Improved Static Compression Behaviors and Tablettabilities of Spherically Agglomerated Crystals Produced by the Spherical Crystallization Technique with a Two-Solvent System

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Purpose. Poorly compressible crystals of acebutolol hydrochloride were agglomerated by the spherical crystallization technique with a two-solvent system to improve the compressibility for direct tabletting. The mechanism of improvements in static compression behaviors and tablettabilities of the spherically agglomerated crystals were investigated. ***Methods.*** The improvement of static compression behaviors of the agglomerated crystals was determined by measuring the stress relaxations and elastic recoveries of compressed powder of original and agglomerated crystals. The improved tablettability of agglomerated crystals was evaluated by the pressure transmission ratio upon compression, the ejection pressure for releasing the tablet from the die and the tablet strength, i.e., tensile strength required for breaking. ***Results.*** The higher relaxation pressure and the lower elastic recovery of the agglomerated crystals than of the original crystals were found. The pressure transmission ratio data showed that the friction pressures of the two crystals were similar during the compression period. The ejection pressure of the agglomerated crystals was lower than that of the original crystals. The tensile strength of the tablet of agglomerated crystals was greater than that of the original crystals. ***Conclusions.*** The compressibility and tablettability of the spherically agglomerated crystals prepared by the spherical crystallization technique were much improved due to their increased plastic property and reduced adhesive property compared to the original crystals.

KEY WORDS: direct tabletting; spherical crystallization; stress relaxation; elastic recovery; ejection pressure; tablet strength.

INTRODUCTION

The direct tabletting technique has been extensively investigated and successfully industrialized for some drugs because of requiring fewer machines and operation steps. Present progress in direct tabletting was accomplished by the addition of large amounts of fillers to the drug powder to improve various micromeritic properties.

The novel spherical crystallization technique[1,2] is an efficient technique for particle design for direct tabletting, during which crystallization and agglomeration can be carried out in one step, and the primary and secondary functional properties of the agglomerated crystals can be controlled simultaneously without using any filler or binder.

Acebutolol hydrochloride is a water-soluble drug. Its strong cohesive property and static electricity result in poor flowability and packability, and therefore direct tabletting cannot be performed. The spherical agglomeration technique is expected to make direct tabletting of this drug possible.

The agglomeration process principally requires a three-solvent system, i.e., a liquid bridge, a good solvent and a poor solvent[3,4]. In this study, the agglomeration process could be carried out in a two-solvent system (i.e., a good solvent and a poor solvent), using the emulsion-solvent-diffusion method[2,4,5]. When the good solvent solution of the drug was poured into the poor solvent under agitation, due to the strong interaction between the drug and the good solvent, the drug solution formed quasi-emulsion droplets and dispersed in the poor solvent. By the diffusion of the good solvent in the poor solvent, crystallization occurred in the droplets. The residual solvent acting as a bridging liquid agglomerated the precipitated crystals.

In the previous work[6] the micromeritic properties such as flowability and packability of the agglomerates produced with the two-solvent system were evaluated and compared with those of the original powder of the drug. It was found that the micromeritic properties of the agglomerates were improved compared to those of the original crystals and that the agglomerated crystals were adaptable to direct tabletting.

In this study the static compression behaviors and the tablettabilities of the agglomerated crystals and the original crystals were further investigated and compared by measuring the stress relaxation, the elastic energy and the pressure transmission ratio. The influences of the compression rate on the particle deformation and consolidation properties during the compression and on the post-compression characteristics were examined.

MATERIALS AND METHODS

Preparation of Agglomerated Crystals of Acebutolol with a Two-Solvent System

Acebutolol hydrochloride (4.5 g) was dissolved in distilled water (4 ml). This drug solution was poured into 180 ml of isopropyl acetate (analytical reagent grade) placed in a cylindrical vessel (500 ml) equipped with three baffles under agitation (500 rpm) using a propeller-type stirrer at room temperature (20–25 °C). When the W/O emulsion was produced under agitation, seed crystals (0.3 g) were added to the system to promote crystallization and agglomeration. A part of the water in the emulsion droplets diffused into the isopropyl acetate and the residual water bridged precipitated crystals. The solidified spherical agglomerated crystals were recovered by filtration and dried at room temperature. The −20+35 mesh sieve fractions of the agglomerated crystals and the original crystals (mean diameter: 7.5 μm) were used for the following compression test.

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Measurement of Stress Relaxation

Stress relaxation measurements were carried out using an Instron-type press (Autograph AG5000-D, Shimadzu Co.). A sample (200 mg) was compressed at a speed of 2 mm/min with a flat-faced punch and die set (8 mm diameter). The punch and the die were lubricated with a small amount of magnesium stearate at each run. When the compression pressure reached a given pressure (30, 50, 80, 100, 150, 200, or 300 MPa), the upper punch was kept stationary and the decay of the upper punch force was measured during a 1000 s holding interval to determine stress relaxation. In order to correct for the effect of the tabletting machine on the data, a blank relaxation test was carried out under the same conditions (speed and pressure) and this pressure drop was subtracted from the tabletting data of the samples. To determine the effect of the compression speed on the stress relaxation, the samples were compressed at different running speeds (0.5, 2, 10, or 100 mm/min). The pressure drops were monitored during a 120 s holding time at a given pressure (70, 140, or 300 MPa). The shorter holding time was chosen to observe clearly the effects of compression speed.

Measurement of Elastic Recovery

The elastic recovery was measured by a multiple recompression test with the Autograph. The punch and die set was the same as that in the stress relaxation test. Each sample (200 mg) was compressed 20 times continuously at a given compression pressure (70, 100, or 140 MPa) and a given speed (0.5 or 10 mm/min) before it was ejected from the die. The work done in every compression was calculated by the integration of each force/displacement curve. When the work done became constant, this value was taken as the work done to produce the elastic deformation during the compression[7], and was an indicator of the elasticity of the material.

Measurement of Pressure Transmission Ratio and Ejection Pressure

Each sample (150 mg) was compressed with a flat-faced upper punch (8mm diameter) under various pressures between 10 and 420 MPa and at a 1800 mm/min compression speed using a single tabletting machine (Model N-30E, Okada Seiko Co.) which was equipped with strain gauges at the upper and lower punchs. The pressure transmission ratio (PTR = PL/Pu) was calculated by measuring the upper punch pressure (Pu) and the lower punch pressure (PL) at a maximum pressure during the compression. When the upper punch pressure reached a given pressure, the lower punch pressure transmitted from the upper punch was measured simultaneously.

The ejection pressure (P_E) and the residual pressure (P_R) were determined from the profile of the lower punch pressure over time, which was recorded during the compression and decompression processes and during the lifting process.

Preparation of Compressed Tablets and Measurement of Tensile Strength

The preparation of tablets and the measurement of tensile strength were carried out using the Autograph. Each sample (200 mg) was compressed with a flat-faced punch (8mm diameter) under different given pressures (70, 100, 140, or 300 MPa) applying different compression speeds (0.5, 2, 10, or 100 mm/min) to investigate the effect of the compression speed on the tablet properties.

The tensile strength required to split the compressed tablets was calculated using eq. 1.

$$Ts = 2F/\pi DL \quad (1)$$

Where, F is the crushing force (N), and D and L are the diameter (m) and the thickness (m) of the tablet, respectively. The crushing force of the resultant tablet was measured by compressing diametrically with a 0.5 mm/min crosshead speed.

Statistical significancies in the differences between the original and agglomerated crystals data for stress relaxation, elastic recovery and tensile strength of their tablets were determined by the pair-wise T test.

RESULTS AND DISCUSSION

Stress Relaxation

It was found that relaxation pressures of original and agglomerated crystals increased with compression pressure up to a compression pressure of 150 MPa and then showed a decrease or remained constant. It is assumed that increasing compression pressure led to closer particle packing and plastic flow during the static holding period. The effect of the compression pressure on the relaxation pressure reached a maximum point with increasing compression pressure. The relaxation pressure decreased above this point, which might be due to the fact that the more closely compressed structure and the decreased porosity prevented the plastic flow from increasing further at higher compression pressures.

The relaxation pressure of the agglomerated crystals was greater than that of the original crystals when the compression pressure was less than 200–250 MPa.

It is known that greater relaxation pressure indicates greater energy required for plastic flow, which promotes intimate particle-particle contact and increases bond strength[8]. The results of this experiment showed that the plastic characteristics of the agglomerated crystals were better than those of the original crystals.

Figure 1 shows the effect of the compression speed on the relaxation pressure at various compression pressures.

As the compression speed was increased up to 10 mm/min, the relaxation pressure increased sharply; however, above this speed very little change of the relaxation pressure was observed. It is considered that a contact time of less than a certain value (in this case, contact time at compression speeds greater than 10 mm/min) was insufficient for the relaxation during the compression period and that the measurable relaxation pressure in the holding period became higher than at slower compression speeds, and reached a nearly constant value.

In addition, at a higher compression pressure (about 300 MPa) the relaxation pressure of the agglomerated crystals was lower than that of the original crystals. This was due to the fact that at high compression pressures, much denser structures were formed in the case of the agglomerated crys-

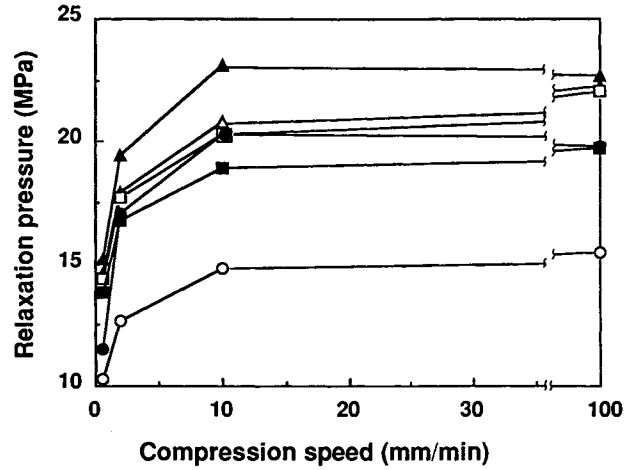

Fig. 1. Relationship between the relaxation pressure and the compression speed at various compression pressures. Key: Compression pressure (○) (●) 70 MPa**, (△) (▲) 140 MPa**, (□) (■) 300 MPa**. Open symbols: original crystals, solid symbols: agglomerated crystals, ** significant at P≥0.01.

tals than in the case of the original crystals during the compression process.

It is assumed that the plastic deformation was related to compression speed and compression pressure, and occurred during the compression period and during the holding time of static pressure after compression. Therefore the relaxation pressures measured in this experiment were considered to be the apparent stress relaxations.

Elastic Energy Recovery

Figure 2 shows the relationship between the number of compression cycles and the work done for compression at various compression speeds. It was found that the work done for the compression decreased rapidly from the first to the second compression and remained constant after the fifth

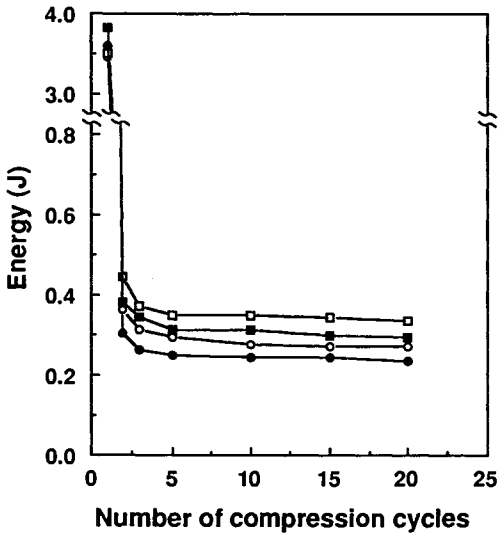

Fig. 2. Effect of the compression speed on the multiple recompression energy at 140 MPa pressure. Key: (○) (●) 0.5 mm/min, (□) (■) 10 mm/min. Open symbols: original crystals, solid symbols: agglomerated crystals.

compression. The plastic deformation was almost completed in the first compression process, and after the fifth compression the work done was solely due to the elastic deformation[9]. The lesser number of compression cycles required for arriving at a constant work, the more readily plastic deformation completed, exhibiting more plasticity[10]. It was evident that both the agglomerated crystals and the original crystals underwent mainly plastic deformation. However, as expected, it was observed that the elastic energy of the agglomerated crystals was lower than that of the original crystals due to the higher plasticity of the agglomerated crystals.

While examining the influence of the compression speed on the elastic energy (Fig.2), it was found that elastic energy was lower at 0.5 mm/min compression speed than at 10 mm/min compression speed, because greater plastic flow occurred during the compression period in the former case than in the latter.

The relationship between the percentage of the elastic energy recovery and the compression pressure at various compression speeds were investigated.

The elastic energy recovery was calculated using eq.2:

$$\text{Elastic Recovery} = \frac{\text{elastic energy}}{\text{input energy}} \times 100\% \qquad (2)$$

Where the input energy is the gross compression energy, i.e., the work done during the first compression.

It was found that the elastic recovery of both original and agglomerated crystals increased with increasing compression pressure, while the elastic energy recovery of the agglomerated crystals was lower than that of the original crystals because more energy was consumed for the plastic deformation in the former case than in the latter.

Pressure Transmission Ratio upon Compression and Ejection Pressure for Releasing Tablet

The pressure transmission ratio (PTR) vs compression pressure profile of the agglomerated crystals and the original powder were identical in all of the pressure ranges. This indicated that the particle-particle friction and particle-die wall friction of the agglomerated crystals were similar to those of the original crystals during compression. A possible reason is that the source material of the agglomerated crystals and the original crystals was the same (i.e., acebutolol) and was compressed in a similar manner. It is assumed that the PTR depended on the material and the level of consolidation and not on its primary (initial) physical form.

Janssen's equation[11] (eq.3) expresses the relationship between (PL/Pu) and the friction force on the die wall surface.

$$\text{Ln}(PL/Pu) = -4\mu KH/D \qquad (3)$$

Where, μ is the coefficient of friction between the die wall and the particles, K is the ratio of the horizontal pressure to the vertical pressure, H is the thickness of the resultant compact, and D is the die diameter. The total friction coefficient (μK), calculated from the slope of the straight line of Ln (PL/Pu) vs (H/D), was found to be 0.37.

Figure 3 shows the changes in ejection pressure and residual pressure with varing compression pressure. The

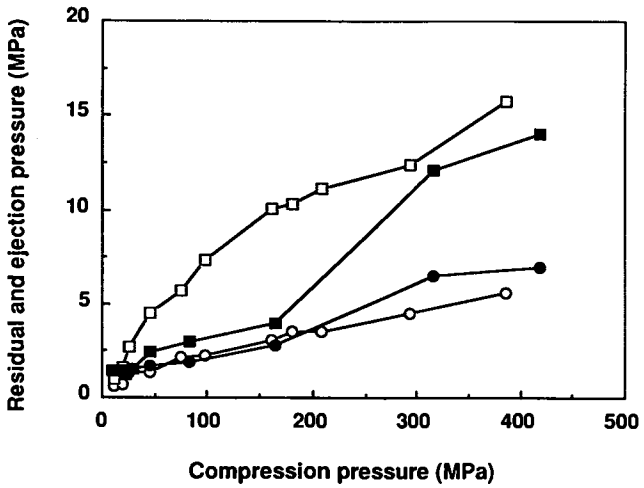

Fig. 3. Relationships between the ejection and residual pressures and the compression pressure. Key: (○) (●) Residual pressure, (□) (■) Ejection pressure**. Open symbols: original crystals, solid symbols: agglomerated crystals, ** significant at P≥0.01.

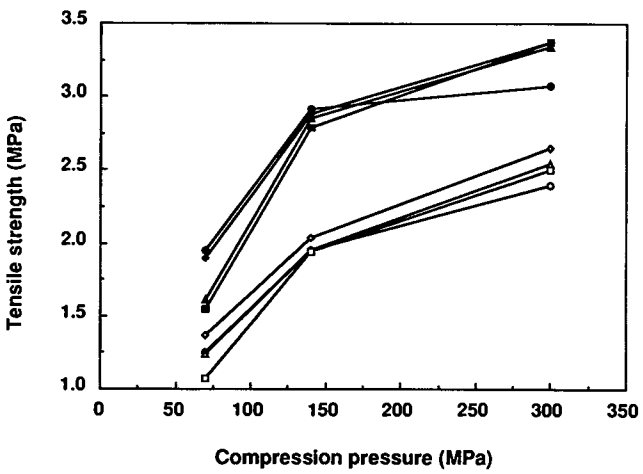

Fig. 4. Effect of compression speed on the tensile strength. Key: (○) (●) 0.5mm/min**, (△ (▲) 2 mm/min**. (□) (■) 10 mm/min**, (◇) (◆) 100 mm/min**. Open symbols: original crystals, solid symbols: agglomerated crystals, ** significant at P≥0.01.

ejection pressure for the original crystals was higher than that for the agglomerated crystals, while no significant difference in residual pressure was found between the two samples. It is known that the ejection force (P_E) is the sum of the adhesive force (P_A), the friction force (P_F) and the residual force (P_R).

The lower ejection pressure for agglomerated crystals might be due to the lower adhesive force and the lower friction force during ejection of the tablet from the die cavity compared with that of the original powder. The adhesive force of the tablet to the die wall is mainly related to the elastic recovery of the compressed tablet and the interaction of the material and the wall. It is evident that the lower elastic recovery of the agglomerated crystals resulted in a lower friction force than in the case of the original crystals.

Influence of Compression Speed on Tensile Strength of Tablet

Many papers have reported that plastic materials showed a compression rate dependency of the tensile strength of tablet to fracture[12,13,14].

Figure 4 illustrates the behavior of the tensile strength of the tablets against compression pressure at various compression speeds. The tablet compressed with the agglomerated crystals exhibited higher tensile strength than that of compressed original crystals. This was due to the greater plastic deformation of the agglomerated crystals resulting in greater permanent interparticle contact and stronger bond force than in the case of the original crystals[15].

However, the differences in speeds showed a little effect on the tensile strength of both the agglomerated crystals and the original crystals. Tablets compressed at low speeds (e.g., 0.5, 2, 10 mm/min) or high speed (1800 mm/min) (using a conventional single-punch tabletting machine) and with a holding time of 120 s or with no holding time showed similar results. The data obtained with the single-punch tabletting machine and with no holding time are not shown in Fig. 7.

CONCLUSIONS

When comparing compression properties of the agglomerated crystals with the original crystals, it was found that:

1. The higher relaxation pressure and the lower elastic recovery of the agglomerated crystals than of the original crystals under the same conditions suggested that the agglomerated crystals exhibit greater plasticity during compression, and the greater tensile strength of the tablet of agglomerated crystals further confirmed the fact that a stronger bonding occurred due to plastic flow during compression of agglomerated crystals than in the case of original crystals.

2. The PTR vs pressure profiles indicated that the total friction pressures of the particle-particle and particle-wall frictions for the two crystals were similar during the compression period. In the tablet releasing period, the ejection pressure for the agglomerated crystals was lower than that for the original crystals. This was due to the smaller adhesive force and friction force between the agglomerated crystals and the die wall compared to the original crystals.

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REFERENCES

1. Y. Kawashima. Development of Agglomerated Crystallization Technique Using New Agglomeration Phenomena of Particles in Liquid System and Particle Designs for Pharmaceutical Preparations. Yakugaku Zasshi 106 : 433–445 (1986).
2. Y. Kawashima, H. Takeuchi, T. Niwa, T. Hino, M. Yamakoshi and K. Kihara. The Development of a Novel Emulsion-Solvent-Diffusion Preparation Method of Agglomerated Crystals for Direct Tableting and Evaluation of Their Compressibilities. J.Soc.Powder Technol. Japan 26 : 659–665 (1989).
3. Y. Kawashima. Spherical Crystallization as a Novel Particle Design Technique for the Development of Pharmaceutical Preparations. Kona 5 : 69–75 (1987).

4. Y. Kawashima, F. Cui, H. Takeuchi, T. Niwa, T. Hino and K. Kihara. Agglomeration Behaviour and Modification of Spherical Crystallization Process of Pharmaceuticals by the Emulsion-Solvent-Diffusion Method and Proposed Closed-Circuit Batch System. Yakugaku Zasshi 111 : 451–462 (1991).
5. F. Cui, Y. Kawashima, H. Takeuchi, T. Niwa, T. Hino, and K. Kihara. Preparation of Pharmaceutical Agglomerated Crystals for Direct Tableting with an Emulsion-Solvent-Diffusion Method. The 6th Symposium on Particulate Preparation and Designs, Japan 6 : 70–74 (1989).
6. Y. Kawashima, F. Cui, H. Takeuchi, T. Niwa, T. Hino and K. Kiuchi, Improvements in Flowability and Compressibility of Pharmaceutical Crystals for Direct Tableting by Spherical Crystallization with a Two-Solvent System. Powder Technol. 78 : 151–157 (1994).
7. J.N. Staniforth. Advances in Excipient Technology Powder and Tableting Characteristics. S.T.P. Pharma. 6 : 162–168 (1990).
8. C.I. Patel and J.N. Staniforth. Determination of the Apparent Failure Viscosity of Tablets. J. Pharm. Pharmacol. 39 : 647–650 (1987).
9. H. C. M. Yu, M. H. Rubinstein, I. M. Jackson and H. M. Elsabbagh. Multiple Compression and Plasto-Elastic Behaviour of Paracetamol and Microcrystalline Cellulose Mixtures. J. Pharm. Pharmacol. 40 : 669–673 (1988).
10. C. I. Patel, J. N. Staniforth and J. P. Hart Determination of True Work of Compaction, J. Pharm. Pharmacol. 39: 30p (1987)
11. H. A. Janssen. Versuche über Getreidedruck in Silozellen. Zeitschrift Vereines Deutscher Ing. 39 : 1045–1049 (1895).
12. J. Lloyd, P. York and G. D. Cook. Influence of Compression Rate on the Mechanical Properties of Compacts. 6th International Conference on Pharm. Technol. 4 : 189–195 (1992).
13. J. E. Rees and S. Malamataris. A Possible Use of Creep Analysis to Determine Optimum Loading Conditions for Precompression. 6th International Conference on Pharm. Technol. 4 : 179–188 (1992).
14. A. N. Armstrong and L. P. Blundell. The Effect of Machine Speed on the Compaction of Some Directly Compressible Tablet Diluents. J. Pharm. Pharmacol. 39 : 28p (1987).
15. J. J. Benbow. Chapter 7, Mechanisms of Compaction, Enlargement and Compaction of Particulate Solids, ed. by Nayland G Stanley-Wood, Butterworths, London. pp. 161–177 (1983).