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Review Article

AN OVERVIEW TO SPHERICAL CRYSTALISATION AND ITS EVALUATION

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ABSTRACT

Spherical Crystallization technique has been developed for improving the flow and compressibility characteristics of microcrystalline drug candidates. The processes involved in spherical crystallization of microcrystals are using agglomerating Solvents, Quasi emulsion solvent diffusion, Ammonia diffusion techniques. Temperature and speed of agitation are to be optimized to obtain spherical agglomerates in a desired range, which is found to be essential to enhance compressibility. The spherically agglomerated crystals can be prepared into tablet form or compounded directly into a pharmaceutical system without further processing such as granulation. Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability and compactability of crystalline drugs. The spherical crystals can be characterized by Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and X-ray diffraction (XRD) to ascertain if there were any physicochemical interactions between drug and carrier that could affect dissolution and evaluated for solubility.

INTRODUCTION

Presently tablet is the most popular dosage form of all pharmaceutical preparations produced .Tablet is the most stable readily portable and consumed dosage form. One of the most economical solutions is to find directly compressible formulations and this is especially at interest for large volume products. These have been renewed interest in examining the potential of direct compression tabletting over recent years since in comparison to the used at the more traditional granulation process[1]. Developing novel methods to increase the bioavailability of drugs that inherently have poor aqueous solubility is a great challenge to solid dosage form formulators. Mechanical micronization of crystalline drugs and incorporation of surfactants during the crystallization process are the techniques commonly used to improve the bioavailability of poorly soluble drugs.[2, 3] Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability and compactability of crystalline drugs[4]. Spherical crystallization transforms crystals directly in to a compact spherical forms during the crystallization process. It also enables co-precipitation of drug and encapsulating polymer in the form of spherical particle .[5]

Need for Spherical Crystallization[6]

Developing novel methods to increase the bioavailability of drugs that inherently have poor aqueous solubility is a great challenge to formulate solid dosage form. Mechanical micronization of crystalline drugs and incorporation of surfactants during the crystallization process are the techniques commonly used to improve the bioavailability of poorly soluble drugs. The micronization process alters the flow and compressibility of crystalline powders and cause formulation problems. Addition of surfactant generally led to less significant increase in aqueous solubility. To overcome this problem Kawashima developed a spherical crystallization technique that led to improving the flow and direct compressibility of number of microcrystalline drugs.

Advantages of spherical crystallization[6]

1) Spherical crystallization technique has been successfully utilized for improving of 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 packability.
4) This technique may enable crystalline forms of a drug to be converted into different polymorphic form having better bioavailability.
5) For masking of the bitter taste of drug.

Methods of spherical crystallization

Quasi emulsion solvent diffusion[7]

The drug is dissolved in the good solvent (solvent that readily dissolves the compound to be crystallized), and the solution is dispersed into the poor solvent (an antisolvent generating the required supersaturation), 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 by which the drug crystallizes inside the droplets. The method is considered to be simpler 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.

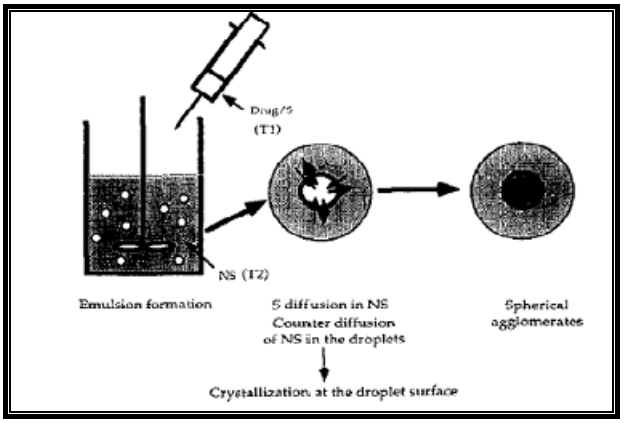

Fig. 1: Principles of Quasi emulsion solvent diffusion[8]

Spherical agglomeration (SA method) [8]

In both processes is used a solvent that readily dissolves the compound to be crystallized (good solvent), and a solvent that act as an antisolvent generating the required supersaturation (poor solvent). In the SA method also a third solvent called the bridging liquid is added in a smaller amount to promote the formation of

agglomerates (Kawashima, 1994). A near saturated solution of the drug in the good solvent is poured into the 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. 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 effects and capillary forces, the bridging liquid act to adhere the crystals to one another (Kawashima et al., 1984). It has been found that the product properties are quite sensitive to the amount of the bridging liquid.[9] Less than the optimum amount of bridging liquid produces plenty of fines and more than optimum produces very coarse particles [10] Also the choice of bridging liquid, the stirring speed and the concentration of solids (or of the solute) are of importance. At increasing stirring rate the agglomeration was reduced in case of lactose because of increasing disruptive forces.[11] Higher stirring rate produce agglomerates that are less porous and more resistant to mechanical stress, and the porosity decreases when the concentration of solid increases.[12] The choice of bridging liquid has an influence on the rate of agglomeration and on the strength of the agglomerates.

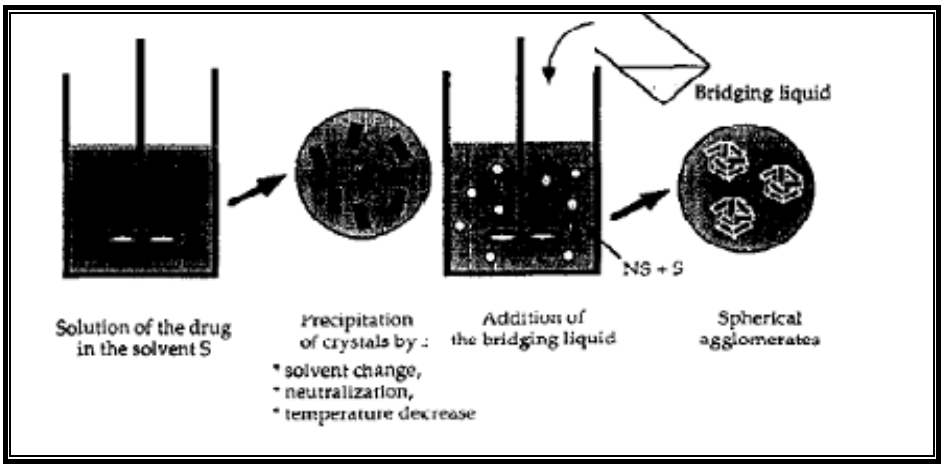

Fig. 2: Principle of Spherical Aglomeration [8]

Various drugs on which spherical agglomeration technique has been tried for improving tabletability are given in **Table no. 1.**

Table 1: List of various drugs on which spherical agglomeration technique has been tried for improving tabletability

Sr.No.	Drug	Method	Solvent used	Reference
1	Aceclofenac	SA	Acetone, water, dichloromethane	13
2	Acetyl salicylic acid	SA	Ethanol, water, carbon tetrachloride	14
3	Ascorbic acid	SA	Water, ethyl acetate, chloroform	15
4	Aspartic acid	SA	Water, methanol	16
5	Aspirin	SA	Acid buffer, methanol, chloroform	17
6	Celecoxib	SA	Acetone, water, chloroform	18
7	DCP	SA	Water, phosphoric acid solution, citric acid	19
8	Ibuprofen	SA	Water, ethanol	20
9	Mefenamic acid	SA	DMF, water, carbon tetrachloride/ chloroform	21
10	Nabumetone	SA	Ethanol,water, cyclohexane/n-hexane	21
11	Naproxen	SA	Acetone ethanol, chloroform, water	22
12	Roxythromycin	SA	Methanol, chloroform, water	23
13	Salicylic acid	SA	Water, ethanol, chloroform	24
14	Tranilast	SA	Ethanol, acetone, water, chloroform, DCM	25

SA: Spherical agglomeration, diffusion, DCP: Dibasic calcium phosphate, DMF: Dimethyl formamide.

Ammonia diffusion method[26]

In this method, the mixture of three partially immiscible solvent i.e. acetone, ammonia water, dichloromethane was used as a crystallization system. In this system ammonia water acted as bridging liquid as well as good solvent, Acetone was the water miscible but a poor solvent, thus Drug precipitated by solvent change without forming ammonium salt. Water immiscible solvent such as hydrocarbons or halogenated hydrocarbons e.g. dichloromethane induced liberation of ammonia water. Various drugs on which Ammonia diffusion method technique has been tried for improving tabletability are listed in Table no. 2

Table 2: List of various drugs on which Quasi Emulsion solvent diffusion and Ammonia diffusion method has been tried for improving tabletability

Sr. No.	Drug	Method	Solvent Used		Reference
1	Acebutalol HCl	QESD	Water, ethanol, Isopropyl acetate	30	26
2	Ibuprofen	QESD	Ethanol, water with sucrose, fatty acid ester		27
3	Ampicilin trihydrate	ADM	Ammonia water, acetone, dichloromethane		28
4	Enoxacin	ADM	Ammonia water, acetone, dichloromethane		29
5	Norfloxacin	ADM	Ammonia water, acetone, dichloromethane		30
6	Mefenamic acid	ADM	Ammonia water, acetone, dichloromethane		31

QESD: Quasi Emulsion solvent diffusion, ADM: Ammonia diffusion method, HCl: Hydrochloride

The principle steps involved in the process of spherical crystallization[6]

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 bridge or lens between them. In this zone, loose open flocs of particles are formed by pendular bridges and this stage of agglomeration process where the ratio of liquid to the void volume is low and air is the continuous phase, is known as the pendular state. Mutual attraction of particles is brought about by surface tension of the liquid and the liquid bridges. The capillary stage is reached when all the void space within the agglomerate is completely filled with the liquid. An intermediate state known as funicular state exists between the pendular and capillary stage. The cohesive strength of agglomerate is attributed to the bonding forces exerted by the pendular bridges and capillary suction pressure.

Zero growth zones

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 of completely filled with the bridging liquid. The driving force for the transformation is provided by the agitation of the slurry causing liquid turbulence, pellet-pellet and pellet-stirrer collision.

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 article following random collision of well formed nucleus is known as coalescence. Successful collision occurs only if the nucleus has slight excess surface moisture. This imparts plasticity on the nucleus and enhances article deformation and subsequent coalescence.

Constant size zone

In this zone agglomerates cease to grow or even show slight decrease in size. Here the frequency of coalescence is balanced by the breakage frequency of agglomeration. The size reduction may be due to attrition, breakage and shatter. The rate determining step in agglomeration growth occurs in zero growth zones when bridging liquid is squeezed out of the pores as the initial 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.

Factors controlling the process of agglomeration[32]

Solubility profile

The selection of solvent is dictated by solubility characteristic of 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 i.e. whether microagglomerate or irregular macro-agglomerates or a paste of drug substance can be controlled by selection of proper solvent proportions. 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.

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 be reflected as change in force acting on agglomerate, which ultimately affects the shape of agglomerate. The extent of mechanical agitation in conjugation with the amount of bridging liquid determines the rate of formation of agglomerate and their final size.

Temperature of the system

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 drug substance in the ternary system.

Residence time

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

Evaluation parameters for spherical agglomerates formed by spherical crystallization techniques

Flow Property[33]

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. Flowability of the agglomerates is much improved as the agglomerate exhibits lower angle of repose then that of single crystals. Following are the methods used for determination of flow property

Angle of repose[34]: Angle of repose is the common method used for determination of flow property. The angle of repose can be obtained from the equation:

$\tan \theta = 2h/d$ Where h-height of the cone, d-diameter of cone.

Compressibility or Carr's index[34]: 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 the powder after being subjected to a standardized tapping procedure and Vo = the volume before tapping. Value below 15% indicates good flow characteristics and value above 25% indicate poor flowability.

Hausner ratio[34]: It is calculated from bulk density and tap density as follows

Hausner ratio = Tapped density / 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 added glident normally to improve flows.

Packability[35, 36]

Improve packability has been reported for agglomerates prepared by spherical crystallization. The angle of friction, shear cohesive stress and shear indexes are lower than that of single crystals, which can improve the packability of the agglomerates. Kawashima, Y., et al. prepared spherical agglomerates of two solvent systems and compared with those of original powder of the drug. It was found that the packability of agglomerates was improved compared with those of the original crystals and that the agglomerated crystals were adaptable to direct tabletting. Packability was assessed by analysis of the tapping process with the Kawakita (I) and Kuno (II) method and using the parameter a, b, 1/b, k in the equation:

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

$$C = (Vo-Vn)/Vo, \quad a = (Vo-V\infty)/Vo.$$

$$\rho_f - \rho_n = (\rho_f - \rho_o) . \exp.(-kn) \quad \text{.....II}$$

Where, N =Number of tapping, C =Difference in volume (degree of volume reduction.), a and b = constant for packability and Flowability, Vo = Initial volume, Vn = Final volume after n th tapping, V∞ = Powder bed volume at equilibrium, ρ_f, ρ_n ρ_o = Apparent densities at equilibrium, nth tapped and initial state respectively.

Constant **a** describe the degree of volume reduction at the time of tapping and called as compactability. **1/b** is considered to be a constant related to cohesion and is called cohesiveness. The compactability **a** and cohesiveness **1/b** are obtained from the slope 1/a and the intercept 1/ab of the plot of modified Kawakitas

equation. The smaller value of parameter **a and** higher value of parameter **b** indicate improve packability and flowability of the spherical crystals. The large value of parameter **(k)** in kunos equation for the agglomerates indicated that the rate of their packing was much higher than that of primary crystals. Stampfvolumeter measurements allow calculation of the rearrangement constant.

$$(Vn-V\infty)/(Vo- V\infty) = (1-Kn)^{-0.25}$$

Where, n = The number of taps, Vo = Initial volume of powder, Vn = the volume after n^{th} taps, V∞ = Final volume.

After transformation of equation regression analysis was performed. The relationship between the variable can be described in term of linear equation (y =1+Kn.) or a exponential model (y = Exp (1+Kn.), where the slop of the curve is the rearrangement constant. If the constant is too small, the compression during tablet pressing can give rise to brittle fracture and plastic flow in certain regions before a close rearrangement has been achieved in other regions.

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 suggest that the surface are freshly prepared by fracture during compression of agglomerates, which enhances the plastic inter particle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation compared to that of single crystals.

Compaction behaviour of agglomerated crystals was evaluated by using following parameters

Heckel Analysis[37]

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

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

Where: D is the relative density of the tablets under compression Pressure and K is the slope of the straight portion of the Heckel Plot, and the reciprocal of K is the mean yield pressure (Py).

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

$$A=1n [1/(1-D0)]+B$$

Where: D0 is the relative density of the powder bed when P=0.

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

$$DA=1-e^{-A}$$

$$DB=DA-D0$$

Stress Relaxation Test[35, 36, 41, 42]

In this test put specific quantity of spherical agglomerated crystals sample in a die specific diameter the surface of which was 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 was held in the same position for 20 min, during which measured time for the reduction amount of the stress applied on the upper punch.[41]The result was 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 As and Bs, and assessed relaxation behaviour.

$$t/Y (t)=1/AsBs-t/As$$

$$Y (t) = (P0-Pt)/P0$$

Where: P0 is the maximum compression pressure, and Pt is the pressure at time t.

Tablet Elastic Recovery Test

In this test put specific quantity of spherical agglomerated crystals sample in a die specific diameter the surface of which was coated with magnesium stearate in advance, then used the universal tensile compression tester to compress the samples at a constant speed. Then measured the thickness of each tablet under maximum pressure (Hc) and at about 24 h after tablet ejection (He). The following equation was used to calculate the elastic recovery ratio (ER).

$$ER= [(He-Hc)/Hc] x100$$

About 24 h after the tablet was ejected, its weight, diameter, and thickness were measured, and its apparent density (ρa) calculated. The following equation was used to calculate internal tablet porosity (ε) from true density (ρt), which was measured with an air comparison pycnometer

$$\varepsilon=1-\rho a/\rho t$$

Tablet Tensile Strength Test[43]

The prepared tablets from agglomerated crystals were kept in desiccators (silica gel) for about 24 h, and then a hardness tester was used to measure a load across the diameter of each tablet at a specific compression speed to find the hardness F when crushing. The following equation was then used to calculate the tensile strength T**.**

$$T=2F/\pi dL$$

Where: d and L are a tablet's diameter (m) and thickness (m).

Study of Plasticity and Compressibility[19]

For this study use single, flat punches 10mm in diameter, furnished with strain gauge and a displacement transducer compression tools. The strain gauge allows the pressure forces on the upper and lower punches to be followed with force-measuring equipment. The equipment transducer was fitted over the upper punch. The tablets were pressed from the control and denoted samples with 0.5% magnesium stearate as a lubricant. A total of 100 tablets were pressed electrically in continuous operation. During tablet pressing, the data were collected by computer. The energy parameters of 10 tablets were fixed for the calculation of plasticity and compressibility values. The measurements were repeated three times during the pressing.

Plasticity (Pls-m) was determined by Stamm-Mathis

Plasticity (Pls-m) = E2/E2+E3X100 (%)

Where, E2=effective work which includes the useful works invested in deformation and the friction during processing, E3=is the degree of elastic recovery during processing.

E2 AND E3 could be calculated from the force displacement curve. If the plasticity value is near 100, the material has plastic property.

Compressibility [Pr(mass)] was calculated via the following equation.

Compressibility [Pr (mass)] = sx/Wspec = sx/(E2/m) X (Pa /JKg^{-1})

Where sx = Tensile strength, Wspec = expresses effective work (E2) invested into the compression of the unit mass of substance (m) at a given compress force.

Mechanical strength

Spherical crystals should posses good mechanical strength as that directly reflects the mechanical strength of compact or tablet. It is determine by using the Crushing strength **[39]**, Friability test.

Wettability

The wettability depends on the crystallinity and elementary crystal size of the agglomerated crystals. Crystals with low crystallinity are

more wettable then crystals with higher crystallinity. Following methods were used to determined wettability spherical crystals.

- Determination of density: Density of saturated solution of drug and spherical crystals in water was determined using a relative density bottle.
- Determination of surface tension: Surface tension of saturated solution of drug and spherical crystals in water was determined employing stalagmometer.
- Determination of porosity: Thickness and diameter of prepared tablet of drug spherical crystals was determined using vernier calliper and porosity was calculated from apparent density of the tablet.

Solubility[38, 39]

Solubility determined quantitatively using distilled water and other solvent (acid or base) at room temperature (25^0c).

Dissolution Rate[44]

It has been elucidated that the dissolution of agglomerates increases as apparent specific surface area increases. Tabletting compacts partially breaks the agglomerated crystals and thus the average particle size is reduced. If agglomerated crystals showed change in wettability or crystalline form then dissolution study is must. If spherical crystallization was carried out in presence of surfactant then improvement in dissolution rate was observed. But compression also increases the particle density, which may adversely affect dissolution. Specific surface area of crystals is found to depend on the method used for spherical crystallization. Therefore it necessary to evaluate the intrinsic dissolution rate of agglomerated crystal sand raw crystals.

Moisture Uptake Study[45]

The study indicates the behaviour of uptake of moisture by drug and the prepared spherical crystals, which affect the stability.

Characterization of Spherical Agglomerates

1) For Particle shape/surface topography Optical microscopy and Electron scanning microscopy are used.

2) X-ray powder diffraction: X-ray powder diffraction is an important technique for establishing batch-to-batch reproducibility of a crystalline form. The form of crystals in agglomerates was determined by using this technique. An amorphous form does not produce a pattern. Each diffraction pattern is characteristics of a specific crystalline lattice for a given compound.

3) Fourier Transform Infrared spectrometer (FTIR): It is much more useful for distinguishing between solvates and anhydrous form then for identifying polymorphs because of the addition of new stretching frequencies resulting from the salvation.

4) 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.

Applications of spherical crystallization in pharmaceuticals

1. To improve the flowability and compressibility.
2. To increase solubility and dissolution rate of poorly soluble drug.
3. Better bioavailability
4. To mask the bitter taste of drug.
5. Preparation of microsponge, microspheres and nanospheres, microbaloons, nanoparticles and micro pellets as novel particulate drug delivery system.

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