ELSEVIER

International Journal of Pharmaceutics 105 (1994) 11–18

international journal of pharmaceutics

Tabletting properties of bucillamine agglomerates prepared by the spherical crystallization technique

Kenji Morishima [a,*], Yoshiaki Kawashima [b], Hirofumi Takeuchi [b], Toshiyuki Niwa [b], Tomoaki Hino [b], Yoichi Kawashima [a]

[a] *Santen Pharmaceutical Co. Ltd, 9-19 Shimoshinjo 3-chome, Higashiyodogawa-ku, Osaka 533, Japan,*
[b] *Gifu Pharmaceutical University, 5-6-1, Mitahora-Higashi, Gifu 502, Japan*

(Received 30 June 1993; Modfied version received 3 September 1993; Accepted 27 September 1993)

Abstract

The tabletting properties of bucillamine agglomerates prepared by two spherical crystallization techniques, i.e., a spherically agglomeration method and an emulsion solvent diffusion method, were investigated. The flow and packing properties of agglomerates, represented in terms of the angle of repose and change in tapping density, were much improved by this technique compared with those of conventional crystals due to the spherical shape and smooth surface. Furthermore, spherical agglomerates possessed superior strength characteristics to conventional crystals, in particular, agglomerates obtained by the emulsion solvent diffusion method were compressed into compacts having considerable hardness without capping at high compaction pressure. The excellent compactibility of agglomerates was attributed to the fragmentation property and a greater degree of plastic deformation under compression.

Key words: Spherical crystallization technique; Bucillamine; Direct compression; Flowability; Packability; Compactibility

1. Introduction

Tablets are the most convenient form of pharmaceutical dosage and are widely used in the chemotherapeutic field. One of the most important changes in the manufacture of tabletting in the last decade is the large-scale introduction of direct compression of tablets. This reduces time and cost by involving faster operations, less machinery and fewer personnel. With great advances in tabletting technology, especially the introduction of a number of directly compressible excipients, the direct compression process has been successfully industrialized for low- and medium-dose formulations. However, direct compression in the production of high-dose formulations is limited, since large quantities of excipients are ordinarily required to produce suitable tablets. To succeed in direct compression with any formulation, particle modification of a drug is required to impart the formula sufficient flowability and compressibility.

* Corresponding author.

SSDI 0378-5173(93)E0302-7

The authors developed the spherical crystallization technique, by which crystallization and agglomeration could be carried out simultaneously in one step (Kawashima et al., 1982, 1984, 1989; Sano et al., 1987; Ueda et al., 1991). In our previous study (Morishima et al., 1993), we developed particle design techniques for bucillamine, an antirheumatic drug with poor packing and compaction characteristics, using two spherical crystallization systems. This technique transformed the microcrystalline drug itself into agglomerates without using any further processing step, such as granulation. The resultant agglomerates were spherical in shape, which gave them excellent micromeritic properties. The aim of the present study was to evaluate the suitability of agglomerates prepared by this technique for direct tabletting together with the attempt to elucidate any differences with agglomerates and conventional crystals in flow, packing and compression characteristics.

2. Materials and methods

2.1. Materials

Bucillamine was obtained from Santen Pharmaceutical Co., Ltd (Osaka, Japan). All other reagents and solvents were purchased from commercial sources.

2.2. Preparation of agglomerates

Particle design of bucillamine by the spherical crystallization technique was accomplished by using a spherical agglomeration (SA) method and an emulsion solvent diffusion (ESD) method. The apparatus is shown in Fig. 1.

2.2.1. SA method

Bucillamine (20 g) was dissolved in a mixture of ethanol (16 ml) and dichloromethane (14 ml) thermally controlled at 35°C. This was poured into 300 ml of water at 5°C, with stirring at 1000 rpm. After agitating the system for 30 min, resultant agglomerates were collected by filtration, washed with water and dried in an oven at 40°C for 5 h. The recovery of agglomerates was approx. 90%.

2.2.2. ESD method

Bucillamine (20 g) was dissolved in ethanol (16 ml) thermally controlled at 60°C, and the solution was poured into 300 ml of water containing hydroxypropylmethylcellulose (HPMC, TC-5RW, Shin-Etsu Chemical Co., Ltd, Japan; 1%, w/v) at 5°C, with stirring at 250 rpm. After agitating the

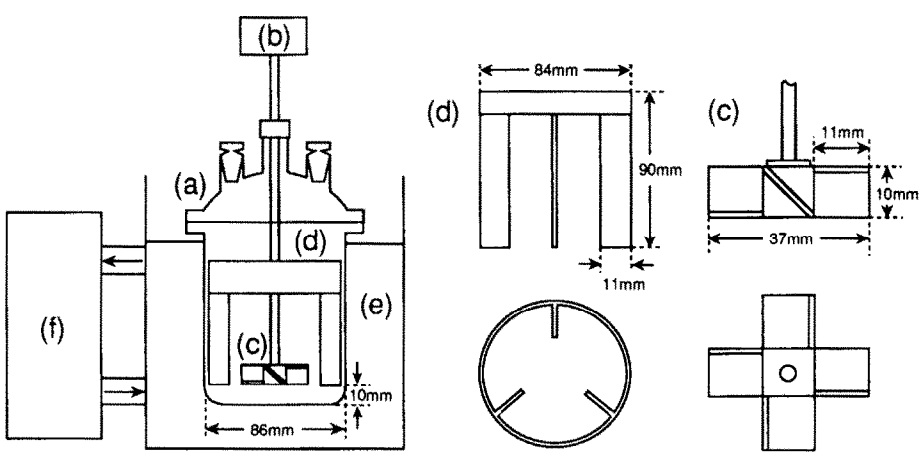

Fig. 1. Apparatus for spherical crystallization of bucillamine: (a) cylindrical vessel (500 ml), (b) motor, (c) propeller agitator, (d) baffle plate, (e) water bath, (f) regulator.

system for 5 min, resultant agglomerates were collected by filtration, washed with water and dried in an oven at 40°C for 5 h. The recovery of agglomerates was approx. 85%.

For both agglomerates, the 177–710 μm sieve fraction was used for all further investigations.

2.3. Micromeritic properties

The shape and surface topography of agglomerates and conventional crystals were observed through a scanning electron microscope (JSM-T330A, Nihon Denshi, Japan) after coating with gold. The shape characteristics were represented by an aspect ratio defined as the ratio of minimum to maximum Feret diameter and a shape factor defined as 4π (area/perimeter^2) with an image analyzer (GALAI cis-1, Galai Production Ltd, Israel). The true density was determined using a helium-air pycnometer (Model 1302, Shimadzu-Micromerictics Instrument Corp., Japan). The flow and packing properties were investigated by measuring the angle of repose and tapped density.

2.4. Compaction procedure

Compaction of agglomerates and conventional crystals was carried out using a compaction test apparatus (Autograph 5000D, Shimadzu, Japan), fitted with flat-faced punches and a die with a diameter of 8 mm. The die was lubricated with a very small amount of magnesium stearate. The samples were stored for at least 2 days at 30°C and 50% relative humidity before compaction. A weighed quantity of 200 mg was compressed with the upper punch moving down at 2 mm/min. When the desired pressure was attained, the crosshead was reversed and run at the same speed as during the compaction process. The load and displacement of the upper punch were continuously recorded. The density changes during compression were determined from the height of the compact, corrected for elastic deformation of the punches under load, diameter of the die and weight of the compact.

2.5. Characterization of compact strength

The compact was stored for 1 day at 30°C and 50% relative humidity before compact characterization. The compact was compressed diametrically at 0.5 mm/min using the Autograph 5000D, and the force fracturing the compact (F) was measured. The tensile strength (T) of the compact was calculated based on the equation (Rudnick et al., 1963; Fell and Newton, 1970), $T = 2F/(\pi Dt)$, where D and t are the diameter and thickness of the compact, respectively. The results presented are mean values of five determinations.

2.6. Size of constitutive crystals in agglomerates

Conventional crystals or agglomerates were added to n-hexane saturated with the drug and containing 0.005% Span 80. The agglomerates were disrupted by ultrasonication (Ultrasonic Cleaner UT-51N, Sharp, Japan) for 30 s. The suspension was then subjected to size analysis in the GALAI cis-1.

2.7. Permeability surface area of compacts

A weighed quantity of 1 g was filled in a die with a area of 2 cm^2, sealed at one end by a filter. The samples were compressed in the Autograph 5000D with the upper punch moving down at 2 mm/min. The die containing the compact was then inserted into the holder of a powder surface area-meter (Model SS-100, Shimadzu). 1 h after compression, the permeability of the compact was measured and its surface area was calculated by using the Kozeny-Carman equation (Alderborn et al., 1985).

2.8. Stress relaxation

Stress relaxation measurements of compressed agglomerates and conventional crystals were carried out using the Autograph 5000D, fitted with flat-faced punches and a die with a diameter of 8 mm. The samples were stored for at least 2 days at 30°C and 50% relative humidity before use. A weighed quantity of 200 mg was compressed at 2

mm/min in a prelubricated die to the required axial force. The crosshead was then halted and the decay in stress followed for 180 s.

3. Results and discussion

In order to achieve uniformity in tablet weight, the feed crystals must flow and pack smoothly into the die cavity of the tablet machine. Therefore, it is an essential purpose of particle design for direct compression to improve the flow and packing properties.

The effect of particle size on the angle of repose is shown in Fig. 2. The angle of repose of

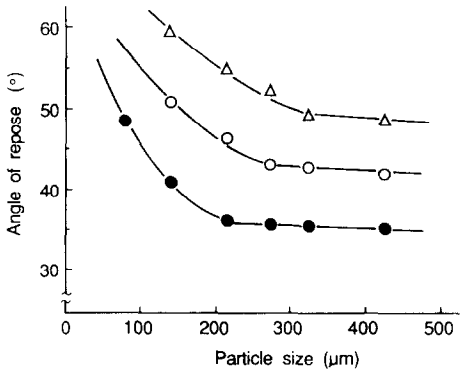

Fig. 2. Angle of repose of conventional crystals and agglomerates as a function of particle size: (△) conventional crystals, (○) agglomerates (SA method), (●) agglomerates (ESD method).

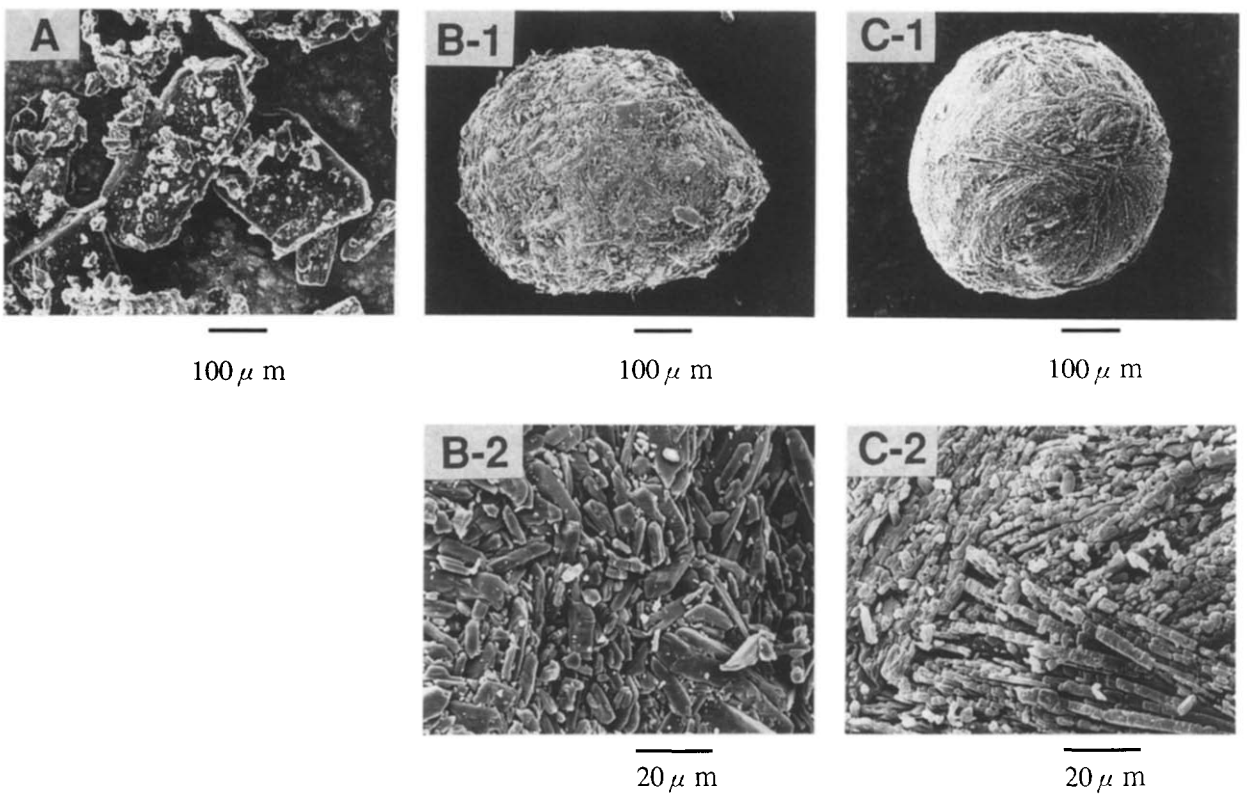

Fig. 3. Scanning electron micrographs of conventional crystals and agglomerates: (A) conventional crystals, (B-1) agglomerates (SA method) (shape), (B-2) agglomerates (SA method) (surface), (C-1) agglomerates (ESD method) (shape), (C-2) agglomerates (ESD method) (surface).

agglomerates was smaller than that of conventional crystals over the entire particle size range, particularly for agglomerates obtained by the ESD method which had low values and even small size fractions flowed readily. The packing properties of agglomerates are listed in Table 1, including those of conventional crystals as a reference. Agglomerates were easily packed by tapping, the process of which was evaluated based on percent compressibility (Carr, 1965) and parameters of the Kawakita equation (Kawakita and Tsutsumi, 1966). The low values of percent compressibility and parameter a of the Kawakita equation for agglomerates indicated their high packability. The apparent packing velocity by tapping, represented by parameter b, for agglomerates was slower than that for conventional crystals, since agglomerates were packed closely even without tapping due to their excellent flowability and packability. These findings suggest that agglomerates flow and pack smoothly from the hopper into the dies and that the tablets formed from agglomerates attain uniformity in weight.

Scanning electron micrographs of conventional crystals and agglomerates are illustrated in Fig. 3

Table 1
Micromeritic properties of conventional crystals and agglomerates

Micromeritic properties		Conventional crystals [a]	Agglomerates	
			SA [b]	ESD [c]
Compressibility (%) [d]		30.9	10.6	6.4
Parameters in Kawakita's equation [e]	a	0.321	0.108	0.073
	b	0.105	0.052	0.073
Bulk density (g/cm^3)		0.50	0.42	0.44
Closest packing density (g/cm^3)		0.81	0.47	0.47
Aspect ratio		–	0.81	0.88
Shape factor [f]		–	0.85	0.90

[a] Average diameter: 330 μm.
[b] Spherical agglomeration method (177–710 μm).
[c] Emulsion solvent diffusion method (177–710 μm).
[d] $(\rho_f - \rho_0)/\rho_f \times 100$, where ρ_f and ρ_0 are the apparent density at equilibrium and initial state, respectively.
[e] $(n/C) = (1/ab) + (n/a)$, $C = (V_0 - V_n)//V_0$, where n is the tap number and V_0 and V_n are the powder bed volumes at initial and n-th tapped state, respectively.
[f] $(\text{area}/\text{perimeter}^2) \times 4\pi$.

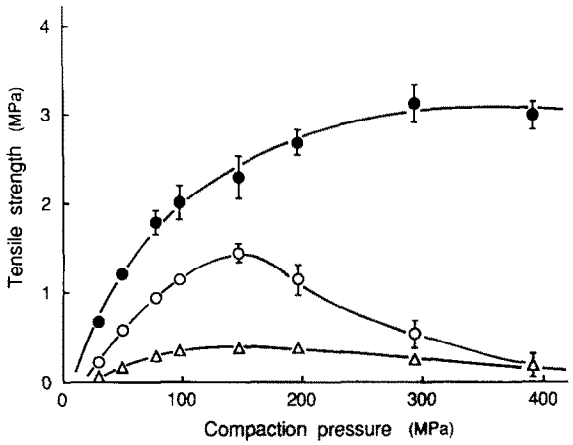

Fig. 4. Tensile strength of conventional crystals and agglomerates as a function of compaction pressure (mean ± S.D.): (△) conventional crystals, (○) agglomerates (SA method), (●) agglomerates (ESD method).

and the sphericity of agglomerates, represented in terms of the aspect ratio and the shape factor, is shown in Table 1. Agglomerates were spherical in shape compared with conventional crystals. On the basis of these findings, it was considered that good flowability and packability for agglomerates were attributable to the spherical shape and smooth surface, since the area of contacts in the powder bed for spherical agglomerates was smaller than that for plate-shaped conventional crystals. This explanation was supported by the fact that agglomerates obtained by the ESD method, which have a more spherical shape and smooth surface, possessed more suitable flow behavior and greater packability than those of the SA method.

Good compactibility and compressibility are also essential properties of directly compressible crystals. Compactibility of agglomerates was evaluated based on the tensile strength of the compact. Fig. 4 shows the tensile strength of the compact compressed at different compaction pressures. Agglomerates possessed superior strength characteristics to conventional crystals. In particular, agglomerates obtained by the ESD method were compressed into compacts having considerable hardness without capping even at high compaction pressure.

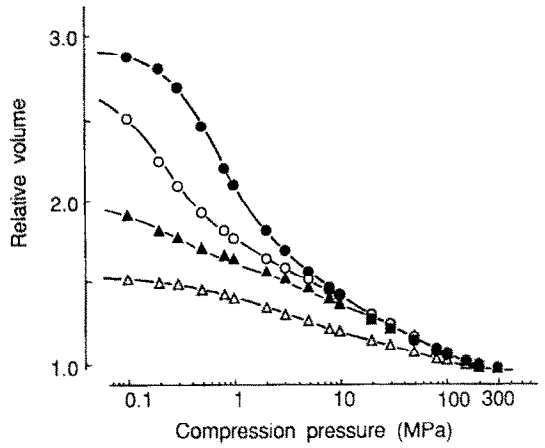

Fig. 5. Relative volume of conventional crystals and agglomerates as a function of compression pressure: (△) conventional crystals (median diameter 330 μm), (▲) conventional crystals (median diameter 22 μm), (○) agglomerates (SA method), (●) agglomerates (ESD method).

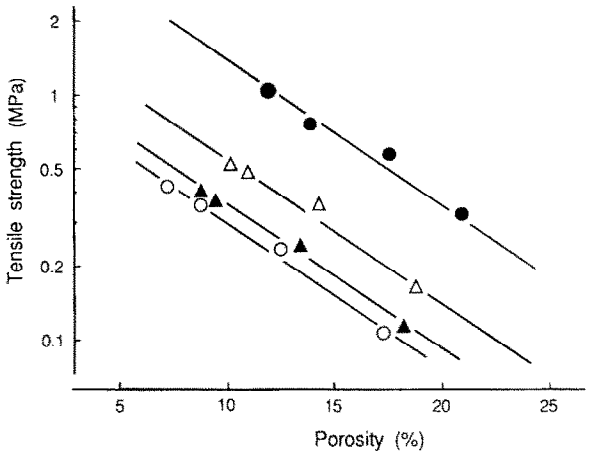

Fig. 6. Tensile strength of conventional crystals as a function of porosity: (○) 177–250 μm fraction, (▲) 104–177 μm fraction, (△) 54–104 μm fraction, (●) 0–54 μm fraction.

The improved compactibility of agglomerates was attributed to their structural characteristics. Agglomerates were built up with extremely small crystals, as shown in Fig. 3 and Table 2. This characteristic structure was responsible for the large relative volume change during the early stage of the compression process due to their fragmentation, as shown in Fig. 5. The fracturing properties of agglomerates were represented by changing the specific surface area at 0.5 and 5 MPa. As shown in Table 2, the specific surface area for agglomerates increased greatly during compression, while for conventional crystals, no change in specific surface area was observed.

McKenna and McCafferty (1982) and Vromans et al. (1988) reported that the tensile strength increased as the crystal size of compacts decreased. For understanding the bonding mechanism of this drug in the compact, the effect of the primary crystal size of conventional crystals on the tensile strength was investigated. As shown in Fig. 6, a good linear relationship between the porosity and logarithm of the tensile strength was found for each crystal size fraction. Smaller crystal fractions provided compacts of higher tensile strength than larger crystal fractions, even though the porosity was the same. This could be explained by the fact that smaller crystals have more contact points between them, so even if the porosity of the compact is equal, smaller crystals can be compacted more tightly than larger crystals. It was also found that the slope of the fitting line was quite similar for any crystal size fraction. These results suggested that the degree of in-

Table 2
Constitutive crystal size and specific surface area

Samples	Constitutive crystal size (μm)	Specific surface area (m^2/g)	
		0.5 MPa	5 MPa
Conventional crystals			
Course	330	0.162	0.153
Fine	22	0.628	0.564
Agglomerates			
SA method	21	0.186	0.421
ESD method	31	0.151	0.513

crease in the adhesion force acting at the contact point with decreasing porosity was comparable among any size fractions of conventional crystals.

For agglomerates, we also observed a good linear relationship between the porosity and logarithm of the tensile strength of compacts, as shown in Fig. 7. These results suggested that the tensile strength of compacts formed from agglomerates was mainly determined by the size of the constitutive crystals in agglomerates. This was supported by the observation that the tensile strength of compact formed from agglomerates obtained by the SA method was close to that of fine crystals, which were similar in constitutive crystal size.

However, for agglomerates obtained by the ESD method, the tensile strength was much higher compared to that in the case of the SA method and fine fraction of conventional crystals, even though the constitutive crystal size was similar. Furthermore, agglomerates obtained by the ESD method had considerable hardness without capping at high compaction pressure, as shown in Fig. 4. Marshall and York (1991) reported that the deformation characteristics of a drug crystallized from different systems were different. The facts indicated that agglomerates obtained by the

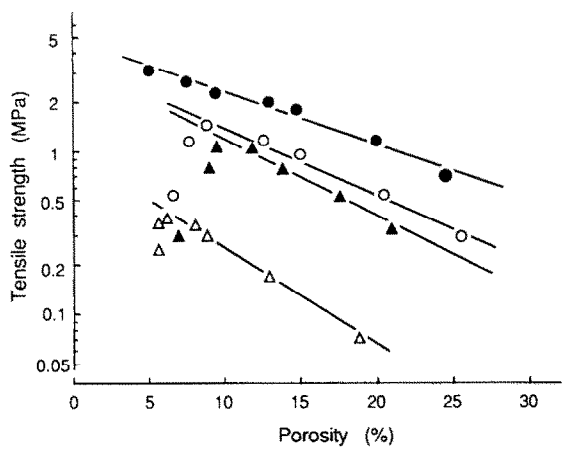

Fig. 7. Tensile strength of conventional crystals and agglomerates as a function of porosity: (△) conventional crystals (median diameter 330 μm), (▲) conventional crystals (median diameter 22 μm), (○) agglomerates (SA method), (●) agglomerates (ESD method).

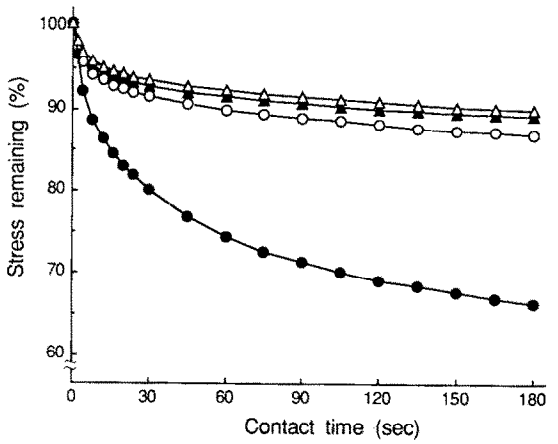

Fig. 8. Stress relaxation behavior of conventional crystals and agglomerates (198 MPa): (△) conventional crystals (median diameter 330 μm), (▲); conventional crystals (median diameter 22 μm), (○) agglomerates (SA method), (●) agglomerates (ESD method).

ESD method differed in deformation characteristics at the contact points with conventional crystals and agglomerates obtained by the SA method.

In order to elucidate the deformation characteristics of crystals, stress relaxation was investigated. Schlanta and Milosovich (1964), David and Augsburger (1977) and Cutt et al. (1987) reported that better compacts result from the compression of plastic materials, and that the amount of plastic deformation which occurs during compression can be examined by stress relaxation at constant strain. The stress relaxation behavior of compacts formed from agglomerates and conventional crystals at 198 MPa is shown in Fig. 8. Agglomerated crystals obtained by the ESD method showed more rapid and extensive relaxation than conventional crystals and agglomerates obtained by the SA method. The result indicated that agglomerates obtained by the ESD method exhibited a greater degree of plastic deformation under compression than conventional crystals and agglomerates obtained by the SA method.

In conclusion, it was found that the spherical crystallization technique was a beneficial approach to the manufacture of agglomerates with excellent micromeritic properties for direct tabletting. The resultant agglomerates were free flowing and easily packable into the dies owing to

their spherical shape and smooth surface and possessed superior strength characteristics due to their fracturing properties. Furthermore, excellent compactibility of agglomerates obtained by the ESD method was attributed to the preferred stress relaxation, indicating a greater degree of plastic deformation under compression.

4. References

Alderborn, A., Duberg, M. and Nystrom, C., Studies on directly compression of tablets: X. Measurement of tablet surface area by permeametry. *Powder Technol.*, 41 (1985) 49–56.

Carr, R.L., Classifying flow properties of solids. *Chem. Eng.*, 72 (1965) 69–72.

Cutt, T., Fell, J.T., Rue, P.J. and Spring, M.S., Granulation and compaction of a model system: II. Stress relaxation. *Int. J. Pharm.*, 39 (1987) 157–161.

David, S. and Augsburger, L.L., Plastic flow during compression of directly compressible fillers and its effect on tablet strength. *J. Pharm. Sci.*, 66 (1977) 155–159.

Fell, J.T. and Newton, J.M., Determination of tablet strength by the diametral-compression test. *J. Pharm. Sci.*, 59 (1970) 688–691.

Kawakita, K. and Tsutsumi, Y., A comparison of equations for powder compression. *Bull. Chem. Soc. Jap.*, 39 (1966) 1364–1368.

Kawashima, Y., Okumura, M. and Takenaka, H., Spherical crystallization: Direct spherical agglomeration of salicylic acid crystals during crystallization. *Science*, 216 (1982) 1127–1128.

Kawashima, Y., Okumura, M., Takenaka, H. and Kojima, A., Direct preparation of spherically agglomerated salicylic acid crystals during crystallization. *J. Pharm. Sci.*, 73 (1984) 1535–1538.

Kawashima, Y., Takeuchi, H., Niwa, T., Hino, T., Yamakoshi, M. and Kihara, K., 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. Jap.*, 26 (1989) 659–665.

Marshall, P.V. and York, P., The compaction properties of nitrofurantoin samples crystallised from different solvents. *Int. J. Pharm.*, 67 (1991) 59–65.

McKenna, A. and McCafferty, D.F., Effect of particle size on the compaction mechanism and tensile strength of tablets. *J. Pharm. Pharmacol.*, 34 (1982) 347–351.

Morishima, K., Kawashima, Y., Takeuchi, H., Niwa, T., Hino, T. and Kawashima, Y., Micromeritic characteristics and agglomeration mechanisms in the spherical crystallization of bucillamine by the spherical agglomeration and the emulsion solvent diffusion methods. *Powder Technol.*, 76 (1993) 57–64.

Rudnick, A., Hunter, A.R. and Holden, F.C., An analysis of the diametral compression test. *Mater. Res. Stand.*, 3 (1963) 283–289.

Sano, A., Kuriki, T., Handa, T., Takeuchi, H. and Kawashima, Y., Particle design of tolbutamide in the presence of soluble polymer or surfactant by the spherical crystallization technique: Improvement of dissolution rate. *J. Pharm. Sci.*, 76 (1987) 471–474.

Schlanta, S. and Milosovich, G., Compression of pharmaceutical powders: I. *J. Pharm. Sci.*, 53 (1964) 562–564.

Ueda, M., Nakamura, Y., Makita, H., Imasato, Y. and Kawashima, Y., Particle design of enoxacin by spherical crystallization technique: I. Principle of ammonia diffusion system (ADS). *Chem. Pharm. Bull.*, 38 (1991) 2537–2541.

Vromans, H., Bolhuis, G.K. and Lerk, C.F., Magnesium stearate susceptibility of directly compressible materials as an indication of fragmentation properties. *Powder Technol.*, 54 (1988) 39–44.