



Review Article

Spherical Crystallization and Agglomeration Methods for Directly Compressible Pharmaceutical Dosage Forms: A Comprehensive Review

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*Keywords:*Spherical Crystallization,
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Manufacturers have opted tablets because to their better stability, near-tamper-proof nature, and low production, packaging, and delivery costs. Spherical agglomeration is a revolutionary technique for creating medicinal dosage forms that are instantly compressible. The process of spherical agglomeration involves assembling small crystals into a sphere. This enhances the powder's qualities, including particle size, shape, flow characteristics, solubility, and bioavailability of pharmaceutical medicinal components. Spherical crystallization was created for use with hydrophilic polymers to increase the dissolving properties of water-insoluble medications. The flow characteristics, particle size analysis, compression, and dissolving behavior of the spherical agglomerates were all improved. The two most prevalent crystallization processes are SA and QESD. These procedures are also classified into two types: ammonia diffusion system (ADS) and crystallo-coagglomeration (CCA). This therapy takes use of the neutralizing approach. Any of the procedures outlined above can be employed concurrently to crystallize.

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INTRODUCTION

Tablets have been a preferred option for manufacturers for a long time because of their superior stability, near-tamper-proof nature, and relatively inexpensive cost of production, packaging, and delivery. Lower solubility of the active ingredient and complex manufacturing processes to produce a compressible granular material, present significant difficulties encountered during the tablet's formulation development. To make the granulation process industrially acceptable, the number of processes also grows, and with it, the validation and documentation [1-4].

Tablets account for approximately half of oral medication delivery methods and seventy % of all pharmaceutical formulations making them an extremely popular dosage form. The time-consuming procedure of directly tableting medicinal ingredients has been used successfully to create various medications on a large scale. The tablet is the most well-known and practical dosing form among all medical treatments.

From a production standpoint, tablets are produced at a substantially higher pace than any other preparation. A tablet is a single-dose solid dosage form. A modern form of tablet production is direct compression of medicinal components. For this method to operate, the bulk powder combination must be made more flowable and compressible, and the compacted tablets must have sufficient mechanical strength [5, 6].

The bulk of commercially available formulations use drugs directly. Certain other drugs, on the other hand, require morphological, chemical, and physical modifications. Following this adjustment, these drugs will be suitable for use in the formulation. Many drugs on the market are classed as BCS class II due to their low water solubility and slow dissolution rates. This difficulty prevents the medication from being effectively concentrated. Crystallization is one method for enhancing the solubility and rate of dissolution of poorly soluble medications. These approaches have successfully boosted medication flowability and compressibility [1- 3].

Spherical Crystallization:

The spherical crystallization procedure has gained favor in realm of API delivery. This

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method not only allows for preparation of spherical crystals, but they opened up various novel paths for medications delivery, particularly those with low solubility and bioavailability. Crystallization is a material property of a particular molecule. The physical as well as mechanical state of an API molecule can influence its properties, including solubility and powder flow characteristics [7-10].

Principle:

The main principle underlying the circular agglomeration process is to use a dissolvable interaction mechanism to form strong crystals. This method involves adding a smaller amount of a third dissolvable, referred to as bridging liquid, to promote the formation of agglomerates. Large circular agglomerates are produced when crystals aggregate during the crystallization process. A near-saturated drug solution is prepared in an excellent solvent and added to a subpar dissolvable. This system's basic motivation is the preference for both bad and good solvents that are readily miscible with one another. Here, there is a stronger bond between the solvents than there is between a medication and a good solvent, which causes the dissolvable to precipitate crystals [11-15].

Need for Spherical Crystallization:

It is extremely difficult to create solid dosage forms that improve the bioavailability of drugs that are not readily soluble in water. Finding innovative ways to accomplish this is a significant problem. One method for growing bioavailability of poorly soluble medications is to manually micronize crystalline pharmaceuticals and combine them with surfactants when they crystallize. The flow and compressibility of crystalline powders change during the micronization process, which might lead to preparation issues. The addition of surfactants typically results in a modest increase in water solubility [16-20].

Advantages of Spherical Crystallization:

1. This technology primarily enhances the physicochemical characteristics of pharmaceutical crystals, improving their suitability for processes such as milling, mixing, and tableting.
2. Improve the drug crystal's micromeritic characteristics significantly.
3. This method enhances the wettability and dissolving rate of some medicines.

4. This process converts crystalline drugs into polymorphic forms, which may improve bioavailability.
5. This procedure can improve efficiency in following processes including separation, filtering, and drying.
6. It enables the creation of innovative particulate drug delivery systems such as microsponges, microspheres, nanospheres, microballons, nanoparticles, and micropellets.

Disadvantages of Spherical Crystallization:

1. Selecting appropriate solvents is a time-consuming process.
2. Optimizing processing parameters is challenging.

Requirement /Solvent System:

Spherical crystallization uses three solvents: an excellent solvent, a wetting medium, and an immiscible final solvent. The polarity and interactions with hydrophobic phases determine agglomerate crystal shape and roundness.

1) Good Solvent:

A solvent that allows the drug to dissolve quickly is considered effective. It is the ideal solvent for the medication. A solvent should be chosen depending on the drug's solubility as well as miscibility with the bridging liquid.

2) Bridging Liquid:

When the bridging liquid was present, crystals suspended in liquid were stirred, resulting formation of agglomerates. Bridging liquid must be capable of cementing the agglomerated particles while remaining immiscible in suspending medium. Finally, solid crystals in liquid suspension agglomeration were shaped into spheres by introducing minor quantity of bridging liquid to bridges between solid crystals, which preferentially wetted the solids' surfaces [21-25].

3) Poor Solvent:

Poor solvent is also referred to as a bad or ant solvent. The solvent system shouldn't be combined with a good as well as bridging solvent, as it has a lower affinity than the solvent-drug combination [10, 11]. When employing this method to increase solubility, H₂O is typically commonly used ant solvent. Typically, trial and error is used to determine the solvent system's composition.

Main Steps Involved in the Growth of Agglomeration:

- 1. Flocculation Zone:** In this, agitation pulls liquid away from crystal surfaces, bringing the crystals closer together; adsorbed bridging liquids join particles through forming a lens bridge [Fig. 1(a)]. Pendulum bridges in region cause particles to form loose, open flocks. Liquid surface tension and liquid bridges cause particles to attract one another. The capillary stage occurs when all vacant areas inside agglomerate are entirely occupied by fluids [26-28].
- 2. Zero Growth Zone:** In order to create densely packed pellets that are completely filled with the bridging liquid, loose flocules is consolidated into closely packed pellets where trapped fluid are released and bridging liquid is sprayed to surface of small flocks. [Fig. 1(b)]. Stirring the slurry generates liquid turbulence, as well as pellet-pellet and pellet-stirrer

collisions, which act as driving factors in the transformation [29, 30].

- 3. Fast Growth Zone:** After removing an adequate amount of bridging liquid from the tiny agglomerates' surface, they proceed into their zone of rapid growth. The word "coalescence" refers to the large particles that arise when a well-formed nucleus collides randomly. A successful collision requires only a little quantity of additional surface moisture on the nucleus. This offers the nucleus flexibility, which promotes particle deformations, eventually, coalescence [Fig. 1(c)].

Constant Size Zone: In this phase, agglomerates stop expanding or may even shrink slightly. Here, the rate of agglomeration breaking equals the rate of coalescence [Fig. 1(d)]. The decline in size might be due to shattering, breaking, or attrition [31-33].

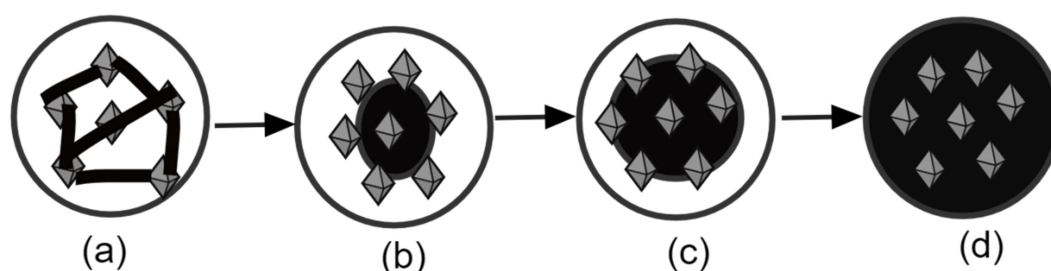


Figure 1: Steps for Agglomeration Growth: (a) Flocculation Zone (b) Zero Growth Zone (c) Fast Growth Zone (d) Constant Size Zone

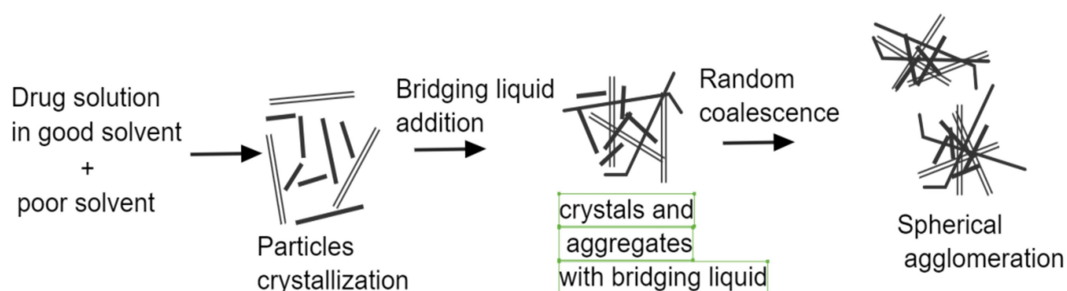


Figure 2: Steps involved in Spherical Agglomeration (SA)

Techniques of Spherical Crystallization:

The different techniques for spherical crystallisation that are available are divided into as follows:

1) Spherical Agglomeration Method (SA):

This process entails adding two or more API to appropriate solvent as well as bridging liquid,

where they crystallize and agglomerate simultaneously. A no solvent is then introduced. To create fine crystals, the medication and a good solvent solution are combined with a weak solvent at a specified temperature and speed. Crystal agglomeration occurs when a bridging liquid is utilized [34]. Good & poor solvent is easily miscible and solvent-to-solvent contact

(binding force) exceeds the drug- good solvent interaction, resulting in fast crystal precipitation. Owing to interfacial tension at solid-liquid interface & capillary negative pressure, bridging liquid creates liquid bridges which bind the suspended crystals in the system together [35-37]. The SA approach consists of three parts, as shown in Fig. 2.

2) Quasi Emulsion Solvent Diffusion Method:

For this approach work, API & high-quality solvent must interact more strongly than the high-quality solvent and low-quality solvent do. Even though the two solvents are miscible, the drug dissolves in the excellent solvent and produces quasi- emulsion droplets when spread in the poor solvent. Drug solubility declines and eventually crystallises within the droplets as the excellent solvent diffuses out of emulsion droplets and into outer poor solvent. Remaining

heat that dissolves in the beads helps the produced diamonds cluster together.

3) Ammonia Diffusion Method:

This approach uses the ammonia-water framework, with the medication's dissolvability determining which is the best or worse dissolveable. Furthermore, the ammonia-water combination acts as a bridge liquid. Generally, this method is recommended for amphoteric drugs that cannot be combined using traditional approaches. Three stages were required to complete the full operation. First, the medication's breakdown in alkaline water is accelerated as the beads collect the precious stones. Simultaneously, the agglomerate's smelling salts disseminate into the naturally dissolvable environment. Because of its reduced capacity to operate, as a bridging fluid, circular agglomerates occur.

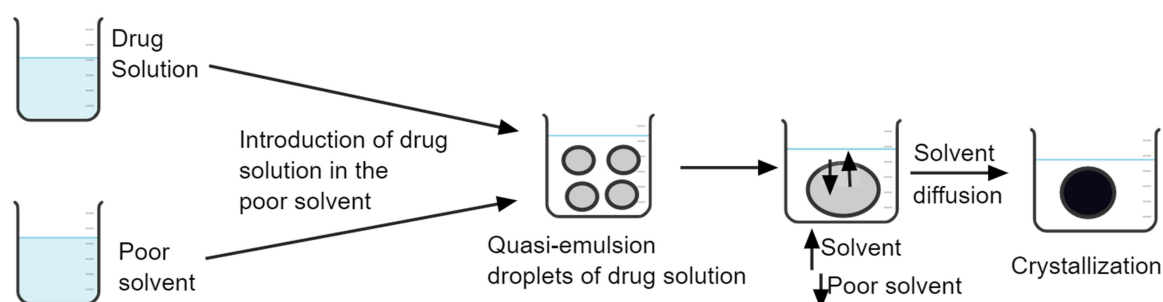


Figure 3: Proposed Mechanism of QESD

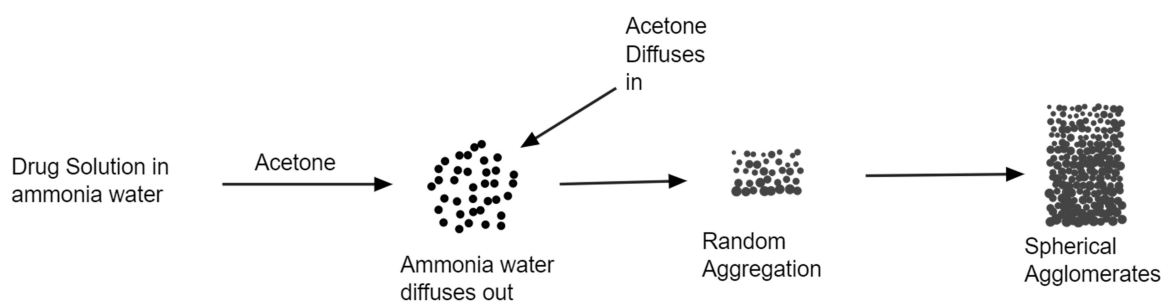


Figure 4: Ammonia Diffusion System

4) Neutralization Method:

This approach crystallizes the subject material with a sodium hydroxide configuration, which is very soluble, whereas hydrochloric acid is corrosive and less soluble. Diluted hydrochloric acid, an effective operator for agglomeration formation, neutralises the medicine and NaOH arrangement, resulting in crystallization and a naturally dissolvable look. Compact circular agglomerates with water-soluble polymer expansion have high packability, free-flowing

capacity, and accurate distribution of contract molecules [38-40].

5) Crystal-co-agglomeration Techniques:

Crystallization happens in the presence of an external inert substance or diluents, as the name crystallo-co-agglomeration (CCA) implies. Although CCA was successful when utilizing another dynamic component or diluent, such as powder, sodium starch glycolate, and starch, in the case of low-measurement dynamic

substances, the SC method was confined to high-measurement medicines. Employing crystal-co-agglomeration processes, some researchers have manufactured blended dosage spherical crystals by employing another medicinal substance as a substrate [41, 42].

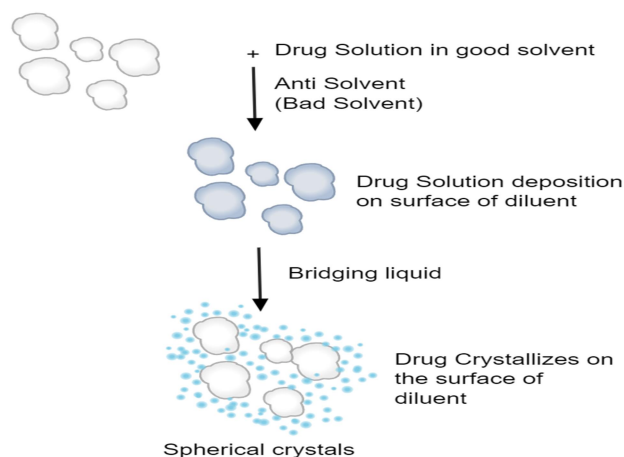


Figure 5: Crystallo-co-agglomeration Process

Characterization of Spherical Agglomerates

i) Physical Appearance:

The organoleptic properties of the spherical crystals like white, odour and physical appearance were checked by visual observant.

ii) Practical Yield:

To calculate the practical yield of crystals, the weigh to the finished product after drying was divided by the combined weight of the medication and polymer used to make the crystals. The method below was then used to calculate the percent practical yield.

$$\text{Practical yield} = \frac{\text{Practical mass of crystals}}{\text{Theoretical mass of drug and polymer}} \times 100 \quad (1)$$

iii) Percentage Drug Loading and Entrapment Efficiency:

The percentage drug content was calculated using following formula given below [11].

$$\% \text{ drug content} = \frac{\text{Practical drug concentration}}{\text{Theoretical mass concentration}} \times 100 \quad (2)$$

$$\% \text{ EE} = \frac{\text{Mass of drug in Spherical crystals}}{\text{Mass of drug used in preparation}} \times 100 \quad (3)$$

iv) Evaluation of Flow property:

Flowing are the methods used for determination of flow property.

a) Angle of Repose:

The Angle of Repose is the maximum angle that can occur between the surface of the sample pile and the horizontal plane. It is used to calculate the inter-particle force between the particles. Using the fixed funnel method, it was measured [11].

Procedures: They were determined utilizing free-standing cone & fixed funnel methods. A level horizontal surface was used to attach a funnel with a 2.5 cm-tall tip above graph paper. The stem end of the funnel was cut perpendicular to the symmetry axis. The powder was gradually added to the funnel until the tip (h) of the funnel was reached by the apex of the expanding conical pile. After calculating the powder cone's average diameter (d), the tangent of the angle of repose was found to be:

$$\theta = \tan^{-1} (h/r) \quad (4)$$

Where,

h=ht of the tip of the funnel from the horizontal plane.

d=diameter of cone.

r=radius of pile made from powder.

b) Bulk Density:

A sample of powder to be analyzed was carefully poured into a graduated cylinder. The volume of the substance was marked on a measuring cylinder and documented.¹⁰

$$\text{Bulk density} = \frac{\text{Weight of sample in gm}}{\text{Bulk volume of sample in mL}} \quad (5)$$

c) Tapped Density:

It is measured by using tap density apparatus [10].

$$\text{Tapped density} = \frac{\text{Weight of sample in gm}}{\text{Tapped volume of sample in mL}} \quad (6)$$

d) Compressibility or Carr's Index:

The compressibility index may be used to provide a straightforward indicator of how easily a material can be made to flow [10].

$$I = (1 - V/V_0) 100 \quad (7)$$

Where,

V = Vol occupied by a sample of the powder after being subjected to a standardized tapping procedure.

V₀ = Volume before tapping.

e) Hausner's Ratio:

Bulk density and tap density are used to calculate it [11].

$$\text{Hausner's ratio} = \rho/A \quad (8)$$

Where,

ρ =Tapped density, A=Bulk density.

f) Flow Rate:

The flow properties of powder & granules are critical in the production of powder, granules, tablets, and capsule. Flow rate of powder and granules can be calculated using following formula:

$$\text{Flow rate} = \frac{\text{Mass of powder}}{\text{Time required to flow}} \quad (9)$$

v) Solubility Studies:

Solubility investigations were done in triplicate using distilled water as a solvent. In produced spherical crystals, internal energy of molecules has a significant impact in solubility [18].

vi) Scanning Electron Microscopy:

Surface topography is studies on shape, overview, dimensions etc.

vii) X-ray Powder Diffraction:

XRD is studies on polymorphism existence [13,15].

viii) FTIR:

With FTIR, it is done to verify the sample's purity. The presence of new stretching frequencies caused by the salvation makes it substantially more useful for recognizing solvates and anhydrous forms than polymorphs.

ix) DSC:

DSC is used to examine thermograms. The heat gain or loss resulting from changes in the physical or chemical composition of a sample is computed using DSC. DSC may be used to analyze changes in the properties of agglomerates consisting of polymers and medications together [18].

x) In-Vitro Dissolution Studies of Spherical Crystals:

Research is conducted by incorporating a medium inside the spherical crystals within the capsule shell to verify the improved disintegration. Research on drug dissolution will

demonstrate that agglomerates are superior to pure medications. Ready-made aggregated crystals Particle size, solubility, particle density, and specific surface area all contribute to increased dissolving rates.

CONCLUSION

Spherical crystallization is a method that reduces tablet compression and increases flowability. It employs techniques such as solvent modification, quasi-emulsion solvent, ammonia diffusion system, and neutralization. Spherical crystals dissolve easier in aqueous solutions, increasing the bioavailability of weakly soluble medicines, notably BCS class II medications. However, monitoring organic solvent residues is required for compliance. Spherical crystallization can also produce sustained-release API microparticles.

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