PHARMACEUTICAL OVERVIEW OF SPHERICAL CRYSTALLIZATION

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Abstract

Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability, compactability and bio-availability of crystalline drugs. General methods of spherical crystallization are spherical agglomeration, emulsion solvent diffusion and ammonia diffusion method. The principle steps involved in the process of spherical crystallization are flocculation zone, zero growth zone, fast growth zone and constant size zone. Spherical crystallization is having wide applications in pharmaceuticals like improvement of flowability and compressibility of poorly compressible drugs, masking bitter taste of drugs and improving the solubility and dissolution rate of poorly soluble drug.

Keywords: Spherical crystallization; Flowability; Compactability; Bioavailability

1. Introduction

In the past, the pharmaceutical industry did not feel that they need to improve the manufacturing efficiency. The elementary reason was that the most important mission for the pharmaceutical industry had been to rapidly bring new products to the market. Nowadays, rising of the energy prices and the inefficient manufacturing have made pharmaceutical companies face cost pressures. Therefore, the pharmaceutical industry needs to improve the performance of their manufacturing operations. Particle design for solid pharmaceutical dosage forms involves improving the efficiency of the manufacturing processes and giving a high degree of functionality to the drug or excipient particles. Tablet is very specific dosage form, accounting for 50 % of all oral drug delivery system and 70 % of all pharmaceutical preparations produced 18. Direct tabletting of pharmaceutical materials is a modern method in tablet manufacturing. Such manufacturing of tablets involve simple mixing and compression of powders, which results in a number of overall benefits including time, cost and energy savings. Direct tabletting as a technique has been successfully applied to numerous drugs on the industrial scale. The success of any procedure resulting in mechanical properties for tabletting is strongly affected by the micromeric properties of the crystals used 20. Compressing a drug directly requires good micromeric properties, such as flowability, and a good reproducible compressibility. Especially, the flowability of needle-shaped or plated-shaped crystals is very poor and these crystals are difficult to handle 7. Kawashima suggested obtaining the size enlargement of particles during the crystallization step by controlling crystal agglomeration with controlled properties. He introduced this technique into pharmaceutical manufacturing and showed that spherically dense agglomerates could be produced and were suitable for direct tabletting and defined it as spherical crystallization. The traditional drug manufacturing procedures (granulation) involves following steps: crystallization → filtration → drying → formulated powders blending → granulation → drying → tabletting. This is a slow and time consuming process, where as in spherical crystallization the process could be reduced to: crystallization → filtration → drying → dry blending → tabletting. It means less equipment and space, lower labor costs, less processing time, and lower energy consumption in the direct tabletting process 19. This technique is also reputed to improve the detectability, bioavailability, and dissolution rate of some poorly soluble drugs like celecoxib and fenbufen 9.

So spherical crystallization can be defined as “a novel particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form” 7. Besides being producing spherical crystals it also enables co-precipitation of drugs and encapsulating polymers in the form of spherical particles 9.
The spherical crystallization technique also involves the use of a bridging liquid that imparts compressibility by acting as granulating fluid\(^1\). Thus spherical crystallization is a method that helps to achieve good flowability and compressibility. Some drugs have also been recrystallized by the spherical agglomeration technique using polymeric materials to modify their release profile\(^3\),\(^3\).

### 2. Benefits of the spherical crystallization process:
- A spherical shape of the final product formed drastically improves the micromeritic property of the drug crystals\(^14\).
- Improvement in wettability and dissolution rate of some drugs were found by utilization of this process\(^6\),\(^28\).
- This technique could enable subsequent process such as separation, filtration, drying etc to be carried out more efficiently\(^3\).
- Furthermore the resultant agglomerated crystals could be easily compounded with other pharmaceutical powders due to spherical shapes.

### 3. Techniques of spherical crystallization:
Spherical crystals can be obtained by two different techniques, either by typical spherical crystallization technique or non typical spherical crystallization technique\(^24\). Non typical spherical crystallization technique can also be considered as the traditional crystallization process (salting-out, cooling, precipitation, etc.). This process is carried out by controlling the physical and chemical factors\(^30\). Typical spherical crystallization employs three solvents: one is the drug dissolution medium i.e. good solvent; another is a medium which partially dissolves the drug and have wetting property i.e. bridging liquid; and the last one is immiscible with the drug substance i.e. bad solvent\(^32\). The spherical crystallization has been applied to several drugs, and it has been found that the product properties are quite sensitive to the amount of the bridging liquid\(^15\). With decreasing amount of bridging liquid in the three-solvent system, the median diameter of agglomerated crystals increased, having a wider size distribution\(^13\). Less than the optimum amount of bridging liquid produces plenty of fines and more than optimum produces very coarse particles. So the amount of bridging is the critical process parameters in crystallization process\(^15\). The median diameter of agglomerates decreased with increasing content of good solvent\(^15\). Also the choice of bridging liquid, the stirring speed and the concentration of solids (or of the solute) are of importance. So various parameters optimized for this are type, amount and mode of addition of bridging liquid, temperature, and agitation speed to get maximum amount of spherical crystals. The two most commonly used techniques of spherical crystallization are wet spherical agglomeration method (WSA), quasi-emulsion solvent diffusion method (QESD, Transient emulsion). But there are two extensions of these techniques, ammonia diffusion system (ADS) and crystal-co-agglomeration technique (CCA)\(^1\). Another technique of this process is Neutralization, where first fine crystals form by neutralization then it will agglomerate by the help of a bridging liquid\(^29\).

#### 3.1 Wet spherical agglomeration method (WSA):
Here the good and the poor solvents are freely miscible and interaction (binding force) between the solvents is stronger than drug interaction with the good solvent, which leads to precipitation of crystals immediately. Bridging liquid collects the crystals suspended in the system by forming liquid bridges between the crystals due to capillary negative pressure and interfacial tension between the interface of solid and liquid. WSA method proceeds in three steps as shown in Fig.\(^24\). The first one is the selection of the crystallization method to precipitate crystals from solution, i.e., thermal method (temperature decrease or evaporation), physicochemical methods (addition of another solvent, salting out) and chemical reaction. The second step is the choice of the wetting agent that will be immiscible with the solvent of crystallization. Finally, the third step is the hardening of the agglomerates.

![Fig. 1 Steps involved in Spherical agglomeration (SA).](image-url)

Chow et al postulated some general guide lines for the spherical agglomeration of drugs\(^3\).
• For compounds that are water soluble, a water-immiscible organic solvent is used as the external medium and salt solutions of high concentration without common ions can be used as the bridging liquid.
• For compounds that are soluble in one or more organic solvents water is employed as the external phase and a water-immiscible organic solvent as the bridging liquid.
• For compounds that are only soluble in water-miscible organic solvents a saturated aqueous solution of the compound can serve as the external phase and an organic solvent mixture as the bridging solvent.
• For compounds that are insoluble in water or any organic solvents a water-immiscible organic solvent can act as the external phase and a 20% calcium chloride solution as the bridging liquid. In addition, a binding agent such as PVP or PEG is required for agglomeration since the powders are not sufficiently soluble in the bridging liquids to allow binding through recrystallization and fusion.

3.2 Quasi-Emulsion Solvent Diffusion method (QESD, Transient emulsion): This technique is usually applied for the preparation of microspheres. Here interaction between the drug and the good solvent is stronger than that of the good and poor solvents; hence the good solvent drug solution is dispersed in the poor solvent, producing quasi emulsion droplets, even if the solvents are normally miscible. This is because of an increase in the interfacial tension between good and poor solvent. Then good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter diffusion of the poor solvent into the droplet induces the crystallization of the drug within the droplet due to the decreasing solubility of the drug in the droplet containing the poor solvent. The steps involved in QESD are shown in Fig. 2.

Fig. 2 Steps involved in Quasi emulsion Solvent Diffusion (QESD).

3.3 Ammonia diffusion system (ADS): In this technique ammonia-water system is used as the good solvent and bad solvent is selected depending upon the drugs solubility in that solvent. The ammonia-water also acts as a bridging liquid. This technique usually meant for amphoteric drugs which cannot be agglomerated by conventional procedures. The whole process is completed in three stages. First, the drug dissolved in ammonia water is precipitated while the droplets collect the crystals (Figure 3I). Simultaneously, ammonia in the agglomerate diffuses to the outer organic solvent (Figure 3II). Its ability to act as a bridging liquid weakens and subsequently spherical agglomerates are formed (Figure 3III).

3.4 Crystal-co-agglomeration technique (CCA): Applications of spherical crystallization to obtain directly compressible agglomerates without diluents are restricted to water insoluble large-dose drugs only. Most of the excipients, such as diluents and disintegrating agents, are hydrophilic in nature; hence, incorporation of these excipients in the agglomerates formed using organic bridging liquid is difficult. Because of this limitation, spherical crystallization could not be applied to obtain agglomerates of low-dose or poorly compressible materials.

Fig. 3 Steps involved in Ammonia Diffusion System (ADS).

To overcome these limitations of spherical crystallization Kadam et al. developed the crystallo-co-agglomeration (CCA) technique. It is a modification of the spherical crystallization technique in which a drug is crystallized and agglomerated with an excipient or with another drug, which may or may not be crystallized in the system. The agglomeration is performed using bridging liquid. The process enables design of agglomerates containing two drugs or a low-dose or poorly compressible drug in combination with diluents. The difference in the physicochemical properties of the drug
molecules and the excipient becomes the major challenge in the selection of a solvent system for the crystallo-co-agglomeration.

3.5 Neutralization technique (NT): This technique involves the formation of fine crystals by neutralization and consequently their agglomeration by a bridging liquid. Spherical crystallization of tolbutamide and phenytoin were reported by this technique. The drug was dissolved in alkaline solution and then poured into an acidic solution containing polymers and bridging liquid under constant agitation. The drug crystals are precipitated out by neutralization of the base with acid. Then the precipitated crystals were simultaneously agglomerated with the incorporated polymer through the wetting action of the bridging liquid.

4. The principle steps involved in the process of spherical crystallization: Bermer and Zuider Was proposed four steps in the growth of agglomeration.

4.1 Flocculation Zone: In this zone, the bridging liquid displaces the liquid from the surface of the crystals and these crystals are brought into close proximity by agitation; the adsorbed bridging liquid links the particles by forming a lens bridge between them. In this zone, loose open flocs of particles are formed by pendular bridges and this stage of agglomeration process where the ratio of liquid to the void volume is low and air is the continuous phase, is known as the pendular state. Mutual attraction of particles is brought about by surface tension of the liquid and the liquid bridges. The capillary stage is reached when all the void space within the agglomerate is completely filled with the liquid. An intermediate state known as funicular state exists between the pendular and capillary stage. The cohesive strength of agglomerate is attributed to the bonding forces exerted by the pendular bridges and capillary suction pressure.

4.2 Zero Growth Zone: Loose flocules get transferred into tightly packed pellets, during which the entrapped fluid is squeezed out followed by squeezing of the bridging liquid onto the surface of small flocs causing poor space in the pellet of completely filled with the bridging liquid. The driving force for the transformation is provided by the agitation of the slurry causing liquid turbulence, pellet-pellet and pellet-stirrer collision.

4.3 Fast Growth Zone: The fast growth zone of the agglomerates takes place when sufficient bridging liquid has squeezed out of the surface on the small agglomerates. This formation of large particles following random collision of well-formed nucleus is known as coalescence. Successful collision occurs only if the nucleus has slight excess surface moisture. This imparts plasticity on the nucleus and enhances particle deformations and subsequent coalescence. Another reason for the growth of agglomerates size is attributed to growth mechanisms that describe the successive addition of material on already formed nuclei.

4.4 Constant Size Zone: In this zone agglomerates cease to grow or even show slight decrease in size. Here the frequency of coalescence is balanced by the breakage frequency of agglomeration. The size reduction may be due to attrition, breakage and shatter. The rate determining step in agglomeration growth occurs in zero growth zones when bridging liquid is squeezed out of the pores as the initial flocules are transformed into small agglomerates. The rate determining step is the collision of particle with the bridging liquid droplets prior to the formation of liquid bridges. The rate is governed by the rate of agitation. The strength of the agglomerates is determined by interfacial tension between the bridging liquid and the continuous liquid phase, contact angle and the ratio of the volumes of the bridging liquid and solid particles.

Conclusion: The spherical crystallization could shorten the manufacturing process in tabletting, so that the cost and time of manufacturing of the tablets could be reduced. But the residues of organic solvent after the formation of agglomerates have to be monitored for passing the regulatory requirements. Agglomerates exhibit excellent physicochemical and micromeritic properties, solubility, dissolution rate, stability and in vivo (preclinical and clinical) performance when compared with pure drug as well as marketed formulation besides exhibiting no preclinical toxicity. If this process can be scaled-up to manufacturing level, this technology has the potential to provide the directly compressed tablets of poorly compressible and poor water soluble drug with improved bioavailability.
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