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Research Article

# SPHERICAL CRYSTALLISATION – A MODERN TECHNIQUE FOR DIRECT COMPRESSION OF PHARMACEUTICAL SUBSTANCES

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**ABSTRACT**

The direct compression is a modern technique in the tablet manufacturing, many processing steps are limited in direct compression compared to conventional wet granulation method and also wet granulation cannot be used with sensitive drugs. Spherical agglomeration is a modern technique for development of directly compressible pharmaceutical dosage forms where the drug crystals are converted to spherical form to improve flowability, compressibility and packability. The spherical crystallization further developed use with hydrophilic polymers to enhance dissolution rate characteristics of poorly water soluble drugs. The spherical agglomerates evaluated in terms of flow properties, particle size analysis, compression and dissolution behavior. Physical characters of the crystals were studied for the morphology of crystals using scanning electron microscope (SEM), identification of polymorphism done by x-ray powder diffraction (XPRD) and for thermo dynamic properties using differential scanning calorimetry (DSC).

**Keywords:** Spherical crystallization, Spherical agglomeration, bridging liquid, Direct compression, flowability, compressibility.

## INTRODUCTION

Today the tablet is the most popular dosage form of pharmaceuticals. The most economical solution to prepare the tablet is the direct compression method especially for large volume products. For the direct compression method less equipment, space, lower labor costs, less processing time and lower energy consumption are required. One of the most recent developments in agglomeration is the invention of spherical crystallization in which spherical agglomerates are produced in situ by the agglomeration of the small crystals during crystallization. These particles gain favorable downstream processing characteristics combined with desirable bioavailability properties. In pharmaceutical production improved flowability and compaction reduces the number of formulation components and processing operations. The advantages of spherical agglomerates are good Physico-chemical properties like compressibility, uniform and predictable dissolution, suitability for microencapsulation, flowability, packability that improve mixing, filling and tableting.

Solvents and solvent composition, amount of bridging liquid, the agitation rate, initial particle size, feeding rate, stirring rate, temperature and concentration of the solid etc are the important parameters which influence the spherical crystallization. These parameters influence not only the productivity but also particle size distribution, morphology and strength of the product. The influence of above parameters has been explored earlier by using different materials as model compounds.

## METHODS OF SPHERICAL AGGLOMERATION

Spherical crystallization is a solvent exchange crystallization method in which crystal agglomeration is purposely induced through the addition of a third solvent, termed the bridging liquid. Crystal agglomeration, which is usually avoided during normal processing, performed in a controlled fashion during spherical crystallization to bring about improved flow and compaction properties to the material. These properties are highly advantageous for pharmaceutical production. Currently, optimization of spherical crystallization is difficult as the mechanism and effect of process parameters are unclear. In-process monitoring of the chord length distribution to track the rate and degree of change to particle dimension and particle count can provide insight into the dynamics of spherical crystallization. The chief requirement in the spherical crystallization system is small amount of bridging liquid. The proportion of bridging liquid in the given system can be determined by plotting a ternary or solubility diagram of the bridging liquid in the given system. In the region above the phase separation curve the system is completely miscible, but the region just below the separation curve indicates the presence of small quantity of bridging liquid. Following are the methods to prepare spherical crystals.

### SIMPLE SPHERICAL AGGLOMERATION

In the simple spherical agglomeration method a third solvent called the bridging liquid is added in a small amount to promote the formation of agglomerates. A near saturated solution of the drug in a good solvent is poured into a poor solvent. The poor and good solvents are freely miscible and the affinity between the solvents is stronger than the affinity between drug and good solvent, leading to precipitation of crystals immediately. Under agitation, the bridging liquid (the wetting agent) is added, which is immiscible with the poor solvent and preferentially wet the precipitated crystals. As a result of interfacial tension effects and capillary forces, the bridging liquid adheres the crystals to one another resulting in the formation of larger size agglomerates.

The most important parameters in spherical agglomeration are the selection and amount of the bridging liquid, the agitation rate, concentration of the solid, temperature, initial particle size and feeding rate.

The agitation speed of the system is one of the main parameter determining the average diameter of agglomerated crystals. With increasing agitation speed of the system, the shear force applied to the droplets increases, leading to more dispersed and consolidated droplets, this resulting in a reduction of the particle size of the product. an increase in stirring speed makes the agglomeration process less efficient (Bos and Zuiderweg 1987; Tambo and Watanabe 1979). Blandin et al., (2003) found that at higher stirring rate the final agglomerates tend to be less porous and more resistant.


**Figure 1: Formation of spherical agglomerates and separate from the suspending liquid by the addition of a small amount of bridging liquid.**

**Ammonia diffusion method**

A mixture of three partially immiscible solvents i.e., acetone-ammonia water-dichloromethane was used as a crystallization system. Here, ammonia water acts as bridging liquid as well as good solvent for enoxacin. Acetone is a water miscible but a poor solvent, thus enoxacin gets precipitated by solvent change without forming ammonium salt. Dichloromethane induces liberation of ammonia water. Thus acetone in the solvent enters into droplets of ammonia water which are liberated from acetone-ammonia water-dichloromethane system, and consequently, enoxacin dissolved in ammonia water is precipitated while the droplet collects the crystals. At the same time, ammonia in the agglomerates diffuses to the outer organic solvent phase and its ability as a bridging liquid becomes weaker and the agglomerates are obtained. This is useful in agglomeration of drugs which are soluble only in an acidic or an alkaline solution.

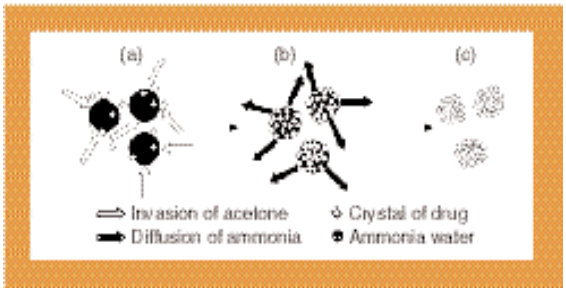


**Figure 2: Spherical crystallization mechanism using ammonia diffusion method.**

**Emulsion solvent diffusion method**[1]

In this technique spherical agglomerates prepared by using a mixed system of two or three partially miscible solvents, i.e. bridging liquid–poor solvent system or good solvent-bridging liquid-poor solvent system. Here the affinity between the drug and good solvent is stronger than affinity between drug and poor solvent. Residual good solvent in droplets acts as a bridging liquid to agglomerate the generated crystals. Due to the interfacial tension between the two solvents, the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The crystallization of drug occurs by counter diffusion of good solvent and poor solvent. Finally the emulsion is stabilized by the selection of suitable polymer which is required for proper crystallization. Kawashima Y[2] attempted emulsion solvent diffusion method for making spherical crystals of anti rheumatic drug bucillamine using HPMC for coating and obtained uniformly coated directly compressible crystal agglomerates of bucillamine.

**Neutralization method**

This process involves the formation of fine crystals and their agglomeration. The spherical crystallization of anti diabetic drug tolbutamide was prepared by this technique. The drug was dissolved in NaOH solution. Aqueous solution of HPMC and HCl was added to neutralize NaOH solution of tolbutamide and tolbutamide was crystallized out. The bridging liquid was added drop wise at the rate of 10 ml /min followed by agglomeration of tolbutamide crystals[3]

Sano et al[4] reported that the tolbutamide agglomerates prepared by neutralization technique found to have more specific surface area, more wettability and better dissolution rate as compared to the agglomerates prepared by Emulsion solvent diffusion and solvent change method. The agglomerates prepared by neutralization method were instantaneously permeated with water showing strikingly greater wettability. The reason for this superior wettability of agglomerated crystals and tablets reported was due to the fact that, at the time of agglomeration, hydrophilic polymer (HPMC) in the crystallization solvent adheres firmly to the agglomerated crystals.

Spherical agglomeration has more importance than the other methods because it is easy to operate and selection of the solvents is easier than the other methods. In other methods quasi emulsion method receives the second importance.

**Solvent selection**

The guidelines to select solvents and proceed further using different methods. The suggested solvents and agglomeration methods for spherical agglomeration of various types of solids (Chow and Leung, 1996). SA= Spherical agglomeration, QESD = Quasi-emulsion solvent diffusion.

**Table 1: Drug solubility and selection of solvents, bridging liquid and method.**

| Drug solubility | Continuous phase | Bridging liquid | Method Used |
|---|---|---|---|
| Soluble in water | Water-immiscible Organic solvent | 20% calcium chloride solution | Spherical agglomeration |
| Soluble in organic solvents | Water | Water-immiscible Organic solvent | Spherical agglomeration |
| Soluble in water-miscible organic solvents | Saturated aqueous solution | Organic solvent mixture | Quasi-emulsion solvent diffusion. |
| In Soluble in water or any organic solvent | Water-immiscible Organic solvent | 20% calcium chloride Solution+ binding agent | Spherical agglomeration |

**PHYSICO CHEMICAL CHARACTERIZATION OF SPHERICAL AGGLOMERATES**

**FLOW PROPERTY**

Several methods are used to determine of flow property, commonly used methods are angle of repose and dispersibility described below.

**Angle of repose**

Among several methods angle of repose is the common method used for determination of flow property. The angle of repose is the angle between the horizontal and the slope of the heap or cone of solid dropped from some elevation. Values for angle of repose ≤ $30^0$ usually indicate free flowing material and angle ≥$40^0$ suggested a poor flowing material.

Angle of Repose ($\phi$) = $\tan^{-1} h / r$

Where h- height of the cone and r- diameter of the cone

| Angle of repose | Flow |
|---|---|
| <25 | excellent |
| 25-30 | Good |
| 30-40 | passable |
| >40 | very poor |

**Dispersibility**

It is the ability of a material to flow or pour easily over planes. Dispersability, dustiness, & floodability are inter- related term.

Dispersibility =

(Weight of powder in watch glass/Initial weight of the sample) x 100

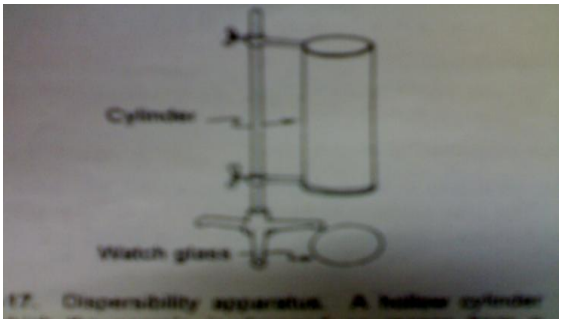


**Figure 3: Dispersibility apparatus: A hallow cylinder through which is Drop from a height 61 cm above the glass watch.**

**Bulk Density**

Density apparatus is used to determine bulk volume.

Bulk density = mass of the powder (w) /bulk volume (Vb)

When particle are loosely packed, lots of gaps in between particle increase the bulk volume by making powder light. Powder classified as 'light'or 'heavy' "light powder have high bulk volume" Higher the bulk volume bigger the size of capsule.

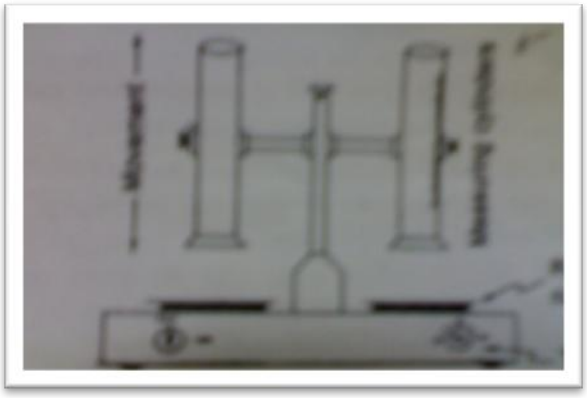

**Figure 4: Bulk density apparatus**

**Compressibility index or Carr index**

Carr derived a simple indication of ease with which a material can be induced to flow is given by application of compressibility index

%Compressibility =
(Tapped density – Bulk density /tapped density) X 100

| Consolidation index (%) | Flow |
|---|---|
| 5-15 | Excellent |
| 12-16 | Good |
| 18-21 | fair to passable |
| 23-25 | Poor |
| 33-38 | very poor |
| >40 | very very poor |

**Hausner's ratio**

It is calculated from bulk density and tap density.

Hausner's Ratio =Tapped density/Bulk density

Hausner's ratio of less than 1.25 (equivalent to 20% carr's) indicates good flow. Greater than 1.5 (equivalent to 33% carr's) indicates flow. Between 1.25 & 1.5- added glidant – improves flow.

**Porosity**

The state of packing of a powder is described by its porosity, which is defined as the ratio of the void volume to the bulk volume of the packing.

Porosity = (Bulk volume – Tapped volume)/Bulk volume

Porosity is frequently expressed in percent. Porosity values were computed for all batches using the formula.

**Compression properties**

This property normally used for the preparation of the tablet. This process also called compaction. During this porosity of powder changes,

Plastic behavior: Deformed on compression, compact powder get deformed which is tapped into close packing.

Dilatant behavior: Shows unexpected expansion under the stress, some substances when compacted exhibits higher porosity than the powder in close packing.

**Strength analysis**

The mechanical strength of single agglomerates was determined by compression in materials – testing machine. As shown in figure 2 the agglomerate was placed and a gradually increasing load was applied to the agglomerate by a constant movement of the upper plane towards the lower plane with a speed of 0.5mm/min. About 100 to 150mg of agglomerates were poured into a cylindrical steel cup (8.2mm in diameter) and the powder bed was compressed.

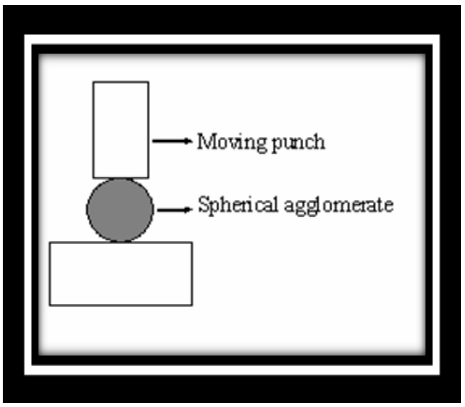


**Figure 5: Compression of the spherical agglomerates.**

$F = (\pi d2/4) x\sigma$

$\varepsilon = l/d$

The measured force (F), stress (σ), strain (ε)

**Optical Microscopy**

The shape, size, dimensions of the spherical crystals are studied by observing under an optical microscope. The observations are made under different magnifications.

**Scanning Electron Microscopy**

The surface morphology, type of crystals, shape and size of the spherical crystals is analyzed by using scanning electron microscopy.

| Nature of particle | Effect on flow property |
|---|---|
| Smooth surface | Increase the flow property |
| Rough surface | Poor flow due to friction |
| Flat and elongated particle | Gives high porosity |
| high density & low porosity | Good flow property |

**Fourier Transform Infrared Spectroscopy (FTIR)**

The structure and Compatibility studies, drug-polymer interactions were studied by Fourier Transform infrared spectroscopy.

**X-ray Powder Diffraction**

Polymorphism existence, the form of crystallinity and intensity of drug crystals in agglomerates are determined by using XPRD technique. An amorphous form does not produce a pattern. The X-ray scattered in a reproducible pattern of peak intensities at distinct

angle (2θ) relative to the incident beam. Each diffraction pattern is characteristics of a specific crystalline lattice for a compound.

**Table 2: Various research spherical crystallization methods to enhance drug flow and compressibility properties.**

| Drug | Method used | Enhanced drug property |
|---|---|---|
| Celecoxib[5] | Spherical agglomeration method. | Flowability, packability, compressibility, dissolution and bio availability. |
| Ibuprofen[6] | Quasi emulation solvent diffusion method. | Flowability, compressibility and solubility. |
| Flurbiprofen[7] | Spherical agglomeration method. | Flowability, compressibility and solubility. |
| Fenbufen[8] | Spherical agglomeration method. | Flowability, packability and compressibility. |
| Mefenamic acid[9] | Spherical agglomeration method. | Flowability, compressibility and packability. |
| Enoxacin[10] | Ammonia diffusion method. | Flowability, packability and compressibility. |
| Norfloxacin[11] | Ammonia diffusion method. | Flowability and compressibility. |
| Aceclofenac[12] | Spherical agglomeration method. | Flowability, packability and compressibility. |
| Acebutalol HCl[13] | Quasi emulation solvent diffusion method. | Flowability and compressibility. |
| Tolbutamide[14] | Neutralization method. | Flowability, compressibility and dissolution rate. |
| Aminophylline[15] | Spherical agglomeration method. | Flowability, compressibility. |

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