

## SPHERICAL CRYSTALLISATION: A REVOLUTION IN THE FIELD OF PARTICLE ENGINEERING

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### ABSTRACT

Now-a-days direct tableting technique is gaining more importance in Pharmaceutical manufacturing because it save money and time for tableting but Good flowability and compressibility is prerequisite for drug to be prepared by direct compression. There are several techniques available to impart desired compressibility to drug, but the Spherical crystallization technique is the most promising one in which the drug crystals are modified using different solvents to directly compressible spherical agglomerates. Spherical agglomeration is particle engineering technique which involves the transformation of fine crystals into spherical shape which in turn enhances the powder properties such as particle size, shape, flow properties, solubility and bioavailability of pharmaceutical drug substances. The spherical crystallization further developed use with hydrophilic polymers to enhance dissolution rate characteristics of poorly water soluble drugs and can also be applied to sustain the drug release from solid dosage forms. The present review aims at the detailed comprehensive study about the technique, advantages and disadvantages, mechanism, different manufacturing methods of spherical agglomerates and characterization of spherical agglomerates.

**Keywords:** Spherical crystallization, Spherical agglomeration, Direct compression, Flowability, Compressibility.

### INTRODUCTION

Tablet is very popular dosage form, which accounts for at least 50 % of all oral drug delivery system and 70% of all pharmaceutical preparations. A modern method in tablet manufacturing is Direct tableting of pharmaceutical materials that has been successfully applied to numerous drugs on the industrial scale. Such manufacturing of tablets involve simple mixing and compression of powders, which results in a number of benefits including time, cost and energy savings. But for Compressing a drug directly it needs to have good micromeritic properties, such as flowability. But the flowability of needle shaped or plated-shaped crystals is very poor and these crystals are difficult to handle. So, Kawashima in 1974 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 tableting which he defined it as spherical crystallization. The model system they used were Silica sand dispersed in agitated carbon tetrachloride and then agglomerated with calcium chloride aqueous solutions. In span of some years, In 1986 Kawashima used the spherical crystallization method for size enlargement of drug particles. With the aid of this method, the precipitated crystals were agglomerated during the final synthesis step (recrystallization) into spherical particles ranging in sizes between 300 and 500 mm without any binders [1].

It is the versatile process that enables to control the type and the size of the crystals. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form.

This technique of particle design of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained great attention and importance due to the fact that crystal habit (form, surface, and size and particle size distribution) can be modified during the crystallization process.

Hence spherical crystallisation process 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" OR,

"An agglomeration process that transforms crystalline drug directly into compact spherical forms for improving the flowability, solubility and compactability"

Agglomeration is a particles technology process which involves the aggregation of smaller crystals to form bigger particles. The bigger particles are important for properties such as filtration, drying, washing etc. and the end properties such as dissolution, product formation and bioavailability.

Spherical crystallisation is a non conventional technique better in comparison to other conventional technique used for enlargement of particle size involves simultaneous agglomeration along with crystallisation with the help of bridging liquid. It is a versatile process that control the type and the size of the crystals.

This technique of particle design of drugs has now emerged as one of the burning areas of active research in pharmaceutical manufacturing and recently came into the limelight due to the fact that crystal habit (surface, form, size and shape) can also be modified during the crystallization process. In consequence of such modifications in the crystal habit, certain micrometric properties like bulk density, flow property, compactability and physicochemical properties like solubility, dissolution rate, bioavailability and stability can also be modified which finally results in improved tableting [2].

### Need for spherical crystallisation [3]

It is a method of choice for low dose drug which are poorly compressible and poorly aqueous soluble. Direct tableting of pharmaceuticals has now been used because of its economical and less labour requiring force but it is only possible if the drug itself has good flow properties. To achieve this goal, the micromeritic properties such as flowability, packability, compressibility, etc. of the drug must be improved by spherical crystallisation process.

This process actually modifies the crystal habit of the drug which in turn influence many morphological, rheological and techno pharmaceutical behavior and, therefore, drug bioavailability from dosage forms. Crystal habit influences particle orientation, thus modifying the flowability, packing, compaction, syringability, suspension stability, and dissolution characteristics of a drug powder. This technique improves the wettability, bioavailability and dissolution rate of some poorly soluble drug.

Developing novel methods to increase the bioavailability of drugs that inherently have poor aqueous solubility is a great challenge to formulate solid dosage form. To overcome this problem, Kawashima developed a spherical crystallization technique that led to improving the Aqueous solubility of number of microcrystalline drugs.

Some drugs have also been recrystallized by the spherical agglomeration technique using polymeric materials to modify their release profile.

#### Advantages of spherical crystallisation process [4]

1. Most simple process in contrast to other size enlargement process.
2. Less number of unit operations required.
3. As less number of operations is there so need of manpower is limited.
4. Economic
5. Proper GMP considerations.
6. It has been traditionally used for improvement of flow, compressibility, solubility and bioavailability.
7. This technique could enable subsequent processes such as separation, filtration, drying etc. to be carried out more efficiently.
8. By using this technique, physicochemical properties of pharmaceutical crystals are improved for pharmaceutical process i.e. milling, mixing and tableting because of their excellent flowability and packability
9. This technique may convert crystalline forms of a drug into different polymorphic form having better bioavailability.
10. For masking the bitter taste of the drug.
11. Preparation of microsponge, microspheres and nanospheres, nanoparticles and micropellets as novel particulate drug delivery system.

#### Disadvantages

1. Selection of solvent is a tedious process.
2. Maintenance of process parameters (stirring rate, temperature, agitation) is difficult.

#### Principle of spherical crystallisation [5]

- This process involves pouring the saturated solution of the drug in good solvent (in which drug is soluble) into poor solvent (in which drug is slightly soluble).
- Third solvent called the bridging liquid is added in small amounts to promote the formation of agglomerates. Bridging liquid wets the crystal surface to cause binding and promotes the formation of liquid bridges between the drug crystals for forming spherical agglomerates.
- Poor and good solvents should be freely miscible and the affinity between the solvents must be stronger than the affinity between drug and the good solvent.
- The bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals.

#### Factors controlling the process of agglomeration

##### • Solubility profile

The selection of solvent is solely dependent on the solubility characteristic of the drug. A mutually immiscible three solvent system consisting of a poor solvent suspending liquid, good solvent and bridging liquid are necessary. Physical form of product whether it is micro agglomerates or irregular macro-agglomerates or a paste of drug, can be controlled by varying solvent proportions. The proportion of solvent to be used is determined by carrying out solubility studies [6].

##### • Mode and intensity of agitation

High speed agitation is necessary to disperse the bridging liquid throughout the system. Any change in agitation pattern or fluid flow would affect the shape of agglomerate. So the extent of mechanical agitation and mode of addition and the amount of bridging liquid determines the rate of formation of agglomerate and their final size.

##### • Temperature of the system

Studies have shown that the temperature has a significant influence on the shape, size and texture of the agglomerates as it indirectly affects the solubility of drug substances [7].

##### • Residence time

The time for which agglomerates remain suspended in poor solvent affects its strength.

##### • Role of bridging liquid

Agglomerates are formed by agitating the crystals in a liquid suspension on adding a bridging liquid, which is immiscible with reaction mixture is capable of aggregating the particles to form agglomerates. Bridging liquid preferentially wets the crystal surface to cause binding. The addition of bridging liquid promotes the formation of liquid bridges between the drug crystals to form spherical agglomerates. The spherically agglomerated crystals are formed by coalescence of these dispersed crystals. With decreasing amount of bridging liquid in the three-solvent system, the median diameter of agglomerated crystals increased, having a wider size distribution. 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

#### Mechanism involved in the process of spherical crystallization

##### • Flocculation zone

In this zone, 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 bridge between them [8].

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.

##### • Zero growth zone

During this growth phase, the entrapped fluid is squeezed out followed by squeezing of the bridging liquid onto the surface of small flocs. Loose floccules are transformed into tightly packed pellets. The driving force for the transformation is provided by the agitation of the slurry causing liquid turbulence, pellet-pellet and pellet-stirrer collision.

##### • Fast growth zone

The fast growth zone of the agglomerate takes place when sufficient bridging liquid has squeezed out of the surface of the small agglomerates. This formation of large size particle after 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 article deformation and subsequent coalescence [9].

##### • 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 rate determining step in agglomeration growth 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 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.

#### Techniques of spherical crystallisation

Spherical crystals can be obtained by two different techniques, either by typical spherical crystallization technique or non typical spherical crystallization technique. 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 [10].

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 has wetting property i.e. bridging liquid; and the last one is immiscible with the drug substance i.e. bad solvent. 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. The median diameter of agglomerates decreased with increasing content of the good solvent. 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 spherical agglomeration or Solvent Change method (SA), quasi-emulsion solvent diffusion method (QESD, Transient emulsion). But there are two extensions of these techniques, ammonia diffusion system (ADS) and crystal-coagglomeration technique (CCA). 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.

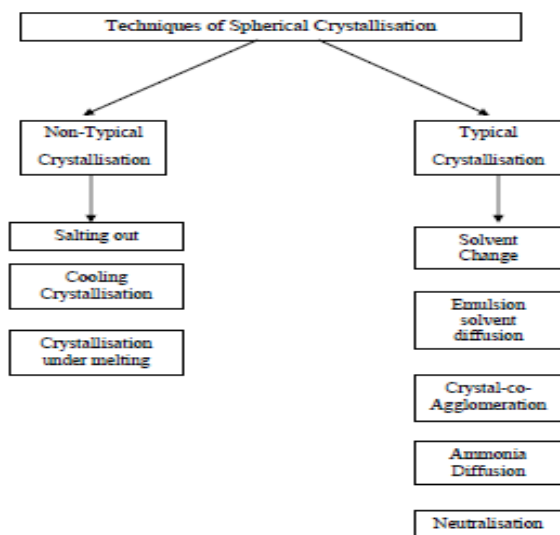


Fig. 1: Techniques of Spherical crystallisation

#### • Spherical agglomeration or solvent change

In this method, a solution of a compound in a good solvent is poured into the poor solvent, which is miscible with the good solvent. The affinity between the solvents must be stronger than the affinity between the good solvent and the compound, which causes immediate precipitation of crystals. In the spherical agglomeration method, a third solvent called the bridging liquid is also added in a

smaller amount and acts as an interparticle binder that promotes agglomeration. The bridging liquid, which should not be miscible with the poor solvent and should wet the precipitated crystals, collects the crystals suspended in the system by forming liquid bridges between the crystals due to capillary negative pressure and interfacial tension at the solid-liquid interface.

There are three steps involve in this method.

- Selection of crystallization method to precipitate crystals from solution i.e. thermal, physiochemical and chemical reaction.
- Choice of wetting agent that will be immiscible with solvent of crystallization.
- Hardening of agglomerates.

Drawback of this system is that it produces the low yield, due to co-solvency effect of crystallization solvent. The bridging liquid, the stirring speed and the concentration of solids are the other factors which need to be taken care of.

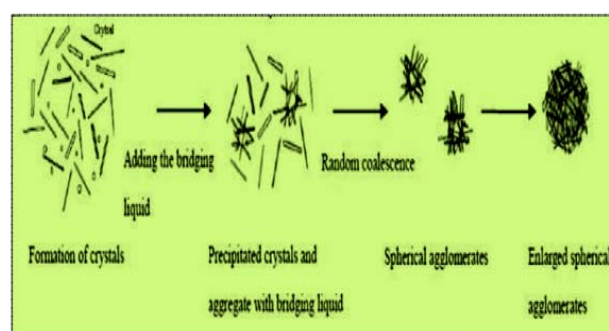


Fig. 2: Solvent change method

#### • Emulsion solvent diffusion

The Quasi-emulsion Solvent diffusion (QESD) or Emulsion Solvent diffusion was first mentioned in 1989 by Kawashima.

In this method, the interaction between the drug and good solvent is stronger than that of the interaction between good solvent and poor solvent. Hence good solvent drug solution is dispersed in bridging liquid producing quasi emulsion droplets, even if the solvent are normally miscible. This results in increase in interfacial tension between good solvent and bridging liquid. As the solubility of the drug in the droplets decreases containing in poor solvent, good solvent diffuses out of emulsion droplets in the outer phase of poor solvent and counter diffusion of poor solvent into the droplets cause the crystallization of the drug. Residual good solvent in the droplets acts as a bridging liquid to agglomerate the generated crystals. Spherical agglomerates of crystals are then formed if the process parameters are set accordingly [11].

Drawback of this method is that 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.

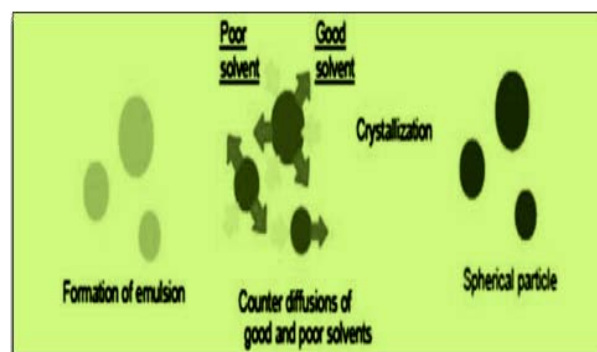


Fig. 3: Emulsion solvent diffusion

#### • Ammonia diffusion method

This is a modified spherical crystallization technique applicable to amphoteric substances, which are only soluble in acidic or alkaline aqueous solutions and insoluble in neutral aqueous solutions or organic solvents. It is therefore impossible to agglomerate them using conventional spherical crystallization techniques. In this method ammonia solution acts as both good solvent and bridging liquid. And poor solvent is selected depending upon the drug solubility in that solvent and good miscibility with ammonia and water. The drug is dissolved in an aqueous ammonia solution and poured into a mixture of a poor solvent and a water-immiscible solvent [12]. It is assumed that the poor solvent enters the droplets of aqueous ammonia solution and causes drug precipitation without forming ammonium salts. Simultaneously, the ammonia diffuses to the outer organic solvent phase and its ability as a bridging liquid becomes weaker, which then determines the final size of agglomerates.

Mechanism of the ammonia diffusion system method: It involves the three steps

- Invasion of acetone into ammonia water droplets.
- Diffusion of ammonia in the agglomerates to the outer solvent.
- Agglomeration ending

Drawback of this method is that it is only meant for amphoteric drugs which cannot be agglomerated by conventional methods.

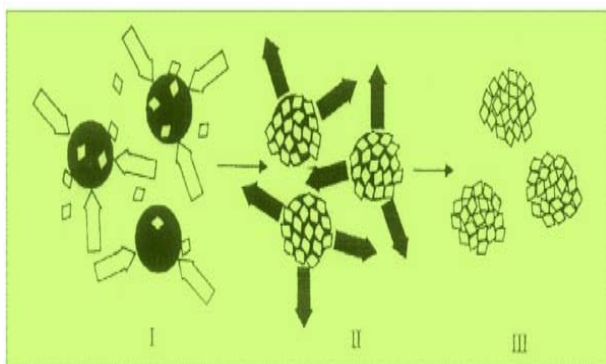


Fig. 4: Ammonia diffusion method

#### • Neutralization technique

It involves the formation of fine crystals by neutralization and their agglomeration by bridging liquid. Drug dissolved in alkaline solution and poured in acidic solution containing polymers and bridging liquid under constant agitation. Drug crystals precipitated out by neutralization of base with acid. Then the precipitated crystals were simultaneously agglomerated with co-operated polymer through wetting action of bridging liquid.

#### • Crystallo-co-agglomeration

Crystallo-co-agglomeration was invented by Kadam and coworkers as an attempt to overcome the limitations of spherical crystallization techniques, which were restricted to size enlargements of single high-dose drugs only. It is a modification of the spherical crystallization techniques described above, in which a drug is crystallized and agglomerated with an excipients or with another drug. Similar to spherical agglomeration, a good solvent is used in this method to solubilize the drug, a poor solvent to cause drug crystallization and the bridging liquid, which is immiscible with the poor solvent, to form liquid bridges during the agglomeration process [13].

Drawback of this method is that the difference in the physicochemical properties of the drug molecules and the excipient are the major challenges in the selection of a solvent system for the crystal-co-agglomeration technique.

#### Evaluation of spherical crystals

As the spherical crystals are formed to show significant effect on the formulation and manufacturing of pharmaceutical dosage forms so it is necessary to evaluate them by using following parameters: [14]

##### Flow properties

Flow property of the material depends on the force developed between the particle, particle size, particle size distribution, particle shape, surface texture or roughness and surface area.

The flow properties of spherical agglomerates were characterized by following methods.

##### a) Angle of repose

The angle of repose can be determined by using the following equation.

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

Where h=height of the pile and d= diameter of the pile

Values for angle of repose  $\leq 30$  usually indicate free flowing material and angle  $\geq 40$  suggested a poor flowing material.

##### b) Compressibility or carr index

The ease with which a material can be induced to flow is given by application of compressibility index.

$$I = (1-V/V_0) \times 100$$

Where V = the volume occupied by a sample of the powder after being subjected to a standardized tapping procedure and

$V_0$  = the volume before tapping.

Value below 15% indicates good flow characteristics and value above 25% indicate poor flowability.

##### c) Hausner ratio

It is calculated from bulk and tapped densities.

$$\text{Hausner ratio} = \text{Tapped density} / \text{Bulk density},$$

Values less than 1.25 indicate good flow (20% Carr index.) and the value greater than 1.25 indicates poor flow (33% Carr index.). If it is between 1.25-1.5 add the glident to improve flow.

##### Density [15]

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

$$\text{Density} = \text{Mass}(M) / \text{Volume}(V)$$

##### Porosity

Porosity has a great influence on compressibility.

Porosities are of two types "Intra granular and Intergranular" and these are measured with the help of true and granular densities.

$$\text{Intra granular porosity} = 1 - \text{Granular density} / \text{True density}.$$

$$\text{Inter granular porosity} = 1 - \text{Bulk density} / \text{Granular density}$$

$$\text{Total Porosity} = 1 - \text{Bulk density} / \text{True density}.$$

##### Packability

Sample packability was assessed by analysis of the tapping process with the Kawakita and Kuno methods, and using the parameters a, b, and k in the equations.

$$n/C = 1/(ab) + n/a.$$

$$C = (V_0 - V_n) / V_0, a = (V_0 - V_\infty) / V_0.$$

$$\rho_f - \rho_n = (\rho_f - \rho_0) \cdot \exp. (-kn)$$

Where, a is the degree of volume reduction when the tap number is infinity, b and k are constants for the apparent packing rate,  $V_0$  and  $V_n$  are the volume in the initial loosely packed and the nth tapped

state, and  $\rho_0$ ,  $\rho_n$ , and  $\rho_f$  are the apparent density in the initial state, the  $n$ th tapped state, and the most densely packed state.

The angle of friction, shear cohesive stress and shear indexes of spherical agglomerates should be less than the pure drug which can improve the packability of the agglomerates.

### Compression behaviour analysis

Good compatibility and compressibility are essential requirements for any material to be directly compressed. 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 surface are freshly prepared by fracture 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 [16]. Compaction behaviour of agglomerated crystals were evaluated by using following parameters

#### (a) Heckel analysis

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

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

Where: D is the relative density of the tablets under compression Pressure

K is the slope of the straight portion of the Heckel Plot

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

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

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

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

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

$$D_A=1-e^{-A} \quad D_B=D_A-D_0$$

#### (b) Stress relaxation test

In this test put specific quantity of spherical agglomerated crystals sample in a die specific diameter the surface of which is coated with magnesium stearate in advance, then used the universal tensile compression tester to compress the samples at a constant speed. After the certain limit of pressure attained, the upper punch held in the same position for 20 min, during which measured time for the reduction amount of the stress applied on the upper punch. The result corrected by subtracting from this measurement the relaxation measured without powder in the die under the same conditions. The following equation finds the relationship between relaxation ratio  $Y(t)$  and time  $t$ , calculated the parameters  $A_s$  and  $B_s$ , and assessed relaxation behavior.

$$t/Y(t) = 1/A_s B_s - t/A_s \quad Y(t) = (P_0 - P_t)/P_0$$

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 that directly reflects the mechanical strength of compact or tablet. It is determined by using the following two methods:

#### a. 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 to measure the tensile strength of spherical crystals.

#### b. Crushing strength

It was 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 was then used as hollow support and the guide tube with close fitting tolerances to the plunger. The hollow plunger with open end served as load cell in which mercury could be added. A window was cut into the barrel to facilitate placement of granule on the base platen. The plunger acted as movable plates and was set directly on the granules positioned on the lower platen as the rate of loading may affect crushing load (gm). Mercury was introduced from reservoir into the upper chamber at the rate of 10 gm/sec. until the single granule crushed; loading time was <3 min. The total weight of the plunger and the mercury required to fracture a granule was the crushing load. Minimum of 10 granules were tested and the average load in gm was taken as the crushing strength [17].

### Friability test

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

$$\text{Friability}(X) = \{1-W/W_0\}/100$$

Where:  $W_0$  = Initial weight of the crystalline agglomerates placed in sieve

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

### Particle size and size distribution

Size of the particle and their distributions can be determined by simply sieve analysis. Now with the help of Ro-Tap sieve shaker, particle size analysis can be determined. In advance technology image-analyzer is used to determine size and volume of the particle [18].

### Particle shape/surface topography

Following methods are used:

#### (a) Optical microscopy

The shape of the spherical crystals is studied by observing these under a optical microscope. The observations are made under the observation like 10X, 45X, 60X etc.

#### (b) Electron scanning microscopy

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

#### (c) 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 determined by using this technique. An amorphous form does not produce a pattern. The X-ray scattered in a reproducible pattern of peak intensities at the distinct angle ( $2\theta$ ) relative to the incident beam. Each diffraction pattern is characteristic of a specific crystalline lattice for a compound.

#### (d) Fourier Transform Infrared spectrometer (FTIR)

It is much more useful for distinguishing between solvates and anhydrous form than for identifying polymorphs because of the addition of new stretching frequencies resulting from the solvation.

#### (e) Differential scanning calorimeter (DSC)

DSC measures the heat loss or gain resulting from physical or chemical changes within a sample. If a mixture of drugs and polymer is agglomerated together then change in properties of agglomerates can be studied with DSC.

#### (f) Thin layer chromatography (TLC)

It determines the drug and polymer interaction of spherical agglomerates and also studies the stability of drug in different solvents.

## Applications of spherical crystallization in pharmaceuticals [19]

### To improve the flowability and compressibility

It has been revealed that agglomerates have properties that make suitable for direct compression tableting. Crystals could be generated employing any of the available techniques like sublimation, solvent evaporation, vapour diffusion, thermal treatment and crystallization from melt precipitation by change in pH, growth in presence of additives or the grinding. Thus the novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during crystallization process has been desired. The use of

spherical crystallization as a technique appears to be an efficient alternative for obtaining suitable particles for direct compression. Due to different crystal habit many drugs show inconvenient flowability and compressibility.

So these problems can be solved by converting them into an agglomerated crystals by changing the crystal habit and spheronization so as to increase the flowability and compressibility.

### To mask the 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. Microcapsules of following drugs were prepared for masking the bitter taste.

### To increase the solubility and dissolution rate of poorly soluble drug

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

**Table 1: List of drugs on which spherical Crystallisation is attempted [20]**

Drugs	Technique	Solvent system		
		Good solvent	Bad solvent	Bridging liquid
Ascorbic	SA,ESD	Water	Ethyl Acetate	Ethyl Acetate
Aceclofenac	SA	Acetone	Water	DCM
Acebutalol HCl	ESD	Ethanol	Water	Isopropyl acetate
Ampicilin trihydrate	AD	Ammonia-water		Ammonia-water
Bromohexin HCl	CCA	DCM	Water	DCM
Benzoic acid	SA	Ethanol	Water	Chloroform
Bucillamine	ESD	Ethanol	DCM	Water
Carbamazepine	ESD	Ethanol	Water	Isopropyl acetate
Cefuroxime axetil	ESD	Acetone	Water	DCM
Celecoxib	SA	Acetone	Water	DCM
Enoxacin	AD	Ammonia-water	Acetone	Ammonia-water
Fenbufen	SA	THF	Water	Isopropyl acetate
Flurbiprofen	SA	Acetone	Water	Hexane
Griseofulvin	ESD	DCM	Water	DCM
Ibuprofen	SA	Ethanol	Water	Ethanol
Ketoprofen-talc	CCA	DCM	Water	DCM
Mephenamic acid	AD	Ammonia-water	Acetone	Ammonia-water
Mebendazole	SA	Acetone	Water	Hexane, Octanol, DCM
Norfloracin	AD	Ammonia-water	Acetone	Ammonia-water
Naproxane	SA	Acetone-ethanol	Water	Chloroform
Propiphenazone	SA	Ethyl alcohol	Water	Isopropyl acetate
Indomethacin-	CCA	Ethyl acetate	Water	Ethyl acetate
Mepirizole				
Tolbutamide	ESD	Ethanol	water	Isopropyl acetate
Theophylline	SA	Ethylene diamine	Aq Sod. Chloride	Water
Tranilast	SA	Acetone	Water	DCM

## CONCLUSION

In recent years spherical crystallization has been evolved as a major technique which not only reduces the steps involved in direct tableting but also improve the micromeritic properties, solubility and dissolution properties. The methods involve in spherical crystallisation are solvent change method, quasi-emulsion solvent, diffusion method, ammonia diffusion system and neutralization method. Due to its crystal shape and nature irregular crystals have different contact points, frictional, cohesive forces between the single crystals which affect the sliding of particle against each other lead to poor flow.

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## CONFLICT OF INTERESTS

Declared None

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