

## How spherical crystallization improves direct tableting properties: a review

Maryam Maghsoodi\*

Drug applied Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

### ARTICLE INFO

#### Article Type:

Review Article

#### Article History:

Received: 15 July 2012

Accepted: 30 July 2012

ePublished: 15 Aug 2012

#### Keywords:

Direct tableting

Spherical crystallization

Flowability

Compactability

### ABSTRACT

Direct tableting has been renewed as a preferable process by simply mixing and compressing powder to save time and cost in comparison with granule tableting. Direct compression tableting as a technique has been successfully applied to numerous drugs on the industrial scale, although the success of any procedure, and resulting mechanical properties of tablets, is strongly affected by the quality of the crystals used. Good flowability, packability and compactability are prerequisite for drug to be prepared by direct tableting. When the mechanical properties of the drug particles are inadequate a primary granulation is necessary. The use of spherical crystallization as a technique appears to be an efficient alternative for obtaining suitable particles for direct tableting. 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 the micromeritic properties of crystalline drugs. In this review, we will discuss how the micromeritic properties of the particles such as flowability, packability and compactability can be improved by spherical crystallization technique.

### Introduction

Today the tablet is the most popular dosage form, representing 50% of all oral drug delivery systems, and accounting for 70% of all pharmaceutical preparations produced. From the manufacturing point of view, the initial capital outlay is high but tablets can be produced at much higher rate than any other dosage form. The dry dosage form promotes stability, and tablets are readily portable and consumed. The formulation of a tablet is optimized to achieve several goals. The focus today in the business is better drug delivery concepts, but also to make the simple standard formulations as economical as possible to produce. One of the most economical solutions is to find direct compressible formulations and this is especially of interest for large volume products. The required number of unit operations in direct compression is lower which means less equipment and space, lower labour costs, less processing time, and lower energy consumption. However, the use of this technique, although conceptually quite simple, depends on generating appropriate: (a) particle size and particle size distribution of the materials, (b) flowability of the crystals, (c) bulk density of the powder, in order to feed the correct amount of drug into a die cavity, and (d) compactability of the powder. Despite some drug crystals exhibiting such appropriate properties, many materials display poor flowability and compactability.<sup>1</sup> Direct tableting of latter materials has been successfully industrialized by coformulating higher amounts of fillers ( $\geq 75\%$ ). However, direct

compression in the production of high dose formulations is limited, since large quantities of excipients are ordinarily required to produce suitable tablets.<sup>2</sup> To overcome this problem, the physicomechanical properties of drug need to be modified to improve flowability, packability and compressibility, so that powder can be delivered stably into die cavity and produce mechanically strong tablets. It is well known that the physical properties of the pharmaceutical raw materials such as crystal size, crystal shape, degree of agglomeration, and agglomerate properties can be modified by crystallization techniques to such an extent that these materials to be suitable for particular applications. Crystallization variables such as temperature profile, solvent composition, method and rate of supersaturation generation, hydrodynamics can be used to produce crystals with specific physicomechanical properties.

One interesting crystallization technique in which synthesis, crystallization, separation and agglomeration can be carried out in one step has been defined as spherical crystallization.<sup>3</sup> Indeed, this technique can promote the effectiveness of mixing, filling and tableting procedures via producing spherical agglomerates with improved physicomechanical properties like compressibility, packability and flowability.<sup>5-7</sup> Spherical crystallization was firstly introduced into pharmaceutical manufacturing by

\*Corresponding author: Maryam Maghsoodi (PhD), Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran.

Tel: +98 (411) 3392608, Fax: +98 (411) 3344798, E-mail: maghsoodim@tbzmed.ac.ir

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Kawashima et al.<sup>8,9</sup> as a simple technique to produce spherical agglomerates appropriate for direct tableting. Spherical crystallization may occur via two mechanisms: spherical agglomeration (SA) and emulsion solvent diffusion (ESD). In both mechanisms there are a good solvent and a poor solvent which their miscibility govern the mechanism of the spherical crystallization. In the ESD mechanism, the pure good solvent and poor solvent are miscible but as affinity between good solvent and drug is stronger than that of good solvent and poor solvent. Accordingly, emulsion droplets are first formed by mixing good solvent solution of the drug with poor solvent.<sup>10</sup> Then, crystallization occurs within droplets as a consequence of counter diffusion of good and poor solvents. In spite of the apparent simplicity of ESD mechanism, finding a suitable emulsifier is really time consuming and difficult.

The SA occurs in three solvent systems, in which good solvent and poor solvent are miscible.<sup>11</sup> The drug is precipitated immediately by mixing a good solvent solution of the drug with a poor solvent as they are freely miscible and the affinity between solvents is stronger than the affinity between good solvent and drug. The third solvent, termed "binder liquid" is usually immiscible with poor solvent but wets the dispersed crystals and collects the crystals to form agglomerates through the action of capillary forces.<sup>12</sup>

It was revealed from several studies spherical crystallization exhibited improved micromeritic properties of spherical agglomerated crystals over single crystals which assists in pharmaceutical processing and expedites the production of tablets by direct tableting. In this review it has been discussed how the micromeritic properties such as flowability, packability and compactibility of particle obtained by spherical crystallization can be improved.

### Flowability and packability

Improvement in flowability and packability of the agglomerated crystals prepared by spherical crystallization in comparison with the single crystals has been shown in several investigation.<sup>13-17</sup>

Kawashima *et al.* in 1994 produced the agglomerates of acebutolol hydrochloride by spherical crystallization. It was shown in this study that the prepared agglomerates had lower angle of repose compared to single crystals which indicated to improved flowability of the agglomerate.<sup>13</sup> According to their results, mean diameter and standard deviation of agglomerates was respectively larger and smaller than those of the single crystals. Therefore, better flowability of the agglomerates was attributed to their larger particle size and narrow size distribution. In other work, the effect of particle size on the angle of repose of the agglomerated and single crystals was<sup>15</sup> studied and it was shown that the angle of repose of agglomerates was smaller than that of original crystals over the entire studied particle size range. Therefore, it was assumable

that in addition of particle size there is another reason for improvement of flowability of agglomerated crystals. It was concluded that good flowability for agglomerates were attributed to the spherical shape and smooth surface, since the area of contacts in the powder bed for spherical shapes was smaller than that for other particle shapes. In various studies which in spherical crystallization was applied to prepare the agglomerates the packing process achieved by tapping was described by percent compressibility (Eq.1), Kawakita (Eq.2) and Kuno(Eq.3) equations as follows.<sup>18-20</sup>

$$\text{Compressibility}\% = \frac{(\rho_f - \rho_o)}{\rho_f} \times 100 \quad \text{Eq.1}$$

$$\frac{n}{c} = \frac{1}{ab} + \frac{n}{a} \quad \text{Kawakita's equation} \quad \text{Eq.2}$$

$$C = (V_o - V_n) / V_n$$

$$\ln(\rho_f - \rho_n) = -Kn + \ln(\rho_f - \rho_o) \quad \text{Kuno's equation} \quad \text{Eq.3}$$

Where  $n$  is the number of tapping;  $V_o$  and  $V_n$  are the initial volume of powder bed before tapping and the volume powder bed after the  $n$ th tapping, respectively;  $\rho_o$  and  $\rho_n$  are the densities of powder bed at the initial stage and at the  $n$ th tapping respectively;  $a$ ,  $b$  and  $k$  are constants representing flowability and packability of powder under mechanical force. As the results of several studies showed the low value of the percent compressibility and parameter  $a$  of Kawakita equation for agglomerated crystals indicated their high packability<sup>13,15,16,21</sup> and the larger parameter  $b$  and  $k$  in Kawakita's and of Kuno's equations respectively, for agglomerates indicated to their slower apparent packing velocity. The slow packing velocity which indicated to low proportion of the consolidation of powder per tap was attributed to high flowability and packability of the agglomerates which result in closely packing of the agglomerates even without tapping. Moreover, as reported by some works, improved packing properties of agglomerates compared to single crystals was due to their larger closest packing density.<sup>16,21</sup> Flowability and packability of the agglomerated Acebutolol hydrochloride crystals were comprehensively investigated by measuring interparticle frictions when sheared.<sup>13</sup> In this work the mechanical characteristics (e.g. friction angle, cohesive stress) of the agglomerates were determined from the yield locus, which was constructed by measuring tensile stress and shear stress of the preconsolidated powder bed. The yield locus was described by Warren Spring<sup>22</sup> as represented by equation 4.

$$\left(\frac{\tau}{\sigma}\right)^n = (\sigma + \sigma_T) / \sigma_T \quad \text{Eq.4}$$

Where  $\tau$  is shear stress,  $C$  is cohesive stress,  $\sigma$  is vertical stress and  $\sigma_T$  is tensile stress. According to this study, the angle of friction, shear cohesive stress and shear index of agglomerates were lower than those of single crystals. Such a low frictional force might be due to the decrease in frictional static electric charge of agglomerates. The major principal stress required to fracture the powder compact (i.e. uniaxial compression strength), was determined by drawing the Mohr circle contacting the yield locus and passing through the origin. The lower tensile stress and uniaxial compression strength proved the reduced cohesiveness of the agglomerates. Thus decreasing friction and cohesive forces during packing, resulted in improved packability and flowability of the agglomerates. According to these studies, it is expectable that the agglomerates flow smoothly from the hopper into the die and hence tablets with appropriate uniformity in weight can be produced from the agglomerates.<sup>15</sup>

### Compactability

In several works, it has been reported that the tablet compressed with the agglomerated crystals exhibited higher tensile strength than that of compressed single original crystals.<sup>13-15,23-25</sup> Superior strength characteristics of the agglomerated crystals to single crystals indicated that a stronger bonding occurred during compression of agglomerated crystals than in the case of single crystals. In Jbilou et al. study it was indicated that the improvement of compression ability of the ibuprofen agglomerated crystals compared to marketed single crystals in spite of their higher crystallinity, might be related to the isotropy of the agglomerate texture.<sup>14</sup> However, in several studies, increasing the contact points to bind particles as a consequence of fracturing of agglomerated crystals has been mentioned as one of the main reasons for improvement in compactibility of agglomerated crystals.<sup>13,15,16</sup> For example, Morishima et al.<sup>15</sup> indicated that the improved compactibility of agglomerated crystals was related to their structural characteristics.

During the early stage of the compression process, the agglomerates consisted of numerous small crystals fragmented and resulted in large relative volume change.

According to results of this study, the specific surface area of the agglomerates increased with increasing the compaction pressure from 0.5 to 5 MPa while no change was observed in the case of single crystals. This fact confirmed the fracturing properties of the agglomerates compared to single crystals. Furthermore, it was shown that, in the case of single crystals, there was a good linear relationship between the porosity and the logarithm of the tensile strength for each size fraction. On the other hand, compacts made from smaller crystals showed superior tensile strength compared to those made from larger crystals with the same porosity. This could be explained by considering

the fact that smaller crystals could be compacted more tightly as a result of higher interparticle contact points compared to larger crystals which was in agreement with some other works.<sup>26,27</sup> Regarding the agglomerates, the tensile strength of the compacts was close to that of single crystal, which was similar in constitutive crystal size. Having considered this finding and the fact that a good linear relationship between porosity and the tensile strength was also observed for agglomerates, it was concludable that the tensile strength of the compacts obtained from the agglomerates was mainly determined by the size of their constitutive crystals.

Kawashima et al.<sup>13</sup> also showed the tensile strengths of tablets from agglomerated crystals were higher than those from single crystals when compared at the same compression pressure and porosity of the tablet. However, they emphasized that the production of fresh surfaces by fracturing during the compression process is necessary to bind the particles strongly for tableting. To confirm the effect of fresh surface, newly produced by fragmentation during compression, on interparticle bonding, tablets were prepared with ground agglomerates and single crystals in mortar. The tensile strength of tablets with ground agglomerates was drastically reduced whereas such phenomena were not found with the original single crystals. This result was attributed to this fact that if the fractured surface is exposed to air for a time after breaking, no improvement in interparticle bonding occurs because of the decrease in the free energy of the surface when adsorbed with air. In this study it was found that produced surfaces by fracturing of the agglomerates in addition of increasing contact points to bind of particle, enhances the plastic interparticle bonding.<sup>13</sup> In this study and some other works the compression process was analyzed by Heckel equation which showed that a surface freshly prepared by fracture increased plasticity of particles, resulting in a lower compressive force required for compressing the agglomerates under plastic deformation compared to that for single crystals.<sup>13,16,28</sup> On the other hand, according to several researches, it is well known that better compacts result from the compression of plastic materials.<sup>29-31</sup> Plastic deformation can be quantitatively measured by stress relaxation at constant strain. Greater relaxation pressure, which is measured when plastic deformation requires higher energy, indicates increasing intimate interparticle contacts and consequently formation of strong bonds.<sup>32</sup> According to studies which elucidated plastic deformation based on relaxation stress, agglomerated crystals showed more rapid and extensive relaxation than single crystals which indicated agglomerated crystals exhibited a greater degree of plastic deformation under compression than single crystals.<sup>15,16,25</sup> Moreover, in another work<sup>23</sup> which deformation of agglomerated crystals as a single particle was studied based on the stress-strain curve it was found that the deformation of these particles was

mainly plastic. Marshall and York<sup>33</sup> reported that the deformation characteristics of a drug crystallized from different systems were different which might be responsible for improving plasticity of the crystals when recrystallized and agglomerated from different crystallization system. Also as mentioned previously, in some works increasing plasticity of the agglomerated crystals was attributed to structural characteristics of them which produced fresh surfaces of particle with higher plasticity as a consequence of fragmentation. In some researches lower elastic recovery of the agglomerated crystals than that of the single crystals was also reported.<sup>25,34</sup> For example, Kawashima et al.<sup>25</sup> showed the elastic recovery of the agglomerated crystals of acebutolol hydrochloride was lower than that of the single crystals because more energy was consumed for plastic deformation in the former case than in the latter. In turn, the lower elastic recovery of the agglomerated crystals resulted in lower ejection pressure for agglomerated crystals compared with that of the single crystals as explained below. It is known that the ejection force is the sum of the adhesive force, the friction force and the residual force. According to results of this study, there was no significant difference in residual pressure between agglomerated crystals and single crystals. Therefore, the lower ejection pressure might be due to the lower adhesive force and the lower friction force during ejection of the tablet from the die cavity for the agglomerated crystals compared to single crystals. The elastic recovery of the compressed tablet and the interaction of the material and wall are two main factors that are determined the adhesive force of the tablet to the die wall. Furthermore, in comparison with the agglomerated crystals and those of single it is obvious that the friction force of the former is lower because of lower elastic recovery.

Therefore, the two facts of the smaller adhesive force and friction force in the tablet releasing period resulted in lowered ejection pressure for agglomerated crystals compared to their single counterparts.

In summary, according to results of various investigation it can be concluded that remarkable fragmentation, increased plastic deformation and lowered elastic recovery of the agglomerated crystals during tableting process were responsible for improving the compactibility of the agglomerated crystals compared to single crystals.

### Conclusion

This study has brought forward that agglomerated crystals may receive properties that make them aimable for direct tableting. Improvement in flowability and packability of the agglomerated crystals obtained by spherical crystallization method in comparison with the single crystals has been shown in several investigations which were attributed to their larger particle size, spherical shape, and smooth surface. Improved flowability and packability should be of great advantage in uniform feed of the agglomerates into the

die cavity and their smooth compression in the direct tableting process. According to several studies, the compactibility improvement brought to crystals by the agglomerate form was clear. It was shown in these studies, the tablet agglomerated crystals compared to single crystals had greater tensile strength which implied the fact that a stronger bonding occurred during compression of agglomerated crystals than in the case of single crystals. The higher tensile strength of the tablets from agglomerated crystals is mainly due to the greater plastic deformation of the agglomerated crystals resulting in greater permanent inter particle contact and stronger bond force than in the case of single crystals.

### Conflict of Interest

There is no conflict of interest in this study.

### References

1. Tanguy D, Marchal P. Relations between the properties of particles and their process of manufacture. 13th Symposium on Industrial Crystallization: 1996; Toulouse-France: 715.
2. York P, Shekunov BYu. Crystallization processes in pharmaceutical technology and drug delivery design. *J Cryst Growth* 2000; 211:122-36.
3. Nocent M, Bertocchi L, Espitalier F, Baron M, Couarraze G. Definition of a solvent system for spherical crystallization of salbutamol sulfate by quasi-emulsion solvent diffusion (QESD) method. *J Pharm Sci* 2001; 90(10):1620-7.
4. Kawashima Y, Cui F, Takeuchi H, Niwa T, Hino T, Kiuchi K. Parameters determining the agglomeration behavior and the micrometric properties of spherically agglomerated crystals prepared by the spherical crystallization technique with miscible solvent systems. *Int Natl J Pharm* 1995;119: 139-47.
5. Lasagabaster A, Martin C, Goni MM. Preparation of spherically agglomerated crystals of the 3, 5-diglucoiside of cyaniding (cyanin). *J Chem Tech Biotechnol* 1994;60(4): 397-403.
6. Farnand JR, Smith HM, Puddington IE. Spherical agglomeration of solids in liquid suspension. *Can J Chem Eng* 1961;39: 94-7.
7. Gordon MS, Chowhan LT. Manipulation of naproxen particle morphology via the spherical crystallization technique to achieve a directly compressible raw material. *Drug Dev Ind Pharm* 1990;16:1279-90.
8. Kawashima Y, Aoki S, Takenaka H. Spherical agglomeration of aminophylline crystals during reaction in liquid by the spherical crystallization technique. *Chem Pharm Bull* 1982;30: 1837-43.
9. Kawashima Y, Okumura M, Takenaka H. Spherical crystallization: direct spherical agglomeration of salicylic acid crystals during crystallization. *Science* 1982;216(4550): 1127-8.
10. Sano A, Kuriki T, Kawashima Y, Takeuchi H, Hino T, Niwa T. Particle design of tolbutamide by

- spherical crystallization technique. V. Improvement of dissolution and bioavailability of direct compressed tablets prepared using tolbutamide agglomerated crystals. *Chem Pharm Bull* 1992;40: 3030-5.
11. Kawashima Y. New processes-application of spherical crystallization to particulate design of pharmaceuticals for direct tableting and coating, and new drug delivery systems. In: Chulia D, Deleuil M, Pourcelot Y, editors. *Powder technology and pharmaceutical processes* New York: Elsevier; 1994. p. 493-512.
  12. Kawashima Y, Okumura M, Takenaka H. The effects of temperature on the spherical crystallization of salicylic acid. *Powder Technol* 1984;39: 41-7.
  13. Kawashima Y, Cui F, Takeuchi H, Niwa T, Hino T, Kiuchi K. Improvements in flowability and compressibility of pharmaceutical crystals for direct tableting by spherical crystallization with a two solvent system. *Powder Technol* 1994; 78: 151-7.
  14. Jbilou M, Ettabia A, Guyot-Hermann AM, Guyot JS. Ibuprofen agglomeration prepared by phase separation. *Drug Dev Ind Pharm* 1999;25(3): 297-305.
  15. Morishima K, Kawashima Y, Takeuchi H, Niwa T, Hino T, Kawashima Y. Tableting properties of buccillamine agglomerates prepared by the spherical crystallization technique. *Int J Pharm* 1994; 105: 11-8.
  16. Kawashima Y, Imai M, Takeuchi H, Yamamoto H, Kamiya K. Development of agglomerated crystals of Ascorbic acid by the spherical crystallization techniques. *Powder Technol* 2003; 130: 283-9.
  17. Maghsoodi M. Effect of process variables on physicommechanical properties of the agglomerates obtained by spherical crystallization technique. *Pharm Dev Technol* 2011; 16(5): 474-82.
  18. Carr RL. Evaluation flow properties of solids. *Chem Eng* 1965; 72: 163-8.
  19. Kawakita K, Ludde KH. Some considerations on powder compression equations. *Powder Technol* 1971; 4: 61-8.
  20. Kuno H. Chapter 5. In: Kubo T, Jimbo G, Saito E, Takahashi H, Hayakawa S. Editors. *Powder Theory and Application*. Maruzen; Tokyo 1979, 341-346.
  21. Kawashima Y, Okumura M, Takenaka H, Kojima A. Direct preparation of spherically agglomerated salicylic acid crystals during crystallization. *J Pharm Sci* 1984;73(11): 1535-8.
  22. Tsunakawa H, Kunii D, Takagi F, Sugita M, Tamura T, Haze H: "Comparing the Flow Properties of Bulk Solids by Tri- axial Shear, Unconfined Yield and Direct Shear Tests". *J Soc Powder Technol* 1986;23:678- 684.
  23. Katta J, Rasmuson AC. Spherical crystallization of benzoic acid. *Int J Pharm* 2008; 348(1): 61-9.
  24. Maghsoodi M, Barghi L. Design of agglomerated crystals of ibuprofen during crystallization: influence of surfactant. *Iran J Basic Med Sci* 2011; 14(1): 161-9.
  25. Kawashima Y, Cui F, Takeuchi H, Niwa T, Hino T, Kiuchi K. Improved static compression behaviors and tablettabilities of spherical agglomerated crystals produced by the spherical crystallization technique with two solvent system. *Pharm Res* 1995; 12(7): 1040-4.
  26. McKenna A, McCafferty DF. Effect of particle size on the compaction mechanism and tensile strength of tablets. *J Pharm Pharmacol* 1982;34: 347-51.
  27. Vromans H, Bolhuis GK, Lerk CF. Magnesium stearate susceptibility of directly compressible materials as an indication of fragmentation properties. *Powder Technol* 1988;54: 39-44.
  28. Paradkar AR, Pawar AP, Chordiya JK, Patil VB, Ketkar AR. Spherical crystallization of celecoxib. *Drug Dev Ind Pharm* 2002;28 (10):1213-20.
  29. Schlanta S, Milosovich G. Compression of pharmaceutical powders: I. Theory and instrumentation. *J Pharm Sci* 1964; 53: 562-4.
  30. David S, Augsburg LL. Plastic flow during compression of directly compressible fillers and its effect on tablet strength. *J Pharm Sci* 1977;66: 155-9.
  31. Cutt T, Fell JT, Rue PJ, Spring MS. Granulation and compaction of a model system: II. Stress relaxation. *Int J Pharm* 1987;39: 157-61.
  32. Patel CI, Staniforth JN. Determination of the apparent failure viscosity of tablets. *J Pharm Pharmacol* 1987;39:647-65.
  33. Marshall PV, York P. The compaction properties of nitrofurantoin samples crystallized from different solvents. *Int J Pharm* 1991;67: 59-65.
  34. Thati J, Rasmuson AC. On the mechanisms of formation of spherical agglomerates. *Eur J Pharm Sci*. 2011;42: 365-79.