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Overview of Particle Engineering: Spherical Crystallization Techniques.

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ABSTRACT

Delivering the drug with maximum bioavailability at the site of action is always a question. Pharmaceutical research work is continuously focused on the improvement of solubility and bioavailability of drug. There are certain new technologies available by which this can be made possible. Spherical crystallization technique is one of such technology. In this technique drug with poor solubility and bioavailability is converted into the spherical crystals by using one of the method such as Spherical Agglomeration (SA), Quasi Emulsion Solvent Diffusion (QESD), Ammonia Diffusion system (ADS) or Neutralization (NT). Crystals obtained by any one of these technique are then evaluated for the physicochemical properties. Spherical crystallization provides the unique advantage to crystals with improved micromeritic properties, helpful for the tablet preparation by direct compression method.

Keywords: particle engineering, spherical crystallization, drug delivery

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INTRODUCTION

Spherical crystallisation technique has gained a wide importance in the field of drug delivery. This technique is not only associated with the mere formation of the spherical crystals but it has also opened the many new ways in the delivery of the drugs specially having low solubility and lesser bioavailability. Crystallisation is an intrinsic material characteristic for a specified molecule. Poor physical and mechanical state of the drug molecule can affect the physical and mechanical properties of molecule such as solubility and poor powder flow properties. Physical characteristics for example crystal habit and size of any molecule are important attributes for the formulation but this factor has major role in the solid oral dosage form than the semi-solid & other dosage forms. Powder flow characteristic is an important phenomenon for the tablet prepared via direct compression procedure. Poor powder flow can affect the drug concentration or in the content uniformity. Other powder micrometrics which can affect on this are smaller particle size, particle size distribution, crystal habit or the electrostatic charges. For solid dosage form dissolution of most of the lower solubility drugs is critical factor in the formulation. Now a day's various types of solutions are available to avoid such problems for example: micronization of drug particles, but this cannot be the always solution to improve the solubility[1].

A foundation stone in the arena of spherical crystallization techniques was led down way back in the 1961 by Farnand *et al*[2], and Sutherland[3] in 1962. During the experiments they found that addition of Barium Sulfate in a mixture of benzene and small amounts of water can leads to formation of spherical clusters of barium sulphate. Canadian National Research Council worked in a path breaking further direction of spherical agglomeration in the 1960's and 1970's (Farnand *et al*[2], 1961; Sutherland[3], 1962; Sirianni *et al*[4], 1969; Kawashima and Capes[5,6], 1974 and 1976). They worked on the selective agglomeration of coal, but along with this they also studied several other compounds like silica sand, glass and calcium carbonate. They majorly studied the mechanisms, kinetics of spherical agglomeration, and the effect of process variables on the agglomerates.

Preliminary work done by Kawashima[5,6] *et al* opened the door of spherical crystallisation technique and its importance with the solubility and dissolution behaviour of a drug moiety. Crystallization technique help to modify the Physico-mechanical properties of crystals, such as melting point, solubility, true density, dissolution profile, flowability and compactibility. In the year 1974 Kawashima and Capes used the silica sand dispersed in agitated carbon tetrachloride and then they agglomerated it with calcium chloride aqueous solutions[5,6]. This experimental work encourages Kawashima and he discovered the spherical crystallization technique which later termed as an agglomeration process in which the crystal transformation takes place directly into the compact spherical forms. This technique helps to prepare the spherical agglomerates (recrystallization) with sizes between 300 and 500 mm without any binders[5].

Precipitation of a solid crystals from a solution, melt or from agas by the natural or artificial process is known as the crystallization. Crystallization is likewise a concoction solid–liquid detachment method, in which mass exchange of a solute from the fluid answer for an unadulterated strong crystalline stage happens. Crystallization depends on the standards of dissolvability: solutes have a tendency to be more solvent in hot fluids as opposed to in cold fluids. The procedure comprises of permitting a hot fluid to cool down to the point where the solute is no longer dissolvable in the dissolvable. This step then results in the fixed shaped crystals from an immaculate substance ("Crystallization").

Nucleation and crystal growth are the main events in the crystallization: Nucleation is the step where the solute molecules start moving in the solvent to create clusters ("Crystal Growth"). The crystal growth shows how the crystals grow in different conditions.

Figure for events of crystallization-

1. Nucleation 2. Crystal formation

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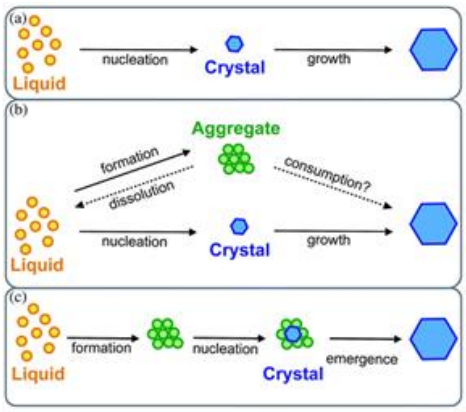


Figure 1: Events of Crystallization[7]

Spherical crystallization

In 1980's Kawashima *et al* research work opened the many gateways of its application and this leads to the revolution in this technique. It was not that this review was restricted to just but rather pharmaceutical sciences additionally it makes ready in different fields of science 1990's by Lasagabaster[8] *et al*, 1994), and new reviews on particular recuperation of fine mineral particles were directed by Sadowski[9] (1995), Protein crystallization by Bausch and Leuenberger[10], (1994). They concentrated the agglomeration of hydrophilic proteins from natural solvents utilizing water as bridging liquid. This bridging liquid wets the particles and on account of which round agglomerates were acquired. For example, acetylsalicylic acid, Goczo[11] *et al,* (2000), fenbufen, Martino[12] *et al*, (1999), aminophylline, Kawashima[13] *et al*, (1982).

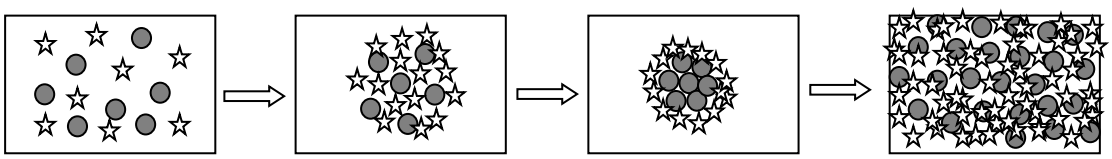
Principle of Spherical crystallization.

The primary guideline behind the circular agglomeration procedure is to set up the strong crystals by utilizing dissolvable interaction system.

In this technique, a third dissolvable known as bridging liquid is included a littler sum for the development of agglomerates [14](Kawashima *et al*, 1994). Crystals are agglomerated amid the crystallization procedure and expansive round agglomerates are created. A near saturated solution of drug is made in a good solvent which is then added into a poor dissolvable. The fundamental drive working behind this system is the fondness of poor and good solvents which are openly miscible with each other. Here the connection between the solvents is more grounded than amongst drug and good solvent, bringing about to precipitation of crystals from the dissolvable. Gradually under stirring or agitation the bridging liquid is added, which have the miscibility with poor solvent and furthermore wet the precipitated crystals. Interfacial tension effects and capillary forces help the bridging liquid to represent adherence of crystals to each other and development of agglomerate[15] (Kawashima *et al*, 1984).

Steps involved in spherical crystallization

There are four steps involved in the growth of crystals and agglomerates, classified by Bermer and Zuider Wag[16].



i.Flocculation zone ii. Zero growth zone iii. Fast growth zone iv. Constant sized zone

Fig 2: Steps involved in the Spherical crystallization

Flocculation zone

In this zone, bridging liquid dislodges the fluid from crystal surfaces and tends to agglomerate with unsettling. The adsorbed bridging liquid links the particles by forming bridge between them, due to which loose flocs are formed.

Zero growth zone

This zone is described by changing over the free flocs into firmly packed pellets, amid which the entangled liquid is moved out, trailed by pressing of bridging liquid on to the surface of little flocs causes poor space in the pellets. The main impetus for change is because of the agitation that came about into pellet-pellet and pellet-stirrer impact. It is the rate deciding stride of response administered by rate of agitation.

Fast growth zone

The development of agglomerates happens as bridging liquid get presses out from the little agglomerates. This arrangement of expansive particles taking after irregular impact of very much shaped nucleus is known as coalescence. Fruitful impact happens just if the core has somewhat get to dampness which bestows plasticity on nucleus. The development of agglomerates likewise happens because of the progressive expansion of materials on shaped nucleus.

Constant sized zone

Agglomeration development is stopped or may diminish in size because of attrition, breakage and break. In this zone recurrence of impact is adjusted by the breakage recurrence of agglomeration.

Factors affecting the agglomeration techniques

Physical:

- Type of instrument: Distinctive sorts of instruments have incredible impact on the size and state of crystal arrangement. Plan of the blending stirrer is additionally valuable for proficient blending of stirrer.
- Speed and time of mixing: Mixing rate and time has high impact on the sort of crystal development. Low or rapid of mixing is required to permit the bridging liquid to mix altogether inside the framework. Variety in mixing sort or example decides the kind of crystals.

Environmental:

- Design of the vessel: Diverse vessel configuration can offer ascent to the distinctive states of crystals. Vessel configuration ought to be chosen precisely.
- Temperature of the system: Temperature of the framework decides the sum and degree of crystals arrangement. Diverse temperature can offer ascent to the distinctive size of crystals since the solubility of solvent is influenced by it.
- Cooling rate: Precipitation rate is enormously influenced by the cooling rate. Moderate or sudden cooling can likewise offer ascent to the different sort of crystals.

Different types of techniques:

This Spherical crystallization can be achieved by using four methods.

- Spherical Agglomeration (SA)
- Quasi Emulsion Solvent Diffusion (QESD)
- Ammonia Diffusion system (ADS)
- Neutralization (NT)

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Spherical Agglomeration (SA)

Agglomeration in liquid frameworks with an extensive variety of targets including partition of colloidal particles from a liquid, round granulation, evacuation and recuperation of fine solids from fluid squanders, and particular detachment of a few segments in a blend of particles has increased expanding consideration as of late because of its relative effortlessness and simplicity of operation. The further finding of spherical agglomeration of crystals amid crystallization forms, named spherical crystallization by Kawashima et al. has offered a promising way to deal with particulate outline for building pharmaceuticals and chemicals[14]. The likelihood of agglomerating the microcrystals specifically inside the reactor presents many focal points for the preparing of these particles. Agglomeration is equipped for changing the micromeritic properties of pharmaceutical powders, for example, flowability, packability and solvency. It can likewise decrease the tidy discharging properties of an intermediate or the last item, and maintain a strategic distance from isolation brought about by vibration amid taking care of and preparing. These favorable circumstances guarantee solid and proficient powder taking care of and preparing (e.g., blending, granulation) and additionally change in the bioavailability of the item[17,18].

In the spherical agglomeration technique a third solvent called the bridging liquid is included a littler add up to advance the development of agglomerates. A saturated solution of the drug in the good solvent is filled the poor solvent. Keeping in view that poor and good solvents are openly dissolvable and the liking between the solvents is more grounded than the fondness between the drug and the good solvent, crystals will encourage promptly. Under unsettling, the bridging liquid (the wetting specialist) is included however the bridging liquid ought not be miscible with the poor solvent and ought to specially wet the encouraged crystals. This will prompt to act the interfacial pressure and fine powers between the bridging liquid to cling the crystals to each other. Not as much as the ideal measure of bridging liquid can produce a lot of fines and more than ideal can shape exceptionally coarse particles. Different elements, for example, the choice of bridging liquid, the blending speed and the concentration of solids (or of the solute) are of significance. Higher blending rate deliver agglomerates that are not so much permeable but rather more impervious to mechanical anxiety, and the porosity diminishes when the grouping of strong increments. The viscosity of the continuous phase affects the size dissemination of the agglomerates. The decision of bridging liquid influences the rate of agglomeration and quality of the agglomerates[14].

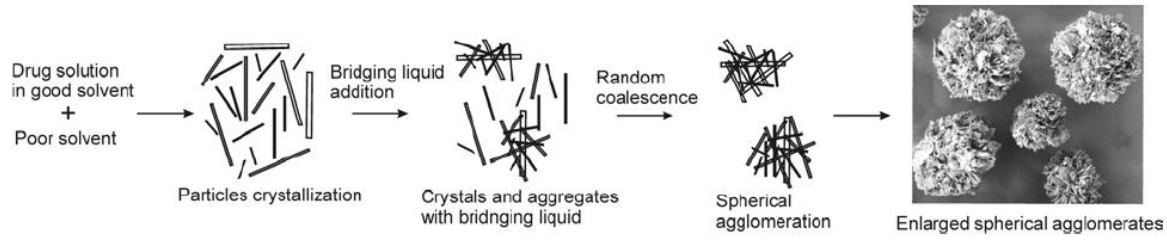

Fig 3: Steps involved in the formation of spherical agglomerates.

Emulsion solvent diffusion

In the emulsion solvent diffusion the partiality between the drug and the good solvent is more grounded than that of the good solvent and the poor solvent. The drug is broken down in the good solvent, and the arrangement is scattered into the poor solvent, delivering emulsion (semi) beads, despite the fact that the pure solvents are miscible. The good solvent diffuses progressively out of the emulsion beads into the encompassing poor solvent stage, and the poor solvent diffuses into the beads by which the drug crystallizes inside the drops. The strategy is thought to be less complex than the SA technique, however it can be hard to locate a reasonable added substance to keep the framework emulsified and to enhance the diffusion of the poor solute into the scattered stage[19,20,21].

Ammonia diffusion method

In this technique, the blend of three somewhat immiscible solvent i.e. acetone, ammonia water, dichloromethane was utilized as a crystallization framework. In this framework ammonia water went about as

bridging liquid and also good solvent. Acetone was the water miscible poor solvent serves to accelerated the drug by solvent change without framing ammonium salt. Water immiscible solvent, for example, hydrocarbons or halogenated hydrocarbons e.g. dichloromethane actuated freedom of alkali water[22,23,24].

Neutralization:

This technique is portrayed by drug broke up in good solvent and put in the barrel shaped vessel with consistent mixing. While blending a aqueous polymer arrangement alongside a neutral arrangement is included which kill the good solvent and inspiring drug crystallization, bridging liquid is included drop savvy with a clear consistent rate, which causes agglomeration of crystals[25].

Following is the basic thumb rule used in selection of solvents postulated by Chow and Leung[26] .

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.
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

Effect of drying on spherical crystals

Drying rate and temperature mainly have effect on the porosity of spherical crystals. It does not have effect on the size and shape of the crystals[27].

Evaluation techniques

Particle Analysis

There are various techniques being used in the evaluation of spherical crystals.

Size distribution

The molecule estimate dispersion is acquired from measuring the weight of the sieve fractions and it is given as total over size mass conveyances. For this procedure sifter shaker can be utilized.

Particle shape

The shape of the spherical crystals can be well observed under an optical microscope.

Particle surface

Polymorphism and crystal habit of the spherical crystals can be analyzed by using scanning electron microscopy.

Particle nature

An amorphous or crystalline type of any molecule can be effortlessly seen under a x-beam diffraction contemplate. Amorphous powder does not demonstrate any pinnacles while crystalline particles indicate example of pinnacle intensitiies at distinct angle (2θ) with respect to the occurrence beam. Every diffraction example is attributes of a particular crystalline grid for a compound.

Polymorph identification

Fourier Transform Infrared spectrometer is used for identification between solvates and anhydrous form for identifying polymorphs. It can also be determined by using a Differential scanning Calorimeter (DSC). This technique measures the heat loss or gain resulting from physical or chemical changes within a sample.

Particle micromeritics

Round crystals size and shape decide its flow property. In pharmaceutical industry this is a standout amongst the most parameter to be considered amid definition improvement. Powder flow capacity of the particles relies on upon the drive created between the particle, particle size, particle size distribution, particle shape, surface or roughness and surface region. Spherical crystallization strategy enhances the lower point of rest then that of single crystals. This could be credited to the noteworthy diminishment in between particle friction, because of their circular shape and a lower static electric charge. Given beneath are the strategies used to decide the stream property.

Angle of repose

The angle of repose is the angle between the horizontal and the slope of the heap or cone of solid dropped from some elevation. The angle of repose can be obtained from equation.

$$\mathbf{Tan\ \theta = h/0.5d}$$

Where h- height of the cone and, d- diameter of the cone

Table 2: Angle of repose

Flow property	Angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable- may hang up	41-45
Poor- must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

Compressibility or Carr index

Table 3: Carr index values

Flow property	Compressibility Index (%)
Excellent	≤ 10
Good	11-15
Fair- aid not needed	16-20
Passable- may hang up	21-25
Poor- must agitate, vibrate	26-31
Very poor	32-37
Very, very poor	>38

A simple indication of ease with which a material can be induced to flow is given by application of compressibility index. **I = (1-V/Vo) *100** Where v = the volume occupied by a sample of powder after being subjected to a standardized tapping procedure and Vo = the volume before tapping. The value below 15% indicates good flow characteristics and value above 25% indicate poor flowability.

Hausner ratio

It is calculated from bulk density and tap density. **Hausner ratio = Tapped density / Bulk density** Values less than 1.25 indicate good flow (20% Carr Index) and the value greater then 1.25 indicates poor flow (33% Carr Index).

Table 4: Hausner ratio values

Flow property	Hausner ratio
Excellent	1.00-1.11
Good	1.12-1.18
Fair- aid not needed	1.19-1.25
Passable- may hang up	1.26-1.34
Poor- must agitate, vibrate	1.35-1.45
Very poor	1.46-1.59
Very, very poor	>1.60

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

Density = Mass(M)/ Volume(V)

Porosity Porosity of granules affects the compressibility. Porosities are of two types "intra granular and Intergranular and these are measured with the help of true and granular densities.

Intra granular porosity = 1- Granular density /True density.

Inter granular porosity = 1- Bulk density / Granular density

Total Porosity = 1- Bulk density/ True density

Packability: Improve packability has been reported for agglomerates prepared by spherical crystallization. The angle of friction, shear cohesive stress and shear indexes are lower then that of single crystals, which can improve the packability of the agglomerates. The packability of agglomerates improved compared with those of the original crystals and that the agglomerated crystals are adaptable to direct tabletting.

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