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Spherical crystallization: A method for improving powder and tablet characteristics

Narendra Kr. Goyal * Nitin Sharma, P. K. Sharma

Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, Bypass Road- Baghpat Crossing, Meerut, Uttar Pradesh, India

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ABSTRACT

Direct tabletting technique is the modern and the most efficient process used in tablet manufacturing which has been successfully used for various drugs. But the process strongly depends upon the quality of the crystals used. For improvement of direct compression properties of different poorly soluble drugs Kawashima and their coworkers developed the spherical crystallization technique in 1986, for size enlargement of the drug in the field of pharmacy. Agglomeration technique can transform directly the fine crystals, produced in the crystallization process into a spherical shape. Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step. This technique has been successfully utilized for improvement of powder properties such as particle size, shape and flow properties of crystalline drugs. Solubility enhancement of pharmaceutical drug is also investigated by spherical crystallization. In this review we will discuss about the advantages, method and parameters which can be improved by spherical crystallization process. In addition current and future prospects of spherical crystallization are also discussed.

Key Words: Direct tabletting technique, Spherical crystallization, flowability, compactability, agglomeration

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INTRODUCTION

Now day's researchers are making attention on the development of new dosage form for the delivery of various kind of drug in keeping focus on better drug delivery system in terms of simple safe and economic formulation. Among them, tablet is still having attention for the

delivery of pharmaceuticals and biopharmaceuticals direct compression of pharmaceutical ingredient is focussed with greater impact. Direct compression is the modern and the most efficient process used in tablet manufacturing because of free flowing property and able to form stable compacts at low punch forces. It is fastest, simplest and least expensive tablet compression procedure in which many processing steps (granulation, drying) are eliminated. Moreover is used for moisture sensitive drugs for which wet granulation technology cannot be used. Method involves the direct compression of ingredient, required certain physical properties of powder such as flowability, bindability and mechanical strength. Due to this reason there are limited number of tables are available in the market that can be made by direct tabletting. [1]

An interesting alternative to improve direct compression tabletting is agglomeration of the small crystals during the crystallization. Crystals could be generated employing any of the available techniques like sublimation, solvent evaporation, vapor diffusion, thermal treatment and crystallization from melt precipitation by change in pH, growth in presence of additives or the grinding. [2]

The use of spherical crystallization as a technique appears to be efficient alternative for obtaining suitable particles for direct compression. [3, 4] 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. Spherical crystallization technique was used in 1986 by Kawashima Y, et al for size enlargement of the drug. According to Kawashima "An agglomeration process that transforms crystals directly into compact spherical forms during the crystallization process is spherical crystallization". [5]

Spherical crystallization makes the pharmaceutical ingredients suitable for direct compression by altering the physical properties. [6, 7] This technique involves the designing of particles by which crystallization and agglomeration are carried out for the improvement of powder and tableting parameters of various pharmaceuticals and biopharmaceuticals by changing the crystal habit (form, surface, size and particle size distribution). This technique involves the rearrangement of crystal lattice in controlled manner to get desired parameters of pharmaceutical ingredients. Moreover this modification of crystal habit also results in the modification of certain physicochemical properties as solubility, bioavailability and stability of pharmaceutical ingredients. Hence, this method may also be used to increase the solubility of poor water soluble drug.

Advantages of Spherical Crystallization

Spherical crystallization method involves a certain numbers of advantages which are discussed here,

1. Spherical crystallization technique causes improvement of flow property and compressibility of drug so this technique promotes direct tabletting process.
2. This technique may convert crystalline form of a drug into different polymorphic form so as to attain better bioavailability.
3. This technique may also utilize for masking of the bitter taste of drug.

4. This technique also helpful in preparation of microspheres, microsponges, microbaloons, micropellets, nanaospheres and nanoparticles as novel particulate drug delivery system.
5. Solubility parameters of poorly soluble drug can improved with this method
6. This is reported in various papers that methods help to improve the stability of pharmaceutical ingredients.

Methods of spherical crystallization

Following methods are use 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 (SA):-** The process involves the formation of fine crystals and their agglomeration. Crystallization is generally achieved by the change of solvent system or salting out. The solution of material in good solvent is poured in a poor solvent, so as to favor formation of fine crystals. Agitating the crystals in a liquid suspension and adding the bridging liquid, which preferentially wets the surface crystals to cause binding, form the agglomerates. The agglomerates may be spherical if the amount of bridging liquid and the rate of agitation are controlled. **[**8]

2. **Quasi-Emulsion Solvent Diffusion Method (QESD):-** By this method, spherical crystallization can be carried out using a mixed system of two or three partially miscible solvents, i.e. bridging liquid-poor solvent system or good solvent-bridging liquid-poor solvent system. When bridging liquid (or plus good solvent) solution of drug is poured into poor solvent (dispersion medium) under agitation, quasi emulsion droplets of bridging liquid or good solvent forms the emulsion droplet into the dispersing medium and induce the crystallization of drug followed by agglomeration. [9]

3. **Ammonia Diffusion System Method (ADS):-** 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 act 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. [10, 11]

4. **Neutralization Method (NT):-** This process involves the formation of fine crystals and their agglomeration. The spherical crystallization of antidiabetic drug tolbutamide was reported by this technique. The drug was dissolved in sodium hydroxide solution. Aqueous solution of Hydroxypropyl methylcellulose and hydrochloric acid was added to neutralize sodium hydroxide solution of tolbutamide, which was then, crystallized out**.** [12]

Besides above mentioned methods there are some other traditional methods for the crystallization which are carried out by controlling the physical and chemical properties and also

called as the non-typical spherical crystallization process. These methods include Salting out precipitation, cooling crystallization and crystallization from the melting. [13]

Parameters of pharmaceutical ingredients improved by spherical crystallization technique

As the spherical agglomerated crystals showing significant effect on the formulation and manufacturing of pharmaceutical dosage forms so this technique cause improvement of following properties.

1. **Particle Size and Size Distribution: -** Particle size and shape of pharmaceutical ingredients can be changed with this method. Generally a large size and spherical shape particle are formed. Size of particles are improved due to the aggregation if particles influenced by the bridging agent. Similarly, agitation of solvent system during process results in the spherical shape of particles. Particle size and shape of spherical crystals can be study by following methods
2.
    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 determine by using technique. An amorphous form does not produce a pattern. The X-ray scattered in a reproducible pattern of peak intensities at distinct angle (2θ) relative to the incident beam. Each diffraction pattern is characteristics of a specific crystalline lattice for a compound.

3. **Mechanical Strength: -** Spherical crystals should posses good mechanical strength as that directly reflects the mechanical strength of compact or tablet. This may be due to increased intrapartical force with in spherical agglomerated crystals. It is determine 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 is measured by using 50ml glass hypodermic syringe. The modification includes the removal of the tip of the syringe barrel and the top end of the plunger. The barrel is then used as hallow support and the guide tube with close fitting tolerances to the Plunger. The hallow plunger with open end served as load cell in which mercury could be added. A window cut into the barrel to facilitate placement of granule on the base platen. The plunger acted as movable plates and set directly on the granules positioned on the lower platen as the rate of loading may affect crushing load (gm). Mercury is introduced from reservoir into the upper chamber at the rate of 10 gm/sec until the single granule crushed; loading time should

be <3 minutes. The total weight of the plunger and the mercury required to fracture a granule is the crushing load.

4. **Flow Property: -** 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 improvement in the flowability of spherical crystals could be attributed to the significant reduction in inter-particle friction, due to their spherical shape and a lower static electric charge Following are the methods used to determine of flow property.

   a) **Angle of Repose**: - This is the common method used for determination of flow property. The angle of repose is the angle between the horizontal and the slop of the heap or cone of solid dropped from some elevation. Values for angle of repose ≤ 30 usually indicate free flowing material and angle ≥ 40 suggested a poor flowing material. The angle of repose can be obtained from equation

$$\mathbf{Tan\ \theta = h/0.5d}$$

   Where h- height of the cone and d- diameter of the cone

   b) **Compressibility or Carr's Index**: - A simple indication of ease with which a material can be induced to flow is given by application of compressibility index

$$\mathbf{I = (1\text{-}V/Vo) *100}$$

   Where v = the volume occupied by a sample of powder after being subjected to a standardized tapping procedure and Vo = the volume before tapping.
   The value below 15% indicates good flow characteristics and value above 25% indicate poor flowability

   c) **Hausner Ratio**: - It is calculated from bulk density and tap density.

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

   Values less than 1.25 indicate good flow (20% Carr Index) and the value greater then 1.25 indicates poor flow (33% Carr Index).
   d) **Density: -** This method involve the size enlargement therefore volume of powder get increase and density get decrease. Density of the spherical crystals is the mass per unit volume.

$$\text{Density} = M/V$$

   Where M na V in mass and volume of powder respectively.

5. **Packability: -** Improve packability has been reported for agglomerates prepared by spherical crystallization. The angle of friction, shear cohesive stress and shear indexes are lower then that of single crystals, which can improve the packability of the agglomerates.

The packability of agglomerates improved compared with those of the original crystals and that the agglomerated crystals are adaptable to direct tabletting. The packability assessed by analysis of the tapping process with the Kawakita(I) and Kuno(II) method and using the parameters a, b,1/b, k in the equation

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

$$C = (Vo-Vn)/Vo,$$

$$a = (Vo-V\infty)/Vo.$$

$$\rho f - \rho n = (\rho f - \rho o) \cdot \exp(-kn) \quad \text{.....II}$$

Where, N =Number of tapping, C =Difference in volume (degree of volume reduction.) and a, b are constant.

6. **Compression Behaviour 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 were evaluated by using following parameters.

7. **Friability Test: -** The friability of the spherical crystals is the combination of the attrition and sieving process in to 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 slop 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

$$\textbf{Friability(X)} = \{1-W/Wo\}/100$$

Where Wo = Initial weight of the crystalline agglomerates placed in sieve
W = Weight of the material which does not passed through sieve after 5 min.

8. **Moisture Uptake Study: -** The study indicates the behavior of uptake of moisture by drug and the prepared spherical crystals, which affect the stability. The weighted quantity of drug and spherical crystals placed in crucible at accelerated condition of temperature and humidity,40 C ± 10C and 75% ± 3%respectively. The gain in weight of drug and spherical crystals is measured.

9. **Dissolution Rate and Bioavailability: -** The dissolution rate and bioavailability of agglomerated crystal depends on particle size, particle density and specific surface area of the

agglomerated crystals. 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. 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.

Current and future prospects of spherical crystallization method

Several pharmaceutical ingredients have been converted into spherical crystals for the improvements of several parameters. Yadav VA, et al. prepared Spherical Crystal of Carbamazepine by using Qussi emulsion solvent diffusion method taking Ethanol (Good Solvent), Chloroform (Bridging Agent) & Water (Poor Solvent) as solvent system and concluded that spherical crystals of CBZ with different hydrophilic and hydrophobic polymers showed an improvement in direct tabletting behaviour as well as bioavailability of the dosage form. [14] Other investigations related to this technique by using different methods are given in table -1.

Table: - 1 Various investigations of spherical crystallization technique

INVESTIGATOR	DRUG	SOLVENT	METHOD	Ref.
Gorodon MS, et al.	Naproxen	Acetone, Water Hexinol, octanol, Toluene	Spherical Agglomeration	15
Takami K, et al.	Dibasic calcium phosphate	Water, Aqueous solution of phosphoric acid, Citric acid	Spherical Agglomeration	16
Goczo Hajnalka., et al.	Acetyl salicylic acid	Ethanol, Water, Carban tetrachloride	Spherical Agglomeration	17
Kawashima Y, et al	Aminophylline	Ethanol, chloroform, water	Spherical Agglomeration	18
Usha AN, et al.	Aceclofenac	Acetone, water, dichloromethane	Spherical Agglomeration	19
Kawashima Y, et al.	Mefenamic acid	DMF, water, carbon tetrachloride/ chloroform	Spherical Agglomeration	20
Kawashima Y, et al.	Acebutalol Hcl	Water, Ethanol, Isopropyl acetate	Quassi Emulsification Solvent Diffusion System	21
Piera Di Martino, et al.	Propyphenazone	Ethyl alcohol, demineralized Water, isopropyl acetate	Quassi Emulsification Solvent Diffusion System	22
Kawashima Y, et al.	Ibuprofen	Ethanol, Water with	Quassi	23

		sucrose, fatty acid ester	Emulsification Solvent Diffusion System	
Bhadra S, et al.	Mefenamic acid	Ammonia water, acetone, dichloromethane	Ammonia Diffusion System	24
Puechagut HG, et al.	Norfloxacin	Ammonia water, Acetone, Dichloromethane	Ammonia Diffusion System	25
Ueda Masumi, et al.	Enoxacin	Ammonia water, Acetone, Dichloromethane	Ammonia Diffusion System	26
Ghol.M, et al.	Ampicillin trihydrate	Ammonia water, Acetone, Dichloromethane	Ammonia Diffusion System	27
Sano A, et al.	Tolbutamide	NaoH solution, Aqueous solution with polymer or surfactant, 1M HCl.	Neutralization Technique.	28

Although several investigation have been done in spherical crystallization method, but still a Method is required to be investigated to remove some limitations related to existing spherical crystallization method. Percentage yield of recovery is the main concern, as it is very low in other method. Large amount of pharmaceutical ingredients are not recovered during the process. Another problem is the selection of solvent system, which is quite problematic to design the system. Again controlling of several factors as agitation speed, amount of bridging liquid and temperature, make these method quite difficult to produced spherical crystals. Hence, there is a promising need to develop a new method for the minimization of above problems associated with existing methods so that spherical crystallization methods can be used in regular manner for the development of direct tabletting technique.

CONCLUSION

The spherical crystallization process can be used successfully to manufacture spherical crystals of poorly soluble drugs to improve flowability, compactibility and cohesivity. When the crystallization process is optimized concerning the form of the crystal agglomerates and the reproducibility of the product in different researches, the results found that this product can be recommended for direct tablet-making. So the spherical crystallization method may be an attractive approach for the improvement of direct tabletting technique.

REFERENCES

[1] Shangraw RF. Compressed tablets by direct compression. In: Lieberman HA, Lachman L, Schwartz JB. Pharmaceutical Dosage Form: Tablets, Vol 1. Marcel Dekker, New York. **1989**; 195–246.

[2] Guillory JK. Polymorphism in pharmaceutical solids. Marcel Dekker, New York. **1989**; 183-226.
[3] Kawashima Y, Ohno H, Takenaka H. *J Pharm Science*. **1981**; 70(8): 913-916.
[4] Kawashima Y, Furukawa K, Takenaka H. *Powder Technol*. **1981**; 30: 211.
[5] Kawashima Y, Ohno H, Takenaka H. *J Pharm Science*. **1981**; 70(8): 913-916.
[6] Kawashima Y , Furukawa K, Takenaka H. *Powder Technol*. **1981**; 30: 211.
[7] Bhadra S, Kumar M, Jain S, Agrawal S, Agrawal G.R. *Pharmaceutical Technology*. **2004**; 66-76.
[8] Viswanathan CL, Kulkarni SK, Kolwankar DR. *AAPS Pharm Science Tech*. **2006**; 7 (2): Article 48.
[9] Kawashima Y, Niwa T, Handa T, Takeuchi H, Iwamoto T Itch. *J Pharm Sci*. **1989**; 78(1): 68-72.
[10] Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y, Furuyama S. *J Pharm Science*. **1991**; 80(5): 472-78.
[11] Bhadra S, Kumar M, jain S, Agrawal S, Agrawal GP. *Pharm Tech*. **2004**; 66-76.
[12] Sano A, Kuriki T, Kawashima Y, Takeuchi H, Hino T, Niwa T. *Chem Pharm Bull*. **1992**; 40: 3030-3035.
[13] Yadav AV, Yadav VB. *Journal of Pharmacy Res*. **2008**; 1, 2: 105-110.
[14] Yadav VA, Yadav VB, *Asian Journal of Pharmaceutics*. **2009**; 18-25.
[15] Gordon MS, Chowhan ZT. *Drug Dev Ind Pharm*. **1990**; 16 (8): 1279-1290.
[16] Takami K, Machimura H, Takado K, Inagaki M, Kawashima Y. *Chem Pharm Bull*. **1996**; 44 (4): 686-870.
[17] Goczo H, Szabo RP, Hasznos NM, Farkas B. *Chem Pharm Bull*. **2000**; 48(12): 1877-81.
[18] Kawashima Y, Aoki S, Takenaka H, Miyake Y. *J Pharm Science*. **1984**; 73 (10): 1407-10.
[19] Usha AN, Mutalik S, Reddy MS, Ranjith AK, Kushtagi P, Udupa N. *Eur J Pharm Biopharm*. **2008**; 70: 674-683.
[20] Viswanathan CL, Kulkarni SK, Kolwankar DR. *AAPS Pharm Science Tech*. **2006**; 7 (2): Article 48.
[21] Kawashima Y, Cui F, Takeuchi H, Hino T, Niwa T, Kiuchi K, *Int J Pharm*. **1995**; 119: 139-147.
[22] Martino PD, Cristofaro RD, Joiris E ,Filippo GP , Sante M. *International Journal of Pharmaceutics.* **2000**; 197: 95–106.
[23] Kawashima Y, Niwa T, Handa T, Takeuchi H, Iwamoto T. *J Pharm Science*. **1989**; 78(1): 68-72.
[24] Bhadra S, Kumar M, jain S, Agrawal S, Agrawal GP. *Pharm Tech.* **2004**; 66-76.
[25] Hector GP, Jorge B, Carlo A. *J Pharm Science*. **1998**; 87(4): 519-23.
[26] Ueda M, Nakamura Y, Makita H, Imasato Y, Kawashima Y. *Chem Pharm Bull*. **1991**; 39(5): 1277-1281.
[27] Gohle MC, Parikh RK, Shen H, Rubey RR. *Ind J Pharm Sci*. **2003**; 634-37.
[28] Sano A, Kuriki T, Kawashima Y, Takeuchi H, Handa T. *J Pharm Science*. **1987**; 76(6): 471-474.