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

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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

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

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.

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DOI: 10.4103/jphi.JPHI_36_16

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obtained.[5] 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 hydrotrophy, 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.[4] Therefore, 
it forms a bridge between the particles and cause binding 
of the particles.[5] 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.[6] 
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.[9] 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.[10]

**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.[9] 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.[3] 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.[14] 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
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. 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.

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.

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.
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:

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

(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

Fracture 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

$$\text{FI} = \left[ \frac{\text{dg}}{\text{dg}_0} \right] \times 100$$

(Equation 2)

Here, $\text{dg}_t$ = mean geometric diameter after time $t$
$\text{dg}_n$ = mean geometric diameter at initial time.$^{[20]}$

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.

$$\frac{dD}{dP} = k(1 - D)$$

(Equation 3)

Where $D = \text{Relative density of the compact at pressure } P$ 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.

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

(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 $\sigma_t$. The hardness value of the compacts is determined by Monsanto hardness tester and the following equation is utilized:

$$\sigma_t = \frac{2F}{\pi Dt}$$

(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:

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

Here, \( H_i \) 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.\(^{[20]}\)

**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.

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