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Spherical Agglomerates: Preparation, Characterization and Solubility Enhancement

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ABSTRACT

Spherical agglomerates are prepared by spherical crystallization technique by which the fine crystals produced in the crystallization process into a uniform spherical shape. It is a fast-developing technique of particle design in which crystallization and agglomeration can be achieved simultaneously in one step. It is a modern technique for direct compression in tablet manufacturing many processing steps are limited in direct compression compared to wet granulation method. This technique has gained great intentness due to the modification of crystal habit during crystallization process in turn which modifies certain micromeritic properties and physicochemical properties. Evaluation and characterization of spherical crystals can be carried out using Optical Microscopy, Scanning Electron Microscopy, Fourier Transform Infrared Spectroscopy, Differential Scanning Calorimetry and Thin Layer Chromatography.

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1. INTRODUCTION

The most common causes of incomplete drug absorption from the gastrointestinal tract are the drug's poor aqueous solubility and/or membrane permeability. Particle size reduction, formation of liquisolid compacts, inclusion complex formation, and solid dispersions with different carriers, spherical agglomeration, and co crystallisation are some of the techniques used to improve the solubility of poorly water soluble drugs[1].

Kawashima defined spherical crystallization as "an agglomeration process that directly transforms crystals into compact spherical forms during the crystallisation process." It also allows for the co-precipitation of drug and encapsulating polymer as spherical particles[2]. The Spherical Crystallization process converts fine crystals obtained during crystallisation into spherical agglomerates. Agglomerates formed improves the flowability and compressibility of pharmaceutical ingredients, allowing for direct tableting of drugs rather than additional processing such as mixing, granulation, sieving, drying, and so on[3]. Because of its free-flowing properties and ability to form stable compacts at low punch forces, direct compression is the most modern and efficient process used in tablet manufacturing. It is the quickest, simplest, and least expensive tablet compression procedure that eliminates many processing steps (granulation, drying). Furthermore, it is used for moisture-sensitive drugs that cannot be processed using wet granulation technology[4].

Spherical agglomeration is the formation of crystal aggregates held together by liquid bridges. Agglomerates are formed by agitating crystals in a liquid suspension with a binding agent present. The bridging liquid should be immiscible with the suspending medium but capable of cementing the agglomerated particles. This method can also be used to improve the solubility, dissolution, and thus bioavailability of poorly soluble drugs (Di Martino, 1999; Sano, 1987; Kawashima et al., 1990). These changes enable the use of more efficient manufacturing methods, which could save time and reduce economic risk[5]. The resulting spherical agglomerates can be used as Spansules or as directly compressible agglomerates. They have benefits such as excellent flow characteristics, uniform size distribution, and reproducible packing/filling[6].

ADVANTAGES OF SPHERICAL CRYSTALLISATION TECHNIQUE[4,7]

1. Because the spherical crystallization technique improves the flow property and compressibility of the drug, it promotes the direct tableting process.

2. This technique can convert a drug's crystalline form into a polymorphic form for improved bioavailability.

3. This technique can also be used to mask the bitter taste of a drug.

4. This technique can also be used to create microspheres, microsponges, micro balloons, micro pellets, nanospheres, and nanoparticles for use as novel particulate drug delivery systems.

5. This method can improve the solubility parameters of a poorly soluble drug.

6. Several papers have reported that methods can help improve the stability of pharmaceutical ingredients.

7. It is necessary to perform fewer unit operations. Its processing costs are very low.

8. In a single step, spherical agglomerates are formed.

9. The entire procedure is handled by a single person, requiring less manpower because it is a single-step procedure carried out in a closed and contamination-free environment according to proper GMP.

10. The spherical agglomerates produced by this procedure are then used for direct compression of tablets and the design of a multi-unit particulate drug delivery system.

METHODS OF SPHERICAL CRYSTALLIZATION:

The following methods are used to prepare the spherical crystals.

1. Spherical Agglomeration method (SA)

2. Quasi-Emulsion Solvent Diffusion method (QESD)

3. Ammonia diffusion system (ADS)

4. Neutralization Technique (NT)

1. Spherical Agglomeration method:

The process involves the formation and agglomeration of fine crystals. In most cases, crystallization is accomplished by changing the solvent system or salting it out. A material solution in a good solvent is poured into a poor solvent to promote the formation of fine

crystals. Agglomerates are formed by agitating the crystals in a liquid suspension and adding the bridging liquid, which preferentially wets the surface crystals to cause binding. If the amount of bridging liquid and the rate of agitation are controlled, the agglomerates can be spherical[4].

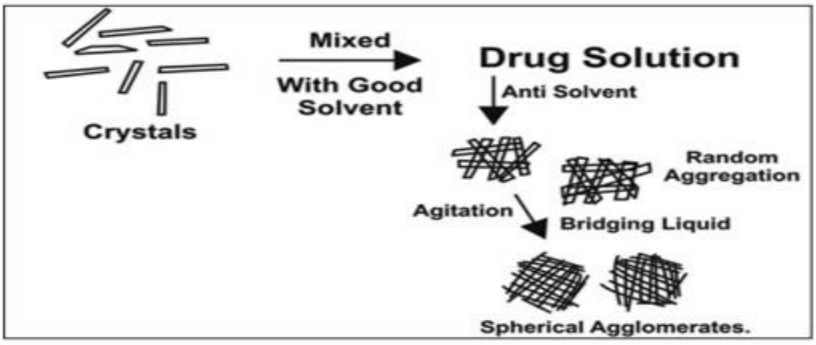

Figure 01: Spherical agglomeration Process

2. Quasi-Emulsion Solvent Diffusion method (QESD)

The transient emulsion method is another name for quasi-emulsion solvent diffusion. Only two solvents are required in this method: one that readily dissolves the compound to be crystallized (a good solvent) and one that acts as an Antisolvent, generating the required supersaturation (poor solvent). The "affinity" between the drug and the good solvent is stronger in the ESD method than between the good solvent and the poor solvent. Even though the pure solvents are miscible, the solution is dispersed into the poor solvent producing emulsion (quasi) droplets due to the increased interfacial tension between the two solvents. The good solvent gradually diffuses out of the emulsion droplets into the surrounding poor solvent phase, and the poor solvent diffuses into the droplets, where the drug crystallizes. The method is thought to be simpler than the SA method, but finding a suitable additive to keep the system emulsified and improve the diffusion of the poor solute into the dispersed phase can be difficult. Hydrophilic/hydrophobic additives, in particular, are used to significantly improve diffusion. The shape and structure of the agglomerate in this method are strongly influenced by the good solvent to poor solvent ratio and the temperature difference between the two solvents[8].

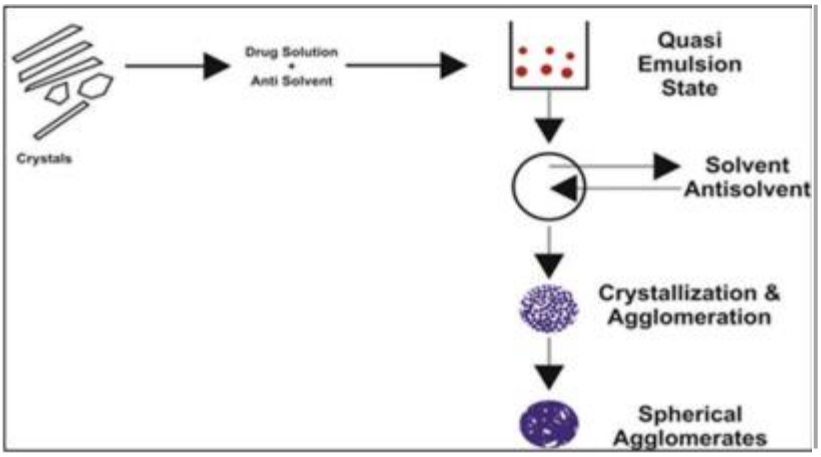

Figure 02: QESM Process

3. Ammonia diffusion system (ADS)

As a crystallization system, a mixture of three partially immiscible solvents, namely acetone, ammonia, and water-dichloromethane, was used. Ammonia water serves as a bridging liquid and a good solvent for enoxacin in this case. Because acetone is a water miscible but poor solvent, enoxacin precipitates without forming ammonium salt. Ammonia water is liberated when dichloromethane is present. As a result of the solvent acetone entering droplets of ammonia water liberated from the acetone-ammonia water dichloromethane system, enoxacin dissolved in ammonia water precipitates while the droplet collects the crystals. Simultaneously, ammonia in the agglomerates diffuses to the outer organic solvent phase, weakening its ability as a bridging liquid and resulting in the formation of agglomerates. This is useful in the agglomeration of drugs that are only soluble in acidic or alkaline solutions[9].

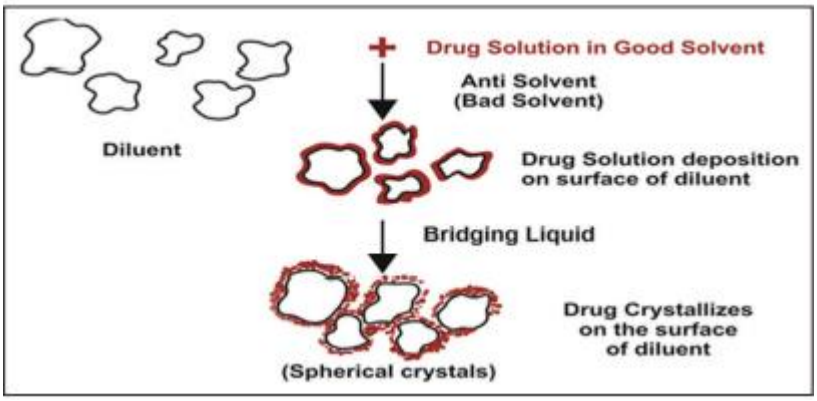

Figure 03: ADS Process

4. Neutralization Technique (NT)

The process involves the formation and agglomeration of fine crystals. This technique was used to report the spherical crystallization of the anti-diabetic drug tolbutamide. The medication was dissolved in a solution of sodium hydroxide. To neutralize the sodium hydroxide solution of tolbutamide, an aqueous solution of hydroxypropyl methylcellulose and hydrochloric acid was added, which was then crystallized[4].

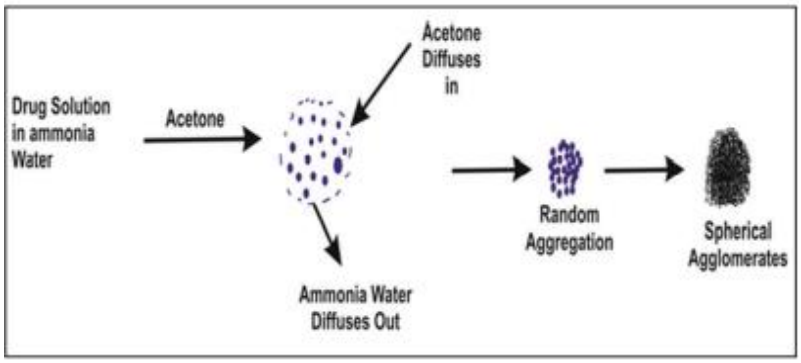

Figure 04: Neutralization technique Process

FACTORS AFFECTING THE AGGLOMERATION PROCESS

1. Role of solvents.
2. Role of temperature.
3. Role of agitation.
4. Role of additives.
5. Duration of residence of agglomerates in crystallization medium.

1. Role of solvents:

The sphericity of the agglomerates obtained is affected by the solvent type, amount, and nature of the bridging liquid. In a typical SA process, the general rule is that as the amount of bridging liquid increases, so does the size of the agglomerate. However, after a certain amount of bridging liquid has been added to the system, no observable change in the size of the agglomerates is observed[10].

Commonly three types of solvents are used in spherical crystallization

1. Good Solvent

2. Bridging Liquid

3. Poor Solvent

Good Solvent:

The solvent in which the drug is well-soluble is referred to as a good solvent. It is an excellent drug solvent. A good solvent is chosen based on drug solubility and affinity/miscibility with the bridging liquid.

Bridging Liquid:

Agglomerates were formed by agitating the crystals in the liquid suspension while the bridging liquid was present. The bridging liquid should be immiscible with the suspending medium but capable of cementing the agglomerated particle. The finely divided solid crystals in the liquid suspension initially separated from each other, but by adding a small amount of bridging liquid that preferentially wets the surface of the solids, bridges between the solid crystals form and the solid crystals eventually agglomerate into spherical form.

Poor Solvent:

The poor solvent is also referred to as Antisolvent or bad solvent. Poor solvents should not be miscible with the solvent system (good solvent and bridging liquid), and their affinity should be greater than that of the drug and solvent. Because this technique is used to improve the solubility of poorly soluble drugs, water is the best antisolvent. Typically, the solvent system and its composition are chosen through trial and error[11].

2. Role of temperature:

Temperature is well known to have a significant impact on crystal nucleation and growth because it determines the level of supersaturation in the crystallizing system. As a result, the temperature will influence the initial crystallization and subsequent properties of the primary particles during the spherical agglomeration process. Furthermore, temperature affects the relative solubility of different components in the spherical agglomeration system and, as a result, their availability in the system. As a result, temperature changes can influence the agglomeration process[12].

3. Role of agitation:

It is clear that agitation has a significant impact on the particle size of the agglomerates. Any variation in the rate and duration of agitation will affect the product's shape and size. Shearing of the agglomerates occurs at higher agitation rates, resulting in smaller agglomerates with

fines or no agglomerates at all. Lower agitation rates result in spheres with irregular sizes, which does not meet the method's objectives. The agitation speed must be optimized in order to produce acceptable products [10].

4. Role of additives:

Polymers such as hydroxypropyl methylcellulose, polyethylene glycol, and polyvinyl pyrrolidone delay nucleation. These polymers prevent spontaneous crystal aggregation, giving plenty of time for the formation of spherical agglomerates. As their crystal habit changes, polymers interfere with sphericity and particle size.

5. Duration of residence of agglomerates in crystallization medium:

The residence time of the agglomerates, i.e. the duration under agitation, is an important parameter affecting the properties of spherical agglomeration products. Kawashima et al. reported that the size of agglomerated crystals of aminophylline increased gradually with residence time and reached an equilibrium state after a certain time. Morishima et al. made a similar observation, observing an increase in agglomerate size with increasing agitation time due to continued coalescence. Blandin et al. observed changes in porosity in salicylic acid agglomerates as residence time increased. The porosity of the agglomerates decreased as they grew, and they became more spherical. Due to the system's continued agitation, this was attributed to compaction via agglomerate-agglomerate collisions or agglomerate-vessel collisions. The compaction process also increases the compressive strength of the agglomerates. Thati and Rasmuson reported similar findings regarding agglomerate size, sphericity, and strength with continued agitation after the completion of feeding in their study on the spherical agglomeration of benzoic acid. Morishima *et, al* observed an increase in bucillamine agglomerate density with agitation time[11].

EVALUATION OF SPHERICAL AGGLOMERATES:

1. CHARACTERIZATION OF PRODUCTS:

A) Differential Scanning Calorimetry:

DSC was used to determine the polymorphic transition of spherical agglomerates[12]. DSC was performed with a DSC 823 calorimeter and Star E software[13].

B) Scanning electron microscopy:

Before scanning, the spherical agglomerates were coated with gold. SEM was used to evaluate the surface morphology of agglomerates[13].

C) FTIR:

At room temperature, FTIR spectral measurements were performed. Separate tests were performed on about 2mg of the drug, as well as re-crystallized crystals and spherical agglomerates. The pure drug and all crystals were dispersed in potassium bromide powder and compressed into pellets at a pressure of 6000kg/cm[12].

D) X-ray diffraction:

To detect possible polymorphic transitions during the crystallization process, X-ray diffraction patterns were used[14].

E) Percent drug content:

In a mortar and pestle, the optimized formulation was triturated. A dose of simvastatin powder was weighed and dispersed in 100 ml of methanol before being sonicated for 20 minutes with an ultrasonicator. The solution was then filtered through Whatman filter paper and the drug content was determined spectrophotometrically at 238 nm (model- ultraviolet (UV) 1700 Shimadzu, Japan).

F) Solubility analysis:

To make a saturated solution of simvastatin, the optimized formulation was mixed with 2 mL of water. The solution was shaken in an orbital shaker for 48 hours before being centrifuged in a laboratory centrifuge at 300 rpm for 15 minutes. The resulting solution was then filtered through Whatman filter paper No. 41 and diluted with distilled water. Solubility was determined spectro photometrically at 238 nm (model-UV 1700 Shimadzu, Japan) [12-13].

G) Dissolution studies:

Drug release studies on prepared agglomerates were carried out using a USP dissolution apparatus 2 (DT 60, Veego Instruments) and 900 ml of phosphate buffer pH-7.0 as the dissolution medium at 37-$^{+}$0.1°C. The paddle's speed was set to 50 rpm. The prepared agglomerates were wrapped in muslin cloth and tied to the paddle. An aliquot of 1 mL was collected every 10 minutes and diluted with Phosphate buffer pH-7.0 up to 10 mL before

being analyzed for simvastatin content using a UV-spectrophotometer at 238 nm. To compensate for the loss, an equivalent volume (1 ml) of fresh dissolution medium was added [17].

2) Determination of spherical crystal properties[15]

a) Flow properties

Using the fixed funnel method, the angle of repose was measured to assess the flowability of spherical crystals. An angle of repose less than 25^0 indicates good flow property, whereas one greater than 40^0 indicates poor flowability.

Tap density (TD) was calculated by tapping samples in a cylinder with a tapping machine. The volume and weight of the powder before tapping were used to calculate the bulk density.

The volume and weight of the powder before tapping were used to calculate Carr's index (CI) and Hausner's ratio (HR). CI less than 15 or HR less than 1.35 indicates good flowability, while CI greater than 35 or HR greater than 1.35 indicates poor flowability.

$$CI = (TD– BD)/TD \times 100$$

$$HR = TD/BD$$

b) Packability

The sample packability was determined by analyzing the tapping process using Kawakita kuno methods and the parameters a, b and k in the equations.

$$N/c = 1/ (ab) + N/A.$$

$$C = (V_o\text{-}V_n)/V_{o,\,a} = (V_o\text{-}V\infty)/Vo.$$

Where the degree of volume reduction when the tap number is infinity, b and k are constants for the apparent packing rate, and Vo and Vn are the volumes in the initial loosely packed, nth tapped, and most densely packed states, respectively.

The angle of friction, shear cohesive stress, and shear and shear indexes of spherical agglomerates should be less than the pure drug to improve agglomerate packability[16].

EVALUATION OF PREPARED TABLETS:

a) Hardness or crushing strength test[18]:

This test determines the amount of force required to fracture the tablet in kilograms or pounds. Aside from the binder concentration and compression force, the hardness of the tablet is also affected by the granules to be compressed, the type and concentration of lubricant used, and the space between the upper and lower punches at the time of compression. The Monsanto hardness tester was used to assess the tablet's hardness. The tablet was placed in the tester, and the pressure required to break the tablet was recorded[18].

b) Weight variation test [19]:

The weight variation test was carried out by individually weighing 20 tablets, calculating the average weight, and comparing the individual tablet weight to the average weight[19].

c) Friability of agglomerates[20]:

A sample from each batch of agglomerates and plastic balls is placed on a sieve and shaken for a predetermined amount of time. The mean geometric diameter is computed for each time interval.

Percentage friability index (FI) as a function of time can be calculated at each time using the following equation.

$$FI= dg /(dg) \times 100$$

Here, dgt = mean geometric diameter after time t

dgt = mean geometric diameter at the initial time.

d) Crushing strength:

The crushing strength of agglomerate can be measured using the Jarosz and Parrot mercury load cell. A minimum of ten granules should be tested, and the average load in grams is used to calculate the crushing strength.

e) Heckel analysis:

It is used to analyze the compressibility of agglomerates with the help of derivation.

$$Dd/dp= k (1-D)$$

Where D is the compact's relative density at pressure P and k is a constant. On further integrating the above equation, it is assumed that the change in relative density in relation to pressure is directly proportional to the leftover porosity.

f) Tensile strength:

The force per unit area of broken face required to split a prepared compact is known as the radial tensile strength σt. The hardness value of the compacts is determined by the Monsanto hardness tester and the following equation is utilized.

$$\sigma_t = 2F/\pi Dt$$

Here F is the crushing force (N), D is the diameter of the tablet, and t is the thickness of the compact.

CONCLUSION:

Due to its superior flowability to the original pure amorphous drug, the spherical crystal technique, which is less expensive, could be useful for direct compression of tablets. Because this technique crystallizes, aggregates, and spheroids in a single step, it takes less time than the wet granulation technique. Spherical crystals are more soluble in aqueous solvents, increasing the bioavailability of poorly soluble drugs, particularly Biopharmaceutical Classification System class II drugs whose bioavailability is dissolution rate limited. As a result, if the technique is scaled up for commercial production of APIs, it will undoubtedly bring about significant changes in current manufacturing methods.

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CONFLICTS OF INTEREST:

The authors declare that there is no conflict of interest.

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