance of lot of documentation.[2] The spherical crystallization (SC) is a technique, which has shown promising results in the improvement of particle size, flowability and compression characteristics of active pharmaceutical agents. The SC by the spherical agglomeration (SA) method is defined as an agglomeration process that transforms crystals directly into a compacted spherical form during the crystallization stage and this process also ensures the tablet size reduction by omitting the use of large amounts of fillers.[3] The direct compression method for tablet manufacturing is cost efficient and easy to validate. Various other techniques such as hydrotropy, sono crystallization, hot melt extrusion technique, steam aided granulation, floating granulation, dried nano suspensions, liquisolid technology, and cryo techniques are available for improvement of solubility, but SA technique not only increases the dissolution it also improves the powder characteristics of the active ingredient.[4]

SPHERICAL CRYSTALLIZATION TECHNIQUES

Spherical agglomeration method

In this process, drug is dissolved in a system of water, ethanol and chloroform behaving as poor solvent, good solvent, and bridging liquid, respectively.[5] As the drug solution is poured in the poor solvent simultaneous crystallization of the API takes place, a third liquid known as bridging liquid that has low miscibility with the poor solvent but having a good affinity with the drug is added in a controlled manner to the crystallization vessel.[6] Therefore, it forms a bridge between the particles and cause binding of the particles.[7] In this process, it should be taken care of that the good solvent and poor solvent should have greater affinity than drug affinity of drug and the good solvent.[8] The process is shown in Figure 1.

Quasi-emulsion solvent diffusion

In quasi-emulsion solvent diffusion process [Figure 2], agglomeration takes place with or without any addition of binding liquid depending on the crystallization system chosen.[9] Here, crystallization is carried out through the addition of a solution of the active agent in a good solvent to a vessel containing poor solvent; although, both the solvents have a degree of miscibility.[10] Under the influence of agitation when the drug solution added to the poor solvent, a quasi-emulsion is produced. In this process, the affinity of drug and good solvent is greater than the good solvent poor solvent interaction. The good solvent here acts as bridging liquid and as it is diffusing out of the emulsion, droplet crystallization takes place.[11]

Crystallo-co-agglomeration

As the crystallo-co-agglomeration (CCA) [Figure 3] name suggests, the crystallization takes place in the presence of an external inert material or diluents.[12] SC technique[13] limited its applicability only to the high dose pharmaceuticals whereas CCA was effective in case of low dose active ingredients utilizing another active ingredient or a diluent such as talc, sodium starch glycolate, and starch. Some researchers have utilized another pharmaceutical entity as a substrate for developing mixed dose spherical crystals.[14]

Ammonia diffusion system

In this technique [Figure 4], ammonia water acts both, as a good solvent and a bridging liquid in one single step.[15] API's which are zwitterionic in nature, are soluble in acidic and alkaline solution but insoluble in neutral and organic solvents, by virtue of which, makes it difficult to use the general SA techniques.[16] Ammonia water (predominantly alkaline) solution of drug when added to the mixture of a water miscible and immiscible organic solvent, the ammonia water diffuses out to the outer layer of organic solvents, the residual ammonia water acts as bridging liquid thereby binding the crystals simultaneously and producing larger uniform shaped particles.[17]

Neutralization technique

In this method, subject entity is crystallized using sodium hydroxide solution as good solvent while hydrochloric acid as poor solvent. Dilute hydrochloric acid neutralizes the drug and sodium hydroxide solution, resulting in crystallization and organic solvent like ether is added as a binding agent for the formation of agglomerates. With the addition of water soluble polymer compact spherical agglomerates can be obtained of narrow particle size distribution and excellent free-flowing ability and packability.[18]

STAGES OF GROWTH OF AGGLOMERATION

The concept of growth in size of agglomerates was explained by Bermer and Zuider Wag in four steps namely, flocculation zone, zero growth zone, fast growth zone, and constant size zone. In the flocculation Zone, the bridging liquid displaces the solvent from the surface of the particle and form of loose flocs by the formation of pendular bridges takes place. In the zero growth zone, the loose floccules convert into tightly packed aggregates. The entrapped liquid seeps to the

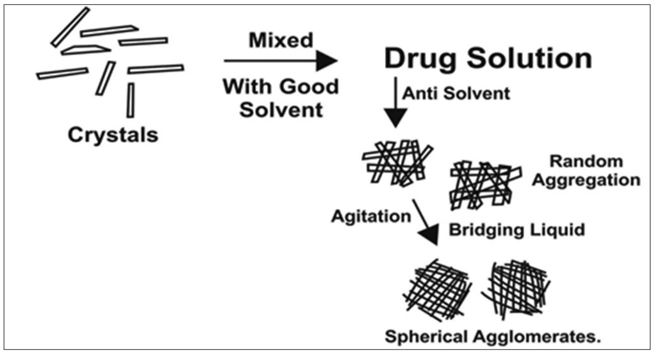

Figure 1: Process of spherical agglomeration

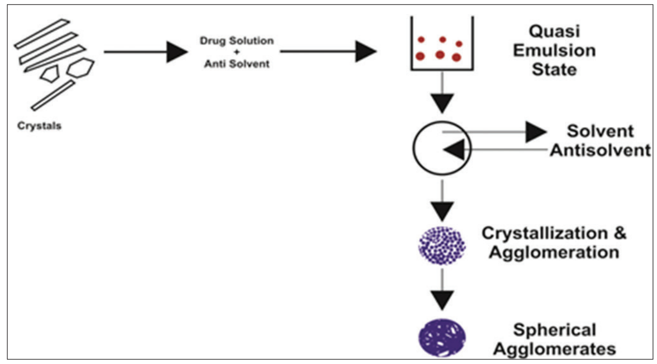

Figure 2: Quasi-emulsion solvent diffusion for preparation of spherical crystals

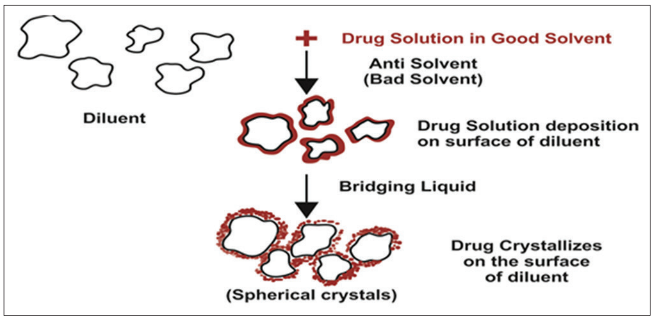

Figure 3: Crytsallo-co-agglomeration process for preparation of spherical crystals

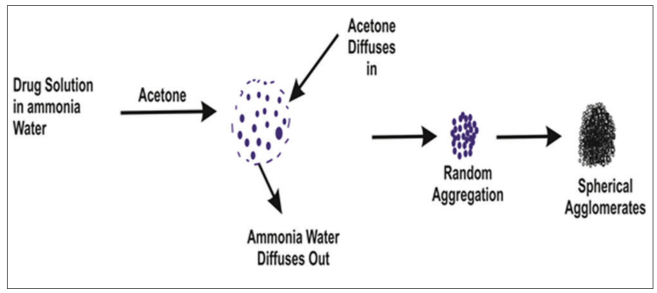

Figure 4: Ammonia diffusion system

surface of the small floccules. In the zero growth zone, the squeezing out of the bridging liquid from the pores of the initial floccules for the formation of the small agglomerates is the rate-limiting step in agglomeration growth process. The fast growth zone can be observed at the point where the sufficient amount of bridging liquid has been squeezed out of the surface of the small agglomerates.[18] In the process of coalescence, the large size particles form by the random collision of the well-formed nucleus. For the collision process to be successful, slightly excess surface moisture on the nucleus is required. The constant size zone involves the arresting of agglomeration growth. Even a slight decrease of size of agglomerates is observed due to attrition, fracture, and shatter.[17]

FACTORS AFFECTING THE AGGLOMERATION PROCESS

Role of solvents

The character of solvent, amount, and nature of bridging liquid affects the sphericity of the agglomerates obtained. In typical SA process, general rule states that as the amount of bridging liquid increases the size of agglomerate also increases.[19] However, observation states that after a certain amount of bridging liquid have been added to the system, further increment sees no observable change in the size of the agglomerates.[20]

Role of temperature

Optimum temperature has a quintessential role to play in the process of agglomeration. At higher temperatures above room temperature, the crystals had a large share of fines and no agglomeration occurred. At lower temperatures, the bigger agglomerates were formed in comparison to the agglomerates formed at room temperature, which certainly reduces the solubility and the mechanical strength.

Role of agitation

It is evident that agitation plays a vital role in the particle size of the agglomerates. Any change in the rate and duration of agitation will affect the shape and size of the product. Higher agitation rates causes shearing of the agglomerates resulting in smaller agglomerates with fines or no agglomerates at all. Lower rates of agitation will produce irregular size of spheres, which does not resolve the objectives of the method. Optimization of the agitation speed is necessity for the production of agreeable products.[21]

Role of additives

The presence of polymers like hydroxypropyl methyl cellulose, polyethylene glycol, polyvinyl pyrrolidone delay the nucleation time. These polymers prevent the spontaneous aggregation of the crystals thereby supplying and ample time for the formation of spherical agglomerates. The polymers interfere with the sphericity and particle size as their crystal habit is modified.[22]

Duration of residence of agglomerates in crystallization medium

It has been seen that increase in the time of residence of agglomerates in the crystallization medium, larger size of agglomerates are produced.

CHARACTERIZATION OF SPHERICAL CRYSTALS

Practical yield

Practical yield of the agglomerates formed can be determined by crushing and dissolving fixed amount of the agglomerates in a suitable solvent and then analyzing by ultraviolet spectrophotometer. Reported by a simple mathematical operation:

$$\text{Practical yield}\,(\%) = \frac{\text{Weight of product}}{\text{Weight of feed}} \times 100 \qquad \text{(Equation 1)}$$

Drug loss in supernatant liquid

Especially for CCA method, after the completion of whole process, the supernatant liquid is analyzed for the drug that is lost. A significant amount of loss of drug indicates insufficient amount of excipient might available for the deposition of the drug.

Micromeritic properties

Micromeritic properties include particle size distribution, roundness, angle of repose, Carr's index, Hausner's ratio, compactibility and packability, densities are physical characteristics that are dependent on the shape, size, and morphology of the spherical crystals obtained as the final product.[23]

Solid state characterization

It is carried out by differential scanning calorimetry (DSC) and powder X-ray diffraction (X-RD) techniques. DSC is used for ascertaining the crystallinity of the sample and polymorphic transitions during the process, whereas X-RD demonstrates the nature of crystalline drug. A purely crystalline substance shows intense peaks, whereas the agglomerates when subjected to X-RD analysis shows that there is marked decrease in the intensity of the peak and appearance of "Halo." This sizeable reduction shows that a slight amorphous of the drug takes place during the SC process.[24]

Mechanical properties

Friability of agglomerates

A sample from each batch of agglomerates and plastic balls are placed on sieve and shaken for a fixed interval of time. For each time interval, mean geometric diameter is calculated.

Percentage friability index (FI) as a function of time can be calculated at each time using the following equation

$$FI = \left[(dg)_t / (dg)_0\right] \times 100 \qquad \text{(Equation 2)}$$

Here, dg_t = mean geometric diameter after time t

dg_t = mean geometric diameter at initial time.[6]

Crushing strength

Mercury load cell designed by Jarosz and Parrot can be used for measuring the crushing strength of agglomerate. A minimum of ten granules should be tested, and the average load in grams is taken as the crushing strength.[25]

Heckel analysis

To analyze the compressibility of the agglomerates it is used, with the help of the derivation.

$$\frac{dD}{dP} = k(1-D) \qquad \text{(Equation 3)}$$

Where D = Relative density of the compact at pressure P and k is a constant. It is assumed that the change in relative density in respect of pressure is directly proportional to the left over porosity on further integrating the above equation.

$$\ln\left(\frac{1}{1-D}\right) = P_y k + A \qquad \text{(Equation 4)}$$

Here, "k" and "A" are constants; D and P_y are the packing fraction and pressure, respectively. The slope, K of the Heckel plot gives a measure of the plasticity of a compressed material.

Tensile strength

Force per unit area of broken face required to split a prepared compact is known as the radial tensile strength σ_t. The hardness value of the compacts is determined by Monsanto hardness tester and the following equation is utilized:

$$\sigma_t = \frac{2F}{\pi D t} \qquad \text{(Equation 5)}$$

Here F is the crushing force (N), D is the diameter of the tablet, and t is the thickness of the compact.[21]

Elastic recovery

For investigating the effects of interparticulate friction on the compacts, elastic recovery measurements required to record. A lower elastic recovery indicates the increase in the point of contact between the particles and thereby assists plastic flow and thus increasing the contact area and therefore forming new high-energy surfaces that bind the particles strongly.

Elastic recovery can be measured by the following formula:

$$\%ER=\left[\frac{\left(H_e - H_c\right)}{H_c}\right]\times 100 \quad \text{(Equation 6)}$$

Here, H_c is the thickness of compact just after ejection and H_e is the thickness of the compact after 24 h.

Residual solvent determination by gas chromatography

The agglomerates are analyzed by gas chromatography method for the residue of the solvent, which might have remained entrapped during the process of agglomeration.[26]

In vitro dissolution studies

To confirm the better dissolution, studies are performed by filling the spherical crystals in the capsule shell in media. Dissolution studies will demonstrate the advantage of agglomerates over the pure drug.[27]

Stability studies

Stability studies should be performed in accordance to ICH guidelines to ensure the stability of the agglomerates during shelf life of the final marketed dosage form.

CONCLUSION

The spherical crystal which is cost effective technique could be useful for direct compression of tablet due better flowability as compare to original pure amorphous drug. As this technique crystallizes, aggregates and spheronizes at a single step consumes less time as compared to wet granulation technique. Spherical crystals have a greater solubility in the aqueous solvents thereby increasing the bioavailability of the poorly soluble drugs specifically Biopharmaceutical Classification System class II drugs where the bioavailability is dissolution rate limited. Therefore, if the technique is scaled up for commercial production of the APIs then definitely it will bring a great change in the current manufacturing methods.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Maghsoodi M. How spherical crystallization improves direct tableting properties: A review. Adv Pharm Bull 2012;2:253-7.
2. Szabo-Revesz P, Goczo H, Pintye-Hodi K, Kasa P Jr., Eros I, Hasznos-Nezdei M, *et al.* Development of spherical crystal agglomerates of an aspartic acid salt for direct tablet making. Powder Technol 2001;114:118-24.
3. Kale V, Ittadwar A, Gadekar S. Particle size enlargement: Making and understanding of the behavior of powder (particle) system. Syst Rev Pharm 2011;2:79-85.
4. Garala K, Patel J, Patel A, Raval M, Dharamsi A. Influence of excipients and processing conditions on the development of agglomerates of racecadotril by crystallo-co-agglomeration. Int J Pharm Investig 2012;2:189-200.
5. Kawashima Y, Cui F, Takeuchi H, Niwa T, Hino T, Kiuchi K, *et al.* Parameters determining the agglomeration behavior and the micromeritic properties of spherically agglomerated crystals prepared by the spherical crystallization technique with miscible solvent systems. Int J Pharm 1995;119:139-47.
6. Gupta MM, Srivastava B. Enhancement of flow property of poorly flowable aceclofenac drug powder by preparation of spherical crystals using solvent change method and making drug powder suitable for direct compression. Int J Curr Pharm Rev Res 2010;1:12-23.
7. Thakur A, Thipparaboina R, Kumar D, Kodukula SG, Shastri NR. Crystal engineered albendazole with improved dissolution and material attributes. CrystEngComm 2016;18:1489-94.
8. Göczõ H, Szabó-Révész P, Farkas B, Hasznos-Nezdei M, Serwanis SF, Pintye-Hódi AK, *et al.* Development of spherical crystals of acetylsalicylic acid for direct tablet-making. Chem Pharm Bull (Tokyo) 2000;48:1877-81.
9. Kawashima Y, Cui F, Takeuchi H, Niwa T, Hino T, Kiuchi K, *et al.* Improvements in flowability and compressibility of pharmaceutical crystals for direct tableting by spherical crystallization with a two-solvent system. Powder Technol 1994;78:151-7.
10. Tahara K, O'Mahony M, Myerson AS. Continuous spherical crystallization of albuterol sulfate with solvent recycle system. Cryst Growth Des 2015;15:5155-6.
11. Kachrimanis K, Nikolakakis I, Malamataris S. Spherical crystal agglomeration of ibuprofen by the solvent-change technique in presence of methacrylic polymers. J Pharm Sci 2000;89:250-9.
12. Maghsoodi M, Taghizadeh O, Martin GP, Nokhodchi A. Particle design of naproxen-disintegrant agglomerates for direct compression by a crystallo-co-agglomeration technique. Int J Pharm 2008;351:45-54.
13. Jadhav N, Pawar A, Paradkar A. Design and evaluation of deformable talc agglomerates prepared by crystallo-co-agglomeration technique for generating heterogeneous matrix. AAPS PharmSciTech 2007;8:E59.
14. Garala KC, Patel JM, Dhingani AP, Dharamsi AT. Preparation and evaluation of agglomerated crystals by crystallo-co-agglomeration: An integrated approach of principal component analysis and Box-Behnken experimental design. Int J Pharm 2013;452:135-56.
15. Ueda M, Nakamura Y, Makita H, Imasato I, Kawashima Y. Particle design of enoxacin by spherical crystallizaion technique. I principle of ammonia diffusion. Chem Pharm Bull 1990;38:2537-41.
16. Puechagut HG, Bianchotti J, Chiale CA. Preparation of norfloxacin spherical agglomerates using the ammonia diffusion system. J Pharm Sci 1998;87:519-23.
17. Gupta MM, Srivastava B, Sharma M, Arya V. Spherical crystallization: A tool of particle engineering for making drug powder suitable for direct compression. Int J Pharm Res Dev 2010;1:1-10.
18. Sano A, Kuriki T, Handa T, Takeuchi H, Kawashima Y. Particle design of tolbutamide in the presence of soluble polymer or surfactant by the spherical crystallization technique: Improvement of dissolution rate. J Pharm Sci 1987;76:471-4.
19. Maghsoodi M. Role of solvents in improvement of dissolution rate of drugs: Crystal habit and crystal agglomeration. Adv Pharm Bull 2015;5:13-8.
20. Katta J, Rasmuson AC. Spherical crystallization of benzoic acid. Int J Pharm 2008;348:61-9.
21. Deshpande MC, Mahadik KR, Pawar AP, Paradkar AR. Evaluation of spherical crystallization as a particle size enlargement technique for aspirin. Ind J Pharm Sci 1997;59:32-4.
22. Raghavan SL, Trividic A, Davis AF, Hadgraft J. Crystallization of hydrocortisone acetate: Influence of polymers. Int J Pharm 2001;212:213-21.

23. Raval MK, Patel JM, Parikh RK, Sheth NR. Dissolution enhancement of chlorzoxazone using cogrinding technique. Int J Pharm Investig 2015;5:247-58.
24. Usha AN, Mutalik S, Reddy MS, Ranjith AK, Kushtagi P, Udupa N. Preparation and, *in vitro*, preclinical and clinical studies of aceclofenac spherical agglomerates. Eur J Pharm Biopharm 2008;70:674-83.
25. Garg N, Pandey P, Kaushik D, Dureja H. Development of novel multifunction directly compressible co-processed excipient by melt granulation technique. Int J Pharm Investig 2015;5:266-74.
26. Dixit M, Kulkarni PK, Vaghela RS. Effect of different crystallization techniques on the dissolution behavior of ketoprofen. Trop J Pharm Res 2013;12:317-22.
27. Pusapati RT, Kumar MK, Rapeti SS, Murthy T. Development of co-processed excipients in the design and evaluation of atorvastatin calcium tablets by direct compression method. Int J Pharm Investig 2014;4:102-6.