



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

Spherical Crystallisation

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ARTICLE INFO

Published: 01 Nov 2024

Keywords:

Direct compression,
Flowability,
Compressibility, Spherical
agglomeration.

DOI:

10.5281/zenodo.14021375

ABSTRACT

The flow and compressibility characteristics of microcrystalline drug candidates can be improved by using the spherical crystallization technique. Agglomerating solvents, quasi-emulsion solvent diffusion, and ammonia diffusion techniques are employed to achieve spherical crystallization of microcrystals. The direct tableting technique is becoming more important in pharmaceutical manufacturing because it saves money and time. A technique used in particle engineering called spherical agglomeration involves transforming fine crystals into a spherical shape. This improves the powder's size, shape, flow characteristics, solubility, and bioavailability of medicinal ingredients. Spherical crystallization is a technique that has been further developed to improve the dissolution rate characteristics of drugs that are poorly soluble in water. It can also be used to sustain drug release from solid dosage forms. the goal of this review is to provide a thorough and in-depth analysis of the method, benefits and drawbacks, mechanism various manufacturing processes, and characterization of spherical agglomerates.

INTRODUCTION

Tablets are a relatively common dosage form, making up 70% of all pharmaceutical preparations and at least 50% of all oral drug delivery systems. Direct tableting of pharmaceutical materials is a contemporary way of producing tablets that has been successfully used to produce a wide range of medications on an industrial scale. Simple powder mixing and compression are used in the tablet production process, which saves time, money, and energy, among other advantages. Thus, Kawashima proposed in 1974 to control crystal

agglomeration with controlled features in order to obtain the size growth of particles during the crystallization step [1]. Finding immediately compressible formulations is one of the most cost-effective alternatives; this is especially important for high volume items. In recent years, there has been a resurgence of interest in exploring the possibilities of direct compression tableting as an alternative to the more conventional granulation technique. Creating new techniques to boost the bioavailability of medications with low water solubility is a major challenge for formulators of

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



solid dosage forms [2]. It has also lately acquired tremendous attention and relevance. Thus, "a unique particle engineering technology by which crystallization and agglomeration can be carried out concurrently in one step to change crystals straight into compacted spherical shape" is the definition of the spherical crystallization process [3].

Need for spherical crystallization

For low lozenge medicines that are weakly compressible and aqueously answerable, this is the preferred fashion. Medicinals are now directly tableted since it's further cost-effective and requires lower labor, but this is only doable if the drug has good inflow rates. The globular crystallization fashion must be used to enhance the medicine's micromeritic rates, similar as flowability, packability, compressibility, etc., in order to negotiate this purpose. This procedure basically alters the medicine's demitasse habit, which influences multitudinous morphological, rheological, and technological pharmaceutical actions as well as the medicine's bioavailability from lozenge forms. In order to alter their release profile, some specifics have also been recrystallized using polymeric accoutrements and the globular agglomeration fashion(4). Formulating solid lozenge forms presents a significant challenge in terms of developing creative approaches to ameliorate the bioavailability of specifics that are constitutionally inadequately answerable in water. In utmost cases, the addition of surfactant increased waterless solubility less noticeably(5).

Advantages of spherical crystallization

1) The spherical crystallization method has proven to be effective in improving the compressibility and flowability of pharmaceutical powders.
2) This technique can facilitate faster and more efficient completion of subsequent processes such as drying, filtration, and separation.

3) It has been used for a long time to increase the bioavailability, compressibility, flow, and solubility of substances.

4) It can help mask the bitter taste of the medication.

Disadvantages

1) Choosing the right solvent is a complex task.
2) The main process parameters (such as stirring rate, temperature, and agitation) are challenging to control.

Principle of spherical crystallisation

- This method involves adding the drug's saturated solution to a suitable solvent, where the drug is soluble, but the solution is not too concentrated. A third solvent, known as the bridging liquid, is added to encourage the formation of clusters. To create spherical clusters, the bridging liquid coats the crystal surfaces, promoting the formation of liquid bridges that help bind the clusters together [7]

Mechanism involved in the process of spherical crystallization

❖ Flocculation zone

The adsorbed bridging liquid connects the particles by creating a bridge or lens between them. Pendular bridges create loose, open flocs of particles in this zone. This stage of the agglomeration process, where air is the continuous phase and the ratio of liquid to void volume is low. The capillary suction pressure and bonding forces provided by the pendular bridges are responsible for the agglomerate's cohesive strength [8].

❖ Zero growth zones

Loose floccules are moved into densely packed pellets, whereupon the trapped fluid is forced out and the bridging liquid is forced onto the surface of the small flocs, creating inadequate space in the pellet that is fully filled with the bridging liquid. The agitation of the slurry, which results in liquid turbulence, pellet-pellet and pellet-stirrer collision, provides the driving force for the transformation [9].



❖ Fast growth zone

The agglomerate's fast growth zone occurs when enough bridging liquid has been forced from the surface of the smaller agglomerates. Coalescence is the process by which a well-formed nucleus randomly collides to form a large article. This gives the nucleus flexibility, promotes article deformation, and leads to subsequent coalescence.

❖ Constant size zone

Agglomerates stop growing or even slightly shrink in size in this zone. In this case, the frequency of agglomeration breakage balances the frequency of coalescence. As the original floccules become small agglomerates, the bridging liquid is forced out of the pores in zero growth zones, which is the step that determines the rate of agglomeration growth. The rate of agitation controls the rate [5].

Techniques of spherical crystallization

- Spherical agglomeration or solvent change
- Quasi- Emulsion solvent diffusion
 - Ammonia diffusion method
- Neutralization technique
- Crystallo-co-agglomeration

Evaluation of spherical crystals

Flow properties

The force between the particles, their size, distribution, and shape, as well as the surface area, surface roughness, and surface texture, all affect the material's flow properties. Because the agglomerate has a lower angle of repose than single crystals, its flowability is significantly improved. The techniques for determining flow property are shown below [10].

(A) Angle of repose

The angle of repose can be calculated by the following formula: $\tan \theta = h/0.5d$

where h = pile height

d = pile diameter Angle of repose values ≤ 30 generally indicate a fluid material, while angles ≥ 40 indicate a non-fluid material [11]

(B) Compressibility or Carr's index

The compressibility index provides a simple indication of how easily a material flows: $I = (1 - V/V_0) \times 100$,

good flow properties are indicated by values below 15% and poor flow properties by values above 25% [12].

(C) Hausner ratio

It is calculated using both packed density and bulk density. Packed density/apparent density is equal to the Hausner ratio.

Good flowability is defined by a value less than 1.25 (20% Carr index). Values greater than 1.25 (33% Carr index) indicate poor flow [11]

(D) Porosity

Compressibility is greatly affected by porosity.

Granular density / true density = 1 - intragranular porosity.

Bulk density / Granular density = 1 - intergranular porosity

Bulk density / True density = 1 - Total Porosity [13].

(E) Packability

It has been reported that agglomerates made by spherical crystallization have improved packability. The compressibility of the aggregates can be improved by reducing the friction angle, shear stress and shear exponent compared to the single crystals. Spherical aggregates of both solvent systems were prepared by Kawashima, Y. et al. and compared with the aggregates of the original drug powder. It was discovered that the agglomerates \ 'Packability had improved compared to the original crystals, and that they could be directly compressed [14].

Compression behaviour analysis

For any material to be compressed directly, it must have good compatibility and compressibility. The compression behavior of single crystals and aggregated crystals can be determined by plotting relative volume versus compression pressure. Spherical aggregates exhibit superior strength properties compared to normal crystals. When

compressing aggregates, the surfaces are assumed to be newly prepared by fracture, which improves the plastic bonding between particles and reduces the compressive forces required to compress aggregates during plastic deformation compared to single crystals [15].

Compaction behaviour of agglomerated crystals were evaluated by using following parameters [16]

The subsequent Agglomerated crystals' compression process was examined using Heckel's equation, which also evaluated the crystals' compactibility.

in $[1/(1-D)] = KP + A$
where D is the tablets' relative density when compressed.

The Heckel Plot's straight section slope is represented by pressure, K, and the mean yield pressure (Py) is the reciprocal of K. The intercept found by extrapolating the plots' straight segment is given by the following equation.

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

where, when P=0, D₀ is the powder bed's relative density.

The relative densities for A and B are provided by the following equation.

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

$$D_B = D_A - D_0$$

Stress Relaxation Test [17]

In this test, a fixed amount of spherical agglomerated crystal samples were placed in a die with a specified diameter, and the surface of the die was coated beforehand with magnesium stearate. The samples were then compressed at a steady speed using a universal tensile compression tester. The upper punch was kept in place for 20 minutes after a specific pressure limit was reached, during which time the amount of stress applied to the upper punch was measured. The relaxation ratio Y (t) and time t are related by the following

equation, which also computes the parameters A_s and B_s and evaluates relaxation behavior.

$$t/Y(t) = 1/A_s B_s - t/A_s$$

$$Y(t) = (P_0 - P_t)/P_0$$

Where: P₀ is the maximum compression pressure, And, P_t is the pressure at time t.

Mechanical strength [18]

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:

Tensile strength: By applying the maximum load necessary to crush the spherical crystal, the tensile strength of spherical crystals is determined. This technique provides a straightforward way to gauge spherical crystals' tensile strength.

Crushing strength: Crushing strength, commonly referred to as compressive strength, is a material's or structure's resistance to forces that cause it to shrink. It is determined by compressing the material until it breaks or fails. The mechanical integrity of a crystalline sphere's resistance is referred to as crushing strength.

Friability test

The attrition and sieving processes combined into one single operation is known as the friability of spherical crystals. The plastic balls and granules were put on a test screen. After the required attrition on the granules, the sieve is subjected to the standard motion of a test sieve shaker. A function of time is used to record the weight of powder that passes through the sieve. Agglomerate friability is calculated using the following formula:

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

Where: W₀ = 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

Sieve analysis is a straightforward method for determining particle sizes and distributions. Particle size analysis is now possible with the Ro-



Tap sieve shaker. Utilizing cutting-edge technology, an image analyzer determines the particle's size and volume [19]

Solubility [20]

Solubility determined quantitatively using distilled water and other solvent (acid or base) at room temperature (250c).

Dissolution Rate

It has been demonstrated that when apparent specific surface area rises, agglomerate dissolution increases. By partially breaking up the agglomerated crystals, tableting compacts lower the average particle size. A higher rate of dissolution was seen when spherical crystallization was conducted with a surfactant present. [21]

Characterization of Spherical Crystallization

1) Powder X-ray diffraction techniques are essential to determine batch-to-batch reproducibility of crystal form. Using this method, aggregated crystal forms have been established. A pattern is not produced by an amorphous form. For a given compound, each diffraction model represents the properties of a particular crystalline network.

2) Fourier Transform Infrared Spectroscopy (FTIR): With the addition of new stretching frequencies brought by hi, it is much more useful in distinguishing solvates and anhydrites than in identifying polymorphs.

Applications of spherical crystallization in pharmaceutical

- 1) To improve the flowability and compressibility.
- 2) Better bioavailability
- 3) To mask the bitter taste of drug.
- 4) Preparation of microsphere, microspheres and nanospheres, microballoons, nanoparticles and micro pellets as novel particulate drug delivery system.

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HOW TO CITE: Jyoti Patil*, Shamal kadam, Pallavi Gaikwad, Spherical Crystallisation, *Int. J. of Pharm. Sci.*, 2024, Vol 2, Issue 11, 9-14. <https://doi.org/10.5281/zenodo.14021375>

