7 Spherical Crystallization

INTRODUCTION

Spherical crystallization is a particle designing technique, by which crystallization and agglomeration can be carried out simultaneously in one step. The spherical crystallization technique also involves the use of a bridging liquid that improves compressibility by acting as granulating fluid. Thus, spherical crystallization (Fig. 7.1) is a method that helps achieve good flow ability and compressibility. Spherical crystallization can be achieved by various methods such as simple spherical crystallization, emulsion solvent diffusion, ammonia diffusion, and neutralization. The principal steps involved in the process of spherical crystallization are flocculation zone, zero growth zone, fast growth zone, and constant size zone. Factors controlling the process of agglomeration are solubility profile, mode and intensity of agitation, temperature of the system and residence time. Spherical crystallization is having wide applications in pharmaceuticals like improvement of flow ability and compressibility of poorly compressible drugs, masking bitter taste of drugs and improving the solubility and dissolution rate of poorly soluble drug. In the pharmaceutical industry, the crystal size growth and the formation of the spherical crystal agglomerates are very important for preparing the solid dosage forms (e.g. capsules, tablets, etc.). The particle size of the agglomerates produced by the spherical crystallization techniques is 300–500 mm in diameter and their shape is more or less spherical. The agglomerates have very good flow property, high bulk density, and compressibility values. They can be used directly for capsule-filling (without excipients) and direct tablet making (without granulation, drying, etc.). The drug materials produced by the spherical crystallization technique are economical in the development of the solid dosage forms. The typical spherical crystallization technique employs three solvents—one is the substance dissolution medium, another is a medium, which partially dissolves the substance, and third is the wetting solvent for the substance. The traditional crystallization processes (salting- out precipitation, cooling crystallization, crystallization from the melting, etc.) can also be used to produce spherical crystal agglomerates. It may be called a nontypical spherical crystallization process.

METHODS OF SPHERICAL CRYSTALLIZATION

The methods of spherical crystallization are categorized as:

- Quasi emulsion solvent diffusion method (QESD)
- Ammonia diffusion method (AD)
- Solvent change method (SC)
- Salting-out method (SO)

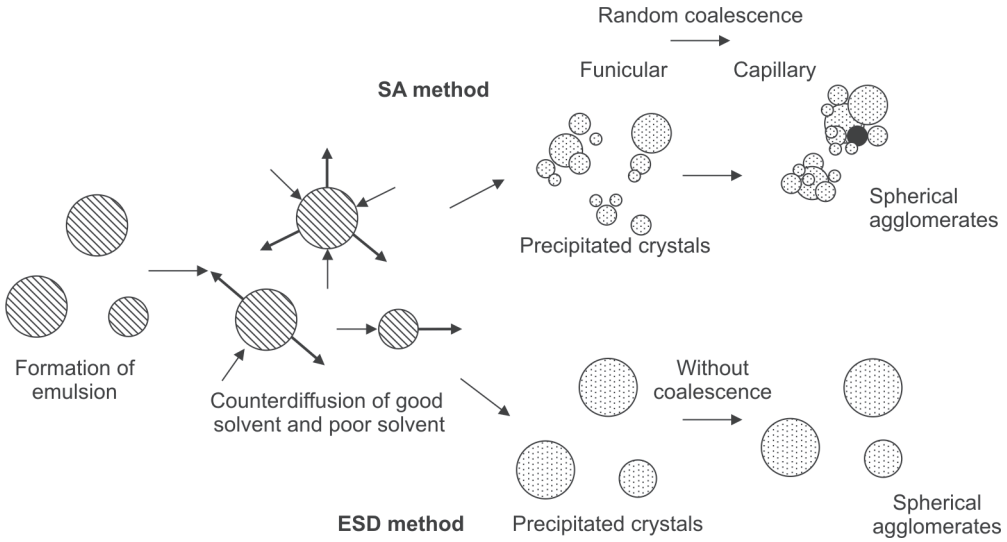


Fig.7.1: Mechanism of spherical crystallization

Quasi Emulsion Solvent Diffusion (QESD)

In the emulsion solvent diffusion, the affinity between the drug and the good solvent is stronger than that between the good solvent and the poor solvent. The drug is dissolved in the good solvent, and the solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even though the pure solvents are miscible. The good solvent diffuses gradually, out of the emulsion droplets into the surrounding poor solvent phase, and the poor solvent diffuses into the droplets resulting into drug crystallization within the droplets. The method is considered to be simple than the SA method, but it can be difficult to find a suitable additive to keep the system emulsified and to improve the diffusion of the poor solute into the dispersed phase.

Ammonia Diffusion (AD) Method

In this method, the mixture of three partially immiscible solvent, i.e. acetone, ammonia water, and dichloromethane was used as a crystallization system. In this system ammonia water acted as bridging liquid as well as a good solvent. Acetone was the water miscible however, it acts as a poor solvent, thus drug precipitated out by solvent change without forming ammonium salt. Water immiscible solvents include hydrocarbons or halogenated hydrocarbons, e.g. dichloromethane induced liberation of ammonia water.

Principle Steps Involved in the Process of Spherical Crystallization

Bermer and Zuider Wag proposed that four steps are involved in the growth of agglomeration.

I. Flocculation zone

In this zone, the bridging liquid displaces the liquid from the surface of the crystals and these crystals are brought in close proximity by agitation; the adsorbed bridging liquid links the particles by forming a lens bridge between them. In these zones, loose open flocs of particles are formed by pendular bridges.

II. Zero growth zone

Loose floccules 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 to be completely filled with the bridging liquid. The driving force for the transformation is

provided by agitation of the slurry causing liquid turbulence, pellet-pellet and pellet-stirrer collision.

III. Fast growth zone

The fast growth of the agglomerates takes place, when sufficient bridging liquid is 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 a slight excess of surface moisture. This imparts plasticity to nucleus and enhances particle deformations and subsequent coalescence. Another reason for the growth of agglomerates is attributed to growth mechanisms that describe the successive addition of material on already formed nuclei.

IV. Constant size zone

In this zone agglomerates cease to grow or even show marginal decrease in size. Here, the frequency of coalescence is balanced by the breakage frequency of agglomeration. The size reduction may result due to attrition, breakage and shatter. The rate-determining step in agglomerates growth that occurs in zero growth zones, when bridging liquid is squeezed-out of the pores as the initial floccules are transformed into small agglomerates. The rate determining step is the collision of particles with the bridging liquid droplets prior to the formation of liquid bridges. The rate is also governed by the speed 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 to solid particles.

Solvent Change (SC) Method

The solution of the drug in a good solvent is poured in a poor solvent under controlled condition of temperature and speed to obtain fine crystals. These crystals are agglomerated in the presence of bridging liquid. The poor solvent has miscibility with good solvent, but low solubility with solvent mixture, so during agitation of the solvent system the crystals formed. The drawback of this system is that it provides low yield because the drug shows significant solubility in the crystallization solvent due to cosolvency effect. This method is not applicable for water insoluble drugs.

Salting-out (SO) Method

This method involves the addition of suitable salt that relatively makes good solvent to be poor solvent, thus drug tends to crystallize out in the presence of bridging liquid.

Crystallization Mechanism of Nanomaterials

The controllable synthesis of new nanostructures has an enormous impact on the fabrication and application of nanomaterials and continues to be a central challenge in nanoscience and nanotechnology. In order to explore the growth kinetics of the crystallization of nanomaterials, endeavors have been made to a large extent to the parallel experiments, in situ observations, and theoretical modelings. Despite some exciting results, essential factors, which can modify and effect the thermodynamics and kinetics are still ambiguous. Understanding of colloidal nanocrystal growth mechanism is essential for the preparation of nanocrystals with desirable chemical/physical properties. Recent in situ experiment has suggested that colloidal nanoparticles can grow either by monomer attachment from solution or by particle coalescence. However, atomic-scale in situ observations are still beyond our scope.

Composition-controlled Crystallization of Nanomaterials

In addition to structural controlled synthesis, composition-controlled crystallization appears especially important for nanomaterials. Doping can enhance the performances of semiconductors by providing a powerful method to control their optical, electronic, transport, and spintronic properties. Furthermore, introducing specific dopants could also lead to dramatic changes in morphology except altering the atomic composition

and structure of the nanocrystals. Doping models of nanomaterials are summarized in Table 7.1. Models proposed at present are aimed at the host crystal, whose structure remains unchanged during the whole doping process, and doping models that take into account the structural transition are thus needed. Moreover, recent study indicates that the influence of shape parameter on doping content and doping state can provide an alternative approach to adjust the doping degrees of doping materials. Ion exchange reaction has been demonstrated to be another effective approach to increase the compositions of inorganic functional materials in various solution-based chemistry approaches. Such crystallization process is associated with localized chemical conversions of the host structure, which can serve as a solid state precursor (Table 7.2).

Spherical Agglomeration (SA)

A near saturated solution of the drug in a good solvent is poured into a poor solvent. Provided that the poor and good solvents are freely miscible and the affinity between the solvents is stronger than the affinity between the drug and the good solvent, crystals will precipitate immediately. In the spherical agglomeration method also a third solvent called the bridging liquid is added in a smaller amount to promote the formation of agglomerates. Under agitation, the bridging liquid (the wetting agent) is added. The bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals. As a result of interfacial tension and capillary forces, the bridging liquid acts to adhere the crystals to one another. The spherical agglomeration method 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. Less than the optimum amount of bridging liquid produces plenty of fines, while more than optimum amount produces very coarse particles. Also the choice of bridging liquid, the stirring speed and the concentration of solids (or of the

Table 7.1: Nanocrystal doping models

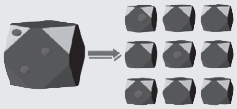
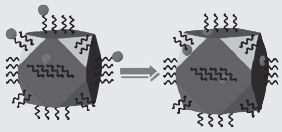
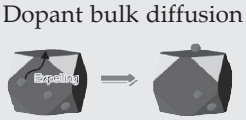
Doping model	*Model description*	*Characteristics*
Statistical model	Dopant solubility remains the same as in the bulk crystal, and nanocrystals tend to be pure simply, since they contain so few atoms owing to their smaller volume.	Decreasing size 
Trapped-dopant model	The impurity adsorbs on the surface of nanocrystal and then incorporates into nanocrystal. Doping is thus relative easy for the nanocrystal exposed surface favorable for impurity binding	Growth and incorporation 
Self-purification model	Nanocrystals are difficult to dope due to thermodynamic limitations and dopants are therefore expelled from bulk.	Dopant bulk diffusion 
Novel models for the doping process accompanied by structural transformation		Structural transformation 

Table 7.2: Different crystallization models of nanoparticles

Crystallization model	*Model description*	*Characteristics*
Classical nucleation theory (CNT)	Surface energy and chemical potential (related to monomer supersaturation) codetermine the nucleation of nanoparticles.	It fails to provide information about the size and distribution. Only Gibbs-Wulff morphology can be simulated.
First-order reaction-diffusion model	By combining Fick's first law and first-order reaction rate, particle radius with time can be obtained.	Size distribution and its role in the nanoparticle growth process is still beyond the scope of this model.
Combination of CNT and reaction-diffusion growth equations	It can simulate the growth state of nanocrystals.	The assumed initial seeding distribution curve has an inten sive relation with final results.
Rate-equation-based growth model	Evolution of the entire size distribution with time can be described	It requires solving rate equations skillfully. No information about growth morphology can be provided. Growth approach should be initially assumed.
Surface area limited model	It combines surface diffusion, step-growth rate and surface site availability to describe an isotropic coarsening of faceted nanoparticles.	The effective number of sites available for monomers adsorbtion determine nanoparticle shape evolution.
Chemical bonding theory of single crystal growth	Chemical-bonding processes play-a critical role in crystallization.	Morphological evolution during crystallization process can be successfully simulated.

solute) are of importance. In case of lactose, the agglomerate size distribution was affected by both the size of raw particles and the amount of bridging liquid used. On increasing stirring rate the agglomeration was reduced because of increasing disruptive forces. Higher stirring rate produces agglomerates that are less porous and more resistant to mechanical stress, while the porosity decreases. The viscosity of the continuous phase has an effect on the size distribution of the agglomerates. The choice of bridging liquid exhibits an influence on the rate of agglomeration and also on the strength of the agglomerates.

Factors Controlling the Process of Agglomeration

Solubility

The selection of solvent is dictated by solubility characteristics of drug. A mutually immiscible three solvent system, consisting of a poor solvent (suspending liquid), good solvent and bridging liquid are necessary. Physical forms of product, i.e. microagglomerates or irregular macroagglomerates or paste of drug substance can be controlled by selection of proper solvent proportion. The proportion of solvent to be used is determined by carrying out solubility studies and constructing triangular phase diagram to define the region of mutual immiscibility by using ternary diagram.

Agitation

High speed agitation is necessary to disperse the bridging liquid throughout the system. Any change in agitation pattern or fluid flow would be reflected as a change in force acting on agglomerate, which ultimately affects the shape of agglomerate. The extent of mechanical agitation in conjuction with the amount of bridging liquid determines the

rate of formation of agglomerate and their final size.

Temperature

Study revealed that the temperature has a significant influence on the shape, size and texture of the agglomerates. The effect of temperature on spherical crystallization is probably due to the effect of temperature on the solubility of a drug substance in the ternary system.

Residence Time

The time for which agglomerates remain suspended in reaction mixture affects their strength.

Advantages of Spherical Crystallization

1. Spherical crystallization technique has been successfully utilized for improving flowability and compressibility of drug powder.
2. This technique could enable subsequent processes such as separation, filtration, drying, etc. to be carried-out more efficiently.
3. By using this technique, physicochemical properties of pharmaceutical crystals are dramatically improved for pharmaceutical process, i.e. milling, mixing, and tabletting because of their excellent flowability and packagability.
4. This technique may enable crystalline forms of a drug to be converted into different polymorphic forms having better bioavailability.
5. For masking of the bitter taste of drug.
6. Preparation of microsponge, microspheres and nanospheres, microbaloons, nanoparticles and micropellets as novel particulates drug delivery system.

Amphiphilic Microenvironments Conducive to Crystallization

The first report of successful membrane protein crystallizations constituted a paradigm for membrane protein crystallization; transfer membrane proteins from their native environment into particulate detergent micelles in order to purify and to crystallize them in the same way as soluble proteins. It was reasoned that homogenous, lipid-free protein detergent micelles of uniform size would be most suitable for crystallization processes. The choice of the detergent for crystallization purposes is based on three factors—(i) stabilization of the native conformation of the membrane protein in monodisperse form, (ii) enabling protein-protein contacts in the packed crystal and, (iii) preventing detrimental phase separations during crystal growth. This line of thinking was expanded in the recent years, particularly with respect to lipids being recognized as beneficial and sometimes crucial crystallization components. Most detergents belong to one of the following categories—ionic, nonionic or Zwitterionic. Their characteristic behavior depends on their shape, stereochemistry of the head group and tail. According to the 'intrinsic curvature hypothesis' they form supramolecular structures in water due to the hydrophobic effect and their shape. At sufficiently high concentrations, i.e. above the critical micellar concentration (CMC), detergents form micelles. These form roughly spherical objects in which detergent molecules are primarily packed with their orienting alkyl chains towards the center and their head groups towards the surface. Detergent molecules in micelles are flexible and exhibit a high degree of mobility, allowing for dramatic fluctuations in overall micellar shape including deformations, fusion, and fission Amphiphiles generally display a rich phase behavior commonly described with help of phase diagrams. Detergents typically have consolute boundaries, separating a single-phase micellar region from a dual micellar phase, wherein the latter of which consists of a detergent rich and a detergent depleted phase. At the cloud point a clear homogenous detergent solution turns to be turbid upon heating. Importantly, the addition of salt, variations of pH, etc. and in particular the introduction of additional components may

have profound, but essentially unpredictable effects on amphiphile phase behavior. The fact that a 'simple' ternary system consisting of oil, water and block copolymer amphiphile may form nine different isothermal phases spectacularly illustrates this polymorphism, which is a typical feature of amphiphiles. Lipid polymorph phases include fluid isotropic phases, planar, positively and negatively curved bilayer phases, rod-shaped hexagonal phases, micellar phases and bicontinuous cubic phases and they occur, among other shapes, as a function of composition, hydration, pressure, and temperature. Some integral membrane proteins may be introduced into detergent micelles following there refolding. Indeed, since β-barrel proteins can be expressed in *Escherichia coli* as inclusion bodies, membrane proteins such as OmpA or NspA can be purified in unfolded form and crystallized without any exposure or contact with lipids, thus ensuring that once reconstituted into detergent micelles they would form true detergent-protein micelles. In most of the cases, however, membrane proteins are extracted concomitantly with associated lipids from their native environment, i.e cellular membranes. Such mixed systems, consisting of detergent, lipids and membrane proteins form the so-called, protein detergent complexes (PDCs). The phase behavior of PDCs is expectedly complex and only in some selects cases portions of phase diagrams have been mapped-out. It is this state; however, that is usually employed in membrane protein crystallization trials and in many cases detergents as well as lipids are present in membrane protein crystals. Two-methodological advances have substantially aided many membrane protein crystallizations based on PDCs—(i) the introduction of small amphiphiles such as 1,2,3-heptanetriol to modify micelle dynamics and size and, (ii) the increase of the size of the hydrophilic portion by complexing with monoclonal antibodies or fragments thereof. The range of alternative amphiphilic vehicles for membrane proteins useful for crystallization purposes has increased in the recent years. Besides protein-detergent micelles and PDCs, membrane protein crystallizations were started from membraneous structures. The latter may be obtained by adding lipids to create structures that are small in size and planar such as bicelles or that are large such as in extended planar membranes or those that exhibit positive, or negative curvature. Curved bilayers membrane proteins include proteoliposomes or bicontinuous lipidic cubic phases. Furthermore, the quantity and type of lipid added to PDCs determine the nature of the resulting amphiphile phase. For some membrane proteins, it is very difficult to identify detergent-based conditions that could preserve their native conformation. This predicament has inspired several research groups to expand the range of solubilization strategies by designing new amphiphiles and to investigate the richness of their phase behavior for the purpose of membrane protein crystallization. Among these, amphiphiles are peptitergents, lipopeptide detergents, amphiphiles and new detergents with reduced alkyl chain mobility such as tripod amphiphiles. They all are self-assembled into small micelles, can be used to disperse lipid membranes. They are gentle, nondenaturing amphiphiles, which preserve the native structure of the test protein such as bacteriorhodopsin and other membrane proteins in solution for an extended periods of time.

Amphiphilic Microenvironment Inside Membrane Protein Crystals

Membrane protein crystals consist of three major molecular species—water, amphiphile, and membrane protein. Water and dissolved solutes form a fluid phase within the rigidly packed protein network, while amphiphiles may tightly bind to the protein surface and/or form a disordered state. The morphology and the strength of intermolecular contacts in protein crystals were investigated by Matsuura and Chernov (2003). It was found

that soluble proteins form crystal contacts frequently involving water molecules, which form specific intermolecular hydrogen bonds on top of nonspecific attractive electrostatic interactions. Similar contacts are present between hydrophilic protein surfaces of membrane proteins in crystals. In some cases amphiphiles form interactions that are crucial to crystal packing. The structures that amphiphiles form within membrane protein crystals, are remarkably diverse and go beyond the simple two-types of classification introduced. According to these categories, type I crystals are consisted of stacked membraneous layers. They stick together via hydrophobic interactions in the plane of the layers, resembling 2D crystals, and polar contacts mediated interlayer interactions. Conversely, type II crystals possess contacts involving the polar regions of membrane proteins only. The hydrophobic perimeter is embedded in a torus of detergent molecules. Typical type I crystals have been found in all cases, where membrane proteins were crystallized with the cubic phase method. Bacteriorhopsin packs in a unidirectional way 'head to tail', while halorhodopsin packs in layers, where heads interact with heads and tails with tails, and sensory rhodopsin II packs in layers with mixed up-down arrangements. Bacteriorhodopsin crystals were shown by mass spectrometry to contain native lipids that were copurified, namely 2,3-di-O-phytanyl derivatives of phosphatidylglycerol, phosphatidylglycerol sulfate, phosphatidylglycerol phosphate methylester, triglycosyldiether, sulfated triglycoside lipid and sulfated tetraglycosyldiphytanylglycerol, when crystallized from lipidic cubic phases and they contained similar lipids, when crystallized as PDCs. Amphiphile phase transitions occur during crystallization. The crystallization process consists of two steps, nucleation, and crystal growth. Nucleation is a critical phenomenon and hardly anything is known specifically for membrane protein crystallizations. Soluble protein crystallization growth is mainly initiated and driven by modification of the water structure, creating conditions that allow and favor the defined association of proteins. Similar conditions need to be created for the hydrophilic sections of membrane proteins, i.e. screening of repulsive electrostatic surface charges by ions and providing conditions, where the protein is at supersaturation. The latter effect was investigated by Rosenow et al. (2003), who concluded from biochemical studies that membrane protein crystallization is favored by those amphiphiles that optimize the solubility of integral membrane proteins. At the same time, conditions are needed to be provided for the hydrophobic sections to maintain or to rearrangement into the suprastructures. Crystallizations involve phase transitions, an initial homogenous medium separates into a depleted phase and rich in amphiphile and membrane protein, the crystal. The association of protein/detergent micelles or PDCs into a type II packed crystal can easily be understood within the framework of present crystallization theory. The mechanism for PDC crystallization was studied and investigated by Marone et al. (1998), for photosynthetic reaction centers. These were shown to exist predominantly in the monomeric form throughout the entire crystallization process. Comparable experiments were used to characterize the effects of crystallization additives on the shape of pure detergent micelles (Littrell et al., 2000). It was found that micelles were elongated and rod-shaped and that their size grew on increasing the ionic strength whilst decrease when glycerol or PEG was added. In order to form continuous structures such as layered type I crystals or crystals with a continuous network of amphiphile phase, PDCs need to fuse and allow detergent and lipid molecules to rearrange into the supramolecular architecture as described above. Snijder et al. (2003) pointed out that the continuous detergent network in their crystals and the hydrophobic crystal contacts suggest that OmpIA molecules approach each other closely and coalesce their

detergent belts. The formation of the polar contacts might actually drive crystallization and induce the merging of micelles. They hypothesized that micelle fusion and the stabilization of a continuous network is mediated by the organic solvent and the amphiphile 2-methyl-2,4-pentanediol. Indeed, many of the putative type III crystal yielding conditions include the use of rather high concentrations of organic solvents or small molecule amphiphiles such as 1,2,3-heptanetriol. The picture emerges that this crystallization process may be driven partly or possibly be dominated by amphiphiles undergoing a phase transition prompted by an increase in system complexity.

Characterization of the Spherical Crystals

The spherical agglomerated crystals show significant effect on the formulation and manufacturing of pharmaceutical dosage forms, therefore, it is necessary to evaluate them by using different parameters.

Particle Size, Size Distribution and Particle Roundness

For the determination of the particle size (length, breadth, and roundness) light microscope fitted with image processing and analysis system is used. Size of the particles and their distributions can also be determined by simple sieve analysis. Now, with the help of Ro-Tap sieve shaker, particle size analysis can be performed. In advance technology, image-analyzer is used to determine the size and volume of the particle.

Roundness is a shape-related factor that provides information about the circularity of particles. It is calculated by using software according to the following formula:

Roundness = $(\text{Perimeter})^2/4$ area *1.064

The perimeter is calculated from the horizontal and vertical projections, with an allowance for the number of corners. An adjustment factor of 1.064 corrected the perimeter for the effect of the corners produced by digitization of the image. When roundness value is close to one, the particles are near to spherical in shape.

Particle Shape/Surface Topography

Following methods are used:

Optical Microscopy

The shape of the spherical crystals is studied by observing them under an optical microscope. The observations are made using 10X, 45X, 60X magnification (Fig. 7.2).

Scanning Electron Microscopy

The surface topography, type of crystals, polymorphism, and crystal habit of the spherical crystals are analyzed by using scanning electron microscopy.

X-ray Powder Diffraction

This is an important technique for establishing batch-to-batch reproducibility of a crystalline form. The form of crystal in agglomerates can be determined by using X-ray diffraction techniques. An amorphous form does not produce a pattern. The X-ray scatters in a reproducible pattern of peak intensities at distinct angle (2θ) relative to the incident beam. Each diffraction pattern is a characteristics of a specific crystalline lattice of a compound.

Flow Property

Flow property of the material largely depends on the force that is developed between the particles, particle size, particle-size distribution, particle shape, surface texture or roughness and surface area. Flowability of the agglomerates is much improved as the agglomerate exhibits lower angle of repose than that of single crystals. The improvement in the flowability of agglomerates could be attributed to the significant reduction in inter-particles friction, due to their spherical shape and relatively a low-static electric charge.

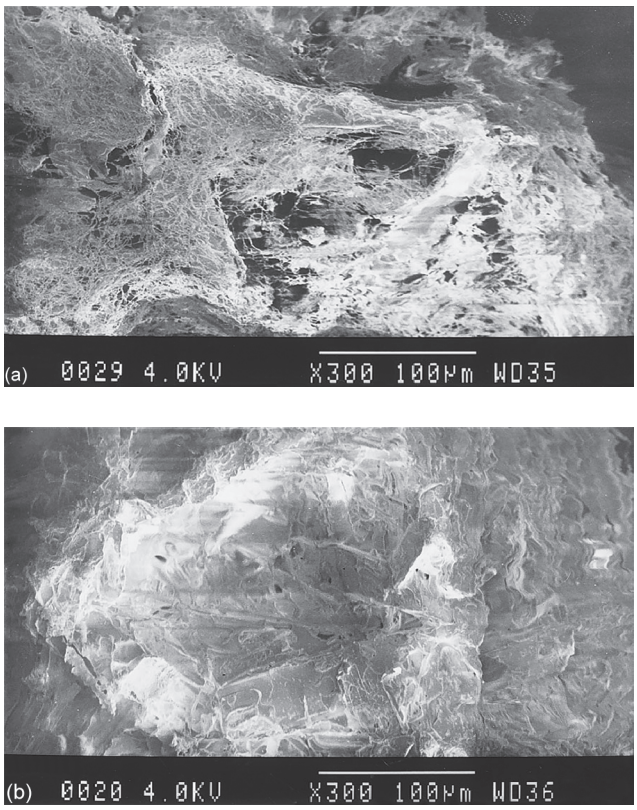


Fig. 7.2: Scanning electron photomicrographs of spherical crystal agglomerates—(a) reference sample, (b) agglomerates of ibuprofen—Eudragit®

Following are the methods used to determine of flow property:

Angle of Repose

This is a common method used to determine the flow property. The angle of repose is the angle between the horizontal plane and the slope of the heap or cone of solid dropped from some elevation. Values for angle of repose 30° usually indicate free flowing material and angle 40° suggest for a poor flowing material. The angle of repose can be obtained using following equation:

$$\tan \theta = h/0.5\ d$$

where, h—height of the cone and d—diameter of the cone

Compressibility or Carr Index

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

$$I = (1 - V/V_0) * 100$$

where, V = the volume occupied by a sample of powder after being subjected to a standardized tapping procedure and V_0 = the volume before tapping. The value below 15%, indicates good flow characteristics and value above 25% indicates poor flowability.

Hausner Ratio

It is calculated from bulk density and tapped density.

Hausner ratio = Tapped density/Bulk density

Values less than 1.25, indicate good flow (20% Carr Index) and a value greater than 1.25 indicates poor flow (33% Carr index).

Density

Density of the spherical crystals is the mass per unit volume.

$$\text{Density} = M/V$$

Porosity

Porosity of granules affects the compressibility. Porosities are of two types namely intragranular and intergranular and these are measured with the help of true and granular densities.

Intragranular porosity = 1–granular density/true density.
Intergranular porosity = 1–bulk density/granular density
Total porosity = 1–bulk density/true density

Packability

Improved packability has been reported for agglomerates prepared by spherical crystallization. The angle of friction, shear cohesive stress and shear index are lower than that of single crystals, which can improve the packability of the agglomerates.

The packability of agglomerates is improved as compared to those recorded for the original crystals and that the agglomerated crystals are adaptable to direct tabletting. The packability assessed by analysis of the tapping process with the Kawakita (I) and Kuno (II) method and using the parameters a, b, $1/b$, k in the equation

$$N/C = 1/(ab) + N/a \quad \text{(i)}$$

$$C = (V_o - V_n)/V_o,$$

$$a = (V_o - V_h)/V_o$$

$$r_f - r_n = (r_f - r_o) \exp(-kn) \quad \text{(ii)}$$

where: N = Number of tapping
C = Difference in volume (degree of volume reduction) and a, b are constants.

Compression Behavior Analysis

Good compactibility and compressibility are essential properties of directly compressible crystals. The compaction behavior of agglomerated crystals and single crystals is obtained by plotting the relative volume against the compression pressure. Spherical agglomerates possess superior strength characteristics in comparison to conventional crystals. It is suggested that the surfaces are freshly created fractures during compression of agglomerates, which enhances the plastic-interparticle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation compared to that of single crystals.

Compaction behavior of agglomerated crystals is evaluated by using following parameters:

Heckel Analysis

The following Heckel's equation is used to analyze the compression process of agglomerated crystals and assessed their comapactibility.

$$In[1/(1-D)] = KP + A$$

where:

A—constant to represent particle rearrangement.
D—relative density of the tablets under compression pressure
K—slope of the straight portion of the Heckel plot

The reciprocal of K is the mean yield pressure (P_y).

The following equation gives the intercept obtained by extrapolating the straight portion of the plots

$$A = In[1/(1-D_0)] + B$$

where:

B is constant to represent particle rearrangement.

D_0 is the relative density of the powder bed when $P = 0$.

The following equation gives the relative densities corresponding to A and B.

$$D_A = 1 - e - A$$
$$D_B = D_A - D_0$$

Stress Relaxation Test

A specific quantity of spherical agglomerated crystals sample is placed in a die of a specific diameter, i.e. the surface of which is coated with magnesium stearate in advance, then used the universal tensile compression tester to compress the sample at a constant pressure. After the certain limit of pressure applied or attained, the upper punch held in the same position for 20 minutes, during which the time

for the reduction of the stress applied on the upper punch is measured. The result is corrected by subtracting the relaxation measured without powder in the die from the measured force under the same conditions.

The following equation establishes the relationship between relaxation ratio $Y(t)$ and time t, calculated parameters A_s and B_s, and also the assessed relaxation behavior.

$$t/Y(t) = 1/A_s\ B_s - t/A_s$$

$$Y(t) = (P_0 - P_t)/P_0$$

where, P_0 is the maximum compression pressure, and P_t is the pressure at time t.

Mechanical strength

Spherical crystals should possess good mechanical strength as directly reflected from the mechanical strength of compact or tablet. It is determined by using the following two methods.

Tensile strength

Tensile strength of spherical crystals is measured by applying maximum load required to crush the spherical crystal. This method is a direct method of tensile strength measurment of spherical crystals.

Crushing strength

It is measured by using 50 ml glass hypodermic syringe. The modification includes the removal of the tip of the syringe barrel and the top end of the plunger. The barrel is then used as hallow support and the guide tube with close fitting tolerances to the plunger. The hallow plunger with open end served as load cell in which mercury could be added. A window is cut into the barrel to facilitate placement of granule on the base platen. The plunger acts as a movable plates and sets directly on the granules positioned on the lower platen, as the rate of loading may affect crushing load (gm). Mercury is introduced from reservoir into the upper chamber at the rate of 10 gm/sec until the single granule crushed; loading time should be <3 minutes. The total weight of the plunger and the mercury required to fracture a granule is measured as the crushing load.

Friability Test

The friability of the spherical crystals is the combination of the attrition and sieving process of a single operation. Granules along with the plastic balls are placed on a test screen. The sieve is then subjected to the usual motion of a test sieve shaker to impart the necessary attrition motion to the granules. The weight of powder passing through the sieve is recorded as a function of time. The friability index is determined from the slop of the plot between % weights of granules remaining on the sieve as a function of time of shaking. Friability of agglomerates is determined by using following formula:

$$\text{Friability}\ (X) = [1 - W/W_o]/100$$

where:

W_o = Initial weight of the crystalline agglomerates placed in sieve;

W = Weight of the material, which does not pass through sieve after 5 min.

Moisture Uptake Study

The study indicates the uptake of moisture by drug and the prepared spherical crystals, which affects the stability. The weighed quantity of drug and spherical crystals is placed in a crucible at accelerated condition of temperature and humidity, 40C ± 10C and 75% ± 3% respectively. The gain in weight of drug and spherical crystals is measured.

Drug Loading Efficiency

The drug loading efficiency of crystals are determined by dissolving 100 mg of crystals in 100 ml of appropriate solvent, followed by measuring the absorbance of appropriately diluted solution by using spectrophotometer, other appropriate analysis procedure may be used.

Solubility Studies

A quantity of crystals (about 100 mg) is shacked with an appropriate solvent in a shaking water bath (100 agitations per min) for 24 hours at room temperature. The solution

is then passed through a 0.45 mm membrane filter and the amount of the drug dissolved is analyzed spectrophotometerically.

APPLICATIONS OF SPHERICAL CRYSTALLIZATION IN PHARMACEUTICALS

To Improve the Flowability and Compressibility

Today the tablet is the most popular dosage form of all pharmaceutical preparations manufactured. From the manufacturing point of view, tablets can be produced at much higher rate than any other dosage form. Tablet is the most stable readily ingestable and conveniently consumed dosage form. The formulation of tablet is optimized to achieve the goals. The focus today in the business is not only a better drug delivery concept, but also the preparation of the simple standard formulations as economical as possible. One of the most economical solutions is to find directly compressible drug materials and this is especially of interest in case of large volume products. There have been renewed interests in examining the potential of direct compressibility for tabletting over recent years. Since in comparison to traditional granulation process, such manufacturing of the tablets involves simple mixing and compression of powders, which give benefits like time and cost saving. An interesting alternative is to manufacture larger particles in situ by agglomeration of the small crystals during the crystallization. In addition, it has been revealed that agglomerates have properties that make them suitable for direct compression or tabletting. Crystals could be generated employing any of the available techniques like sublimation, solvent evaporation, vapor diffusion, thermal treatment and crystallization from melt precipitation by change in pH, growth in presence of additives or the grindings. Thus, the novel agglomeration techniques that transform crystals directly into a compact spherical form during crystallization process are desired. The use of spherical crystallization as a technique, thus appears to be an efficient alternative for obtaining suitable particles for direct compression. Due to different crystal habit(s), many drugs show inconvenient flowability and compressibility. These problems can be solved by converting them into agglomerated crystals by changing the crystal habit and spheronization, so as to increase both the flowability and compressibility. Patents on spherical crystallization are shown in Table 7.3.

Table 7.3: Patents on spherical crystallization

Patent	*Year*	*Original assignee/inventor*	*Title*
US 4675339	1987	Nippon Kayaku Kabushiki	Spherical amino acid preparation Kaisha
US 5817173	1998	Josuke Nakata	Method for making spherical crystals
US 6150364	2000	Roche Vitamins Inc.	Purification and crystallization of riboflavin
US 6825218	2004	Aventis Pharma S.A.	Spherical agglomerates of telithromycin, their preparation process and their use in the preparation of pharmaceutical forms
US2006/0275219A1	2006	Taisho pharmaceutical co. Ltd.	Radial spherical crystallization product, process for producing the same, and dry powder preparation containing the crystallization product
US 7427413	2008	Skendi Finance Ltd.	Stable shaped particles of crystalline organic compounds
US2009/0176096A1	2009	Council of scientific & industrial research, New Delhi, IN	Free flowing 100–500 micrometer size spherical crystals of common salt and process for preparation thereof
US2011/0033707A1	2011	National institute for materials science, Ibaraki JP	Spherical boron nitride nanoparticles and synthetic method thereof

For Masking Bitter Taste of Drug

Microcapsules are prepared to mask the bitter taste of the drug. They are suitable for coating granules, since spherical material can be uniformly coated with a relatively small amount of polymer.

For Increasing Solubility and Dissolution Rate of Poorly Soluble Drug

Spherical crystallization has been described as an effective technique in improving the dissolution behavior of some drugs, which possess low water solubility and a slow dissolution profile.

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