Particle Design of Tolbutamide by the Spherical Crystallization Technique. III. Micromeritic Properties and Dissolution Rate of Tolbutamide Spherical Agglomerates Prepared by the Quasi-Emulsion Solvent Diffusion Method and the Solvent Change Method

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With the objective of modifying the micromeritic properties of tolbutamide (*i.e.*, to manufacture a highly functional powder form), particle design was attempted using a quasi-emulsion solvent diffusion (QESD) method, and the micromeritic properties and dissolution rate of the obtained spherical agglomerates were evaluated by comparison with agglomerates prepared by the solvent change (SC) method. For the production of tolbutamide agglomerates by the QESD method, a necessary condition was the addition of a sucrose fatty acid ester to the system as an emulsifying agent. The particle diameter of the agglomerates obtained by the QESD method depended on the size of the initially formed quasi-emulsion droplets, which in turn depended on the viscosity of the solution. In addition, the agglomerates were nearly perfectly spherical in shape. In the QESD method, the quasi-emulsion droplets crystallized instantaneously from the droplet surface inward. The resultant agglomerates were dense, had great mechanical strength and showed excellent flowability due to their perfect spherical shape. On the other hand, the agglomerates produced by the SC method were conglomerates of primary crystals, and fine, needle-like crystals formed on their surface. As a result, these agglomerates had a large specific surface area, and they therefore showed greater solubility than the agglomerates prepared by the QESD method.

Keywords quasi-emulsion solvent diffusion; solvent change; tolbutamide; spherical crystallization technique; particle design; friability; surface area; dissolution rate; micromeritic property

Particle design for solid dosage forms of drugs consists of improving the efficiency of the manufacturing processes and giving a high degree of functionality to the particles. On the basis of this approach, the authors previously developed the spherical crystallization technique.[1)] Briefly, the authors were able to improve the efficiency of the initial steps of the manufacturing operation by combining the process for crystallization (design of the primary particles) and agglomeration (design of the secondary particles), and then succeeded in increasing the added value of the product by endowing the primary and secondary particles with greater functionality. The spherical crystallization technique, as the name indicates, provides crystalline agglomerates that are spherical in shape, which gives them excellent micromeritic properties (flowability, packability, *etc.*).[2,3)] In addition, depending on the crystallization method employed with this technique, the product has improved compressibility.[4)] and by the addition of polymers to the crystallization system it is possible to improve the properties of the secondary particles and ensure that it has high functionality, such as improved solubility[5)] and controlled released rate.[6,7)]

During recent years, the authors attempted particle design of tolbutamide (TBM), a poorly soluble drug, by the neutralization spherical crystallization technique method and by the solvent change (SC) method. With the neutralization method, addition of water-soluble polymers and surfactants to the crystallizing solvent method resulted in a striking improvement of the solubility of TBM,[8)] while with the SC method, control of the crystallization process made it possible to obtain crystalline polymorphs having more advantageous secondary characteristics.[9)] It was therefore reported that the spherical crystallization technique was an extremely useful particle design method.

In the present research, with the objective of endowing TBM agglomerates with high functionality, the authors prepared crystalline agglomerates of TBM by the quasi-emulsion solvent diffusion (QESD) method and studied their micromeritic properties and dissolution rate in comparison with those of TBM agglomerates prepared by the SC method.

Experimental

Preparation of Crystalline Agglomerates by the QESD Method The equipment diagrammed in Fig. 1 was employed for these studies. As an emulsifying agent, 200 ml of an aqueous solution containing 0.025% of sucrose fatty acid ester DK-F70 (DKF; Daiichi Kogyo Seiyaku) was placed in the cylindrical vessel equipped with a baffle plate. While this was agitated at 300 rpm with a propeller-type agitator, 5 ml of dimethylformamide (DMF) containing 2.5—5 g of TBM (Hoechst Japan) was added, and agglomeration was allowed to proceed for 15 min at 25 °C. In addition, water was employed as the crystallization solvent, in place of the 0.025% DKF solution.

Preparation of Crystalline Agglomerates by the SC Method Using the equipment described in a previous report,[9)] 50 ml of an ethanol solution containing 5 g of TBM was placed in the cylindrical vessel (500 ml; 84 mm i.d.), followed by addition of 250 ml of 0.025% DKF solution while agitating at 600 rpm with a turbine-type agitator having 6 blades (50 mm in diameter). Two minutes after the TBM crystals had been formed, 21.2—21.9 ml of a mixed solution of isopropyl acetate and ethanol was dripped into the system at a rate of 10 ml/min as a bridging liquid. This system was then held at 25 °C for 20—40 min to allow agglomeration to occur. In addition, in the same manner as for the QESD method, was employed as the crystallization solvent, and the process was carried out.

Determination of Particle Size Distribution and Particle Diameter of Crystalline Agglomerates These values wre determined by the sieving method using the standard sieve stipulated in the Japanese Pharmacopoeia XIth edition.

Determination of Apparent Density and Apparent Specific Surface Area of Crystalline Agglomerates The apparent density (ρ_{app}) was calculated using Eq. 1, where W is the known sample weight, n is the number of particles counted on the micrograph of the known weight sample, d is the value for the mean particle diameter obtained as the circle equivalent diameter (Heywood diameter) with an image analyzing processing apparatus, and ϕ is the specific surface shape factor of spherical agglomerates, assumed to be 6.

$$\rho_{\text{app}}=\frac{W}{n\pi d^3/\phi} \tag{1}$$

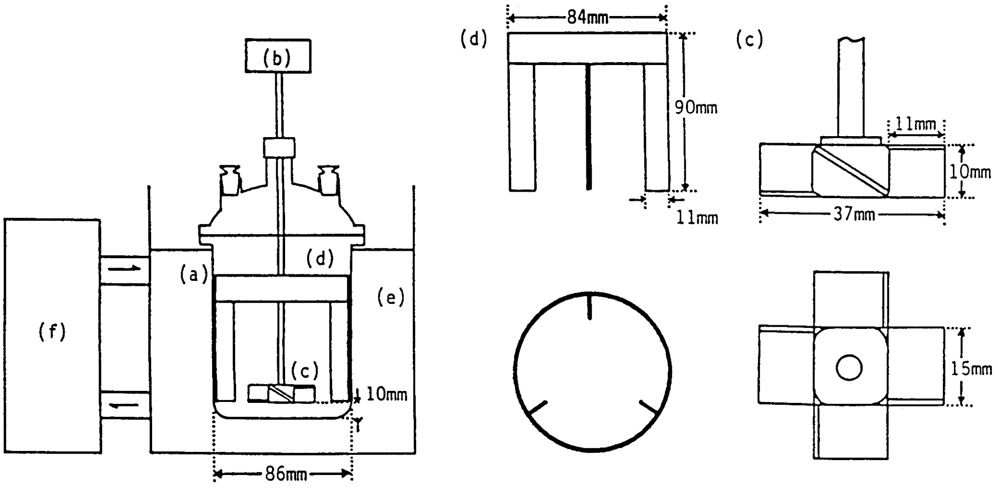

Fig. 1. Apparatus for QESD Process

(a) Cylindrical vessel (500 ml), (b) motor, (c) propeller-type agitator, (d) baffle plate, (e) water bath, (f) regulator.

$$SW_{\text{app}}=\frac{\phi}{\rho_{\text{app}}}\frac{1}{d} \qquad (2)$$

when spherical $\phi=6$

Determination of Micromeritic Properties of Crystalline Agglomerates The specific surface area was measured with a specific surface area measuring device (Flowsorb 2300; Shimadzu), using the adsorption isotherm (BET method). The wettability of the crystalline agglomerates was evaluated from the contact angle. The contact angle was measured directly with a contact angle meter (CA-A; Kyowa Kagaku) after compressing the agglomerates into a shape (8 mm in diameter; porosity; 0.1 or less) and placing a drop of saturated TBM aqueous solution on the surface thereof with a microsyringe. Because the contact angle changes with the passage of time as the liquid drop permeates into the compressed material, the extrapolated value at $t=0$ was employed in this study, in accordance with the report of Itoh and Koishi.[10]

Determination of Viscosity of DMF Solution of TBM The kinetic viscosity was measured at 25 °C using an Ubbelode-type viscosimeter.

Determination of Mechanical Strength of Crystalline Agglomerates Two grams (W_0; particle size: 250—600 μm) of the crystalline agglomerates was placed in a friability tester (TA3R; Erweka), and this was subjected to the impact test at 50 rpm for a certain length of time. After passing this through a sieve having a mesh size of 125 μm, the weight (W) of the material which did not pass through the sieve was determined, and the friability (X) was calculated using Eq. 3 below.

$$X=\frac{W_0-W}{W_0} \qquad (3)$$

Dissolution Behavior of Crystalline Agglomerates In conformity with the Japanese Pharmacopoeia XIth edition, a dissolution test (NTR-VS6; Toyama Industrial Co.) was employed to determine this property for a 0.5 g amount of agglomerates having various particle diameters. The test fluid was 900 ml of pH 6.5 phosphate buffer solution [0.2 M K_2HPO_4 (250 ml) : 0.2 M NaOH (76 ml): water (674 ml)], and the test was carried out for 60 min at 100 rpm by the paddle method. The amount of dissolved TBM was measured at $\lambda_{\max}$ 229 nm using a spectrophotometer (Hitachi, model 340). In addition, a physical mixture of 0.5 g of agglomerate sample and 0.1 g of Kollidone CL® (polyvinylpyrrolidone cross-linked micronized; particle diameter: <20 μm; BASF, Japan), a hydrophilic agent, was also employed as a sample for the determination of the dissolution behavior.

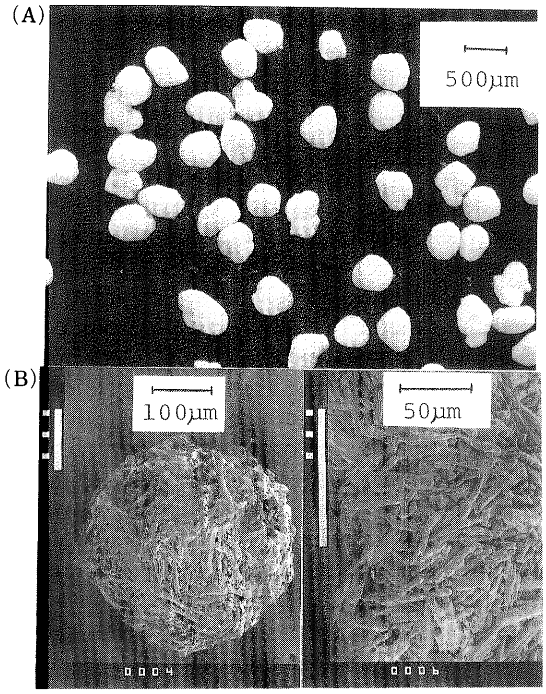

Fig. 2. (A) Micrograph (B) Scanning Electron Microphotograph of Agglomerates Obtained by the SC Method

Crystallization solvent: 0.025% sucrose fatty acid ester DK-F70. Bridging liquid: isopropyl acetate 21.2 ml.

Results and Discussion

Agglomeration Processes of the SC Method and QESD Method In the SC method, TBM is crystallized out as microcrystals when the ethanolic TBM solution is added to water or DKF solution while agitating. Then, when the isopropyl acetate/ethanol mixed solution, which has an affinity for TBM particles but is immiscible with water, is added to this suspension, phase separation occurs, liquid bridges are formed by the minute amounts of isopropyl acetate dispersed between the particles, and the particles are agglomerated. As a result of the agitation, the TBM particles make repeated contact with each other, and finally spherical crystalline agglomerates of TBM are formed.

On the other hand, in the case of the QESD method, TBM is dissolved in DMF, and quasi-emulsion droplets are formed immediately when this is added to the DKF solution; these droplets are dispersed in the water. As a result of agitation, the DMF gradually diffuses from the quasi-emulsion droplets into the water, and the process of crystallization begins from the surface of the droplets. In the end, spherical agglomerates of TBM are obtained which

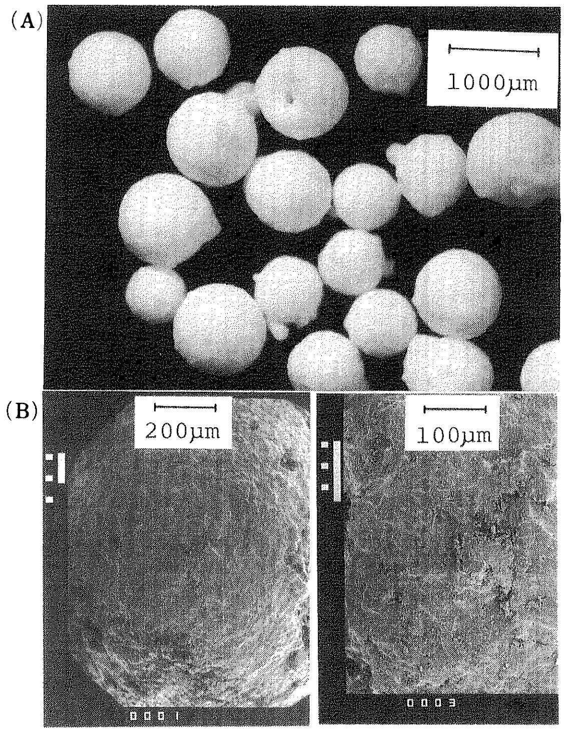

Fig. 3. (A) Micrograph (B) Scanning Electron Microphotograph of Agglomerates Obtained by the QESD Method

Crystallization solvent: 0.025% sucrose fatty acid ester DK-F70. Loading weight of tolbutamide: 5 g.

preserve the shape of the initially-formed quasi-emulsion droplets.

Thus, it is seen that the agglomeration processes of the SC method and the QESD method are different. In addition, as is apparent from the scanning electron microphotographs presented of the obtained agglomerates in Figs. 2 and 3, it can be surmised that the agglomeration mechanisms of these two methods are different. Accordingly, we proceeded to investigate the factors which influence the agglomeration of TBM, and the physical properties of the crystalline agglomerates.

Influence of Sucrose Fatty Acid Ester DK-F70 on TBM Agglomeration In the SC method, when water was employed as the crystallization solvent, the particle diameter of the agglomerates increased (mean diameter: *ca.* 300—*ca.* 1000 μm) in proportion to the volume (21.2—21.9 ml) of bridging liquid added to the system. However, when a DKF solution was employed as the crystallization solvent, the obtained agglomerates had almost the same particle diameter (mean diameter: *ca.* 300—400 μm), regardless of the volume of bridging liquid added (Figs. 4 and 5). Without any addition of DKF, the cohesive force between particles increases as the volume of added bridging liquid is increased, but it was shown that this is suppressed by the presence of DKF. That is, it has been surmised that DKF in the aqueous phase reduces the interfacial tension of the bridging liquid (isopropyl acetate) between the particles, thereby lowering the capacity for aggregation.[11] On the other hand, in the case of the QESD method, the addition of DKF yielded almost perfectly spherical agglomerates. Without any addition of DKF, however, quasi-emulsion droplets were not formed and only the irregular mass of TBM was obtained. With no DKF addition, crystallization was thought to occur, without stable formation of quasi-emulsion droplets. Because the QESD method consists of solidification[5] of quasi-emulsion droplets, an essential condition is the stable formation of quasi-emulsion droplets, at least temporarily (for the time needed to achieve solidification). For this reason, the presence of DKF, an emulsifying agent, was found to be indispensable.

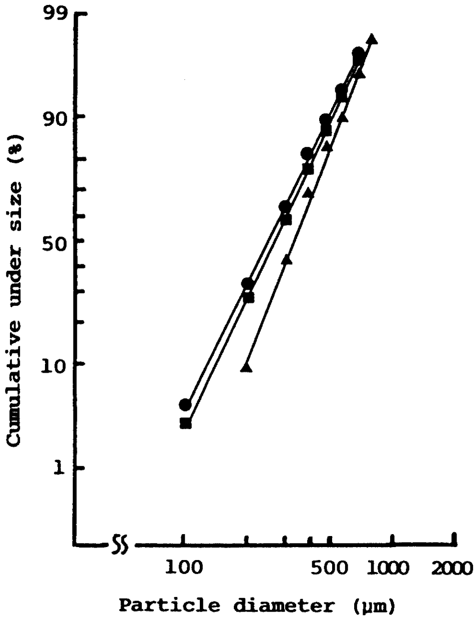

Fig. 4. Particle Size Distribution of Agglomerates Obtained by the SC Method

Crystallization solvent: 0.025% sucrose fatty acid ester DK-F70. Amount of bridging liquid: ●, 21.2 ml; ■, 21.6 ml; ▲, 21.9 ml.

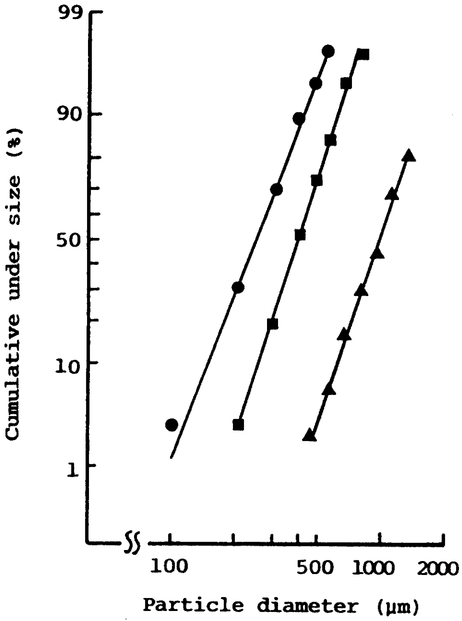

Fig. 5. Particle Size Distribution of Agglomerates Obtained by the SC Method

Crystallization solvent: water. Amount of bridging liquid: ●, 21.2 ml; ■, 21.6 ml; ▲, 21.9 ml.

Relationship between TBM Concentration and Particle Diameter in the QESD Method The particle diameter of the obtained agglomerates increased in direct proportion to

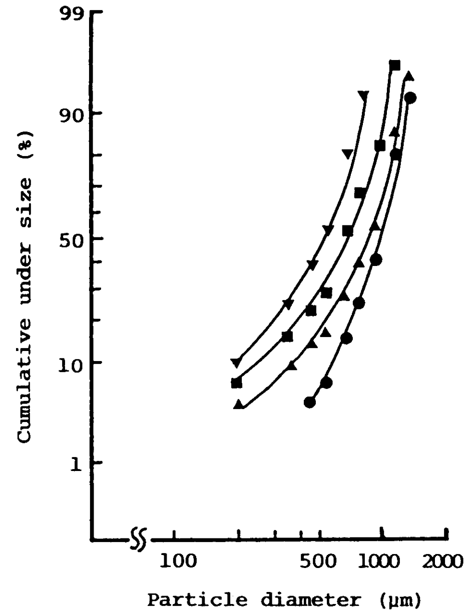

Fig. 6. Particle Size Distribution of Agglomerates Obtained by the QESD Method

Loading weight of TBM: ▼, 2.5 g; ■, 3 g; ▲, 4 g; ●, 5 g.

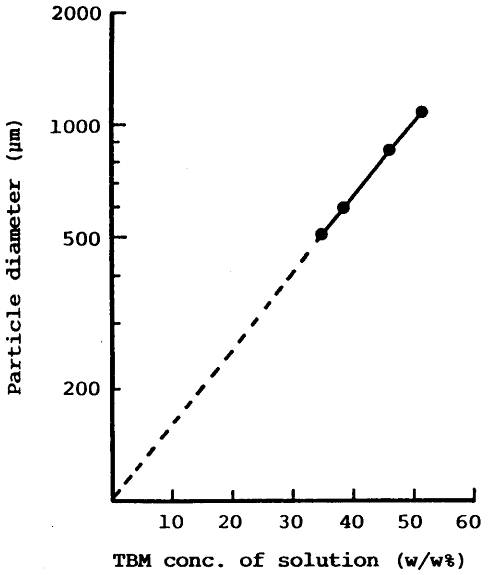

Fig. 7. Relation between Concentration of TBM and Particle Diameter of Agglomerates Obtained by the QESD Method

the concentration of TBM in the DMF (Figs. 6 and 7), and the particle diameter showed a linear relationship with the viscosity of the TBM solution (Fig. 8). Since the QESD agglomeration method consists of solidification of the quasi-emulsion droplets, the solidified particles do not aggregate with each other, and thus the particle diameter of the agglomerates depends on the size of the quasi-emulsion droplets which initially form in the aqueous phase. In addition, even when the concentration of TBM in DMF is increased (34.5—51.3 w/w%), the surface tension of the DMF solution remained almost constant at about 38 dyn/cm. These findings indicate that the size of the initially formed liquid droplets depends on the viscosity of the TBM solution. In other words, it is thought that the diameter of the formed quasi-emulsion droplets increases because the dispersion of the TBM solution is suppressed by its increasing viscosity. This concept of the events occurring in the system is supported by the fact that the diameter of the particles of the formed agglomerates decreased when the agitation rate was increased.

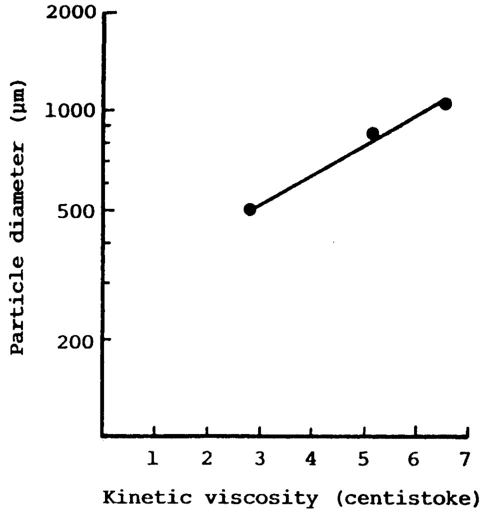

Fig. 8. Relation between Kinetic Viscosity and Particle Diameter of Agglomerates Obtained by the QESD Method

Table I. Micromeritic Properties of Agglomerates Prepared by the QESD Method[a] and SC Method[b]

Method	Mean particle size[c] (μm)	Apparent specific surface area (cm^2/g)	Apparent density (g/cm^3)
QESD	1046	51	1.12
	740	70	1.15
	444	116	1.16
SC	1353	72	0.61
	500	176	0.62
	306	276	0.70

[a] Quasi-emulsion solvent diffusion method. [b] Solvent change method. [c] Measured using an image analyzing processing apparatus.

Apparent Density and Apparent Specific Surface Area of the Crystalline Agglomerates When the specific surface area of the agglomerates was determined by the BET method, the agglomerates prepared by the SC method gave a value of 11200—12400 cm^2/g, being larger than those obtained by the QESD method (10200—10700 cm^2/g). However, there was no relationship between the specific surface area and the particle diameter for the agglomerates prepared by either the QESD or SC method. As there seemed some effect arising from the presence of voids or pores in the agglomerate, the values for the agglomerates' apparent density and apparent specific surface area were calculated using Eqs. 1 and 2. As shown in Table I, the agglomerates prepared by the SC method had smaller values of apparent density and larger values of apparent specific surface area than those obtained by the QESD method. These results are also supported by the results of SEM observations. That is, the SC method aggregates precipitated microcrystals to form agglomerates and therefore the resultant agglomerates have low density and a microscopically rough surface covered with numerous needle-shaped crystals. On the other hand, with the QESD

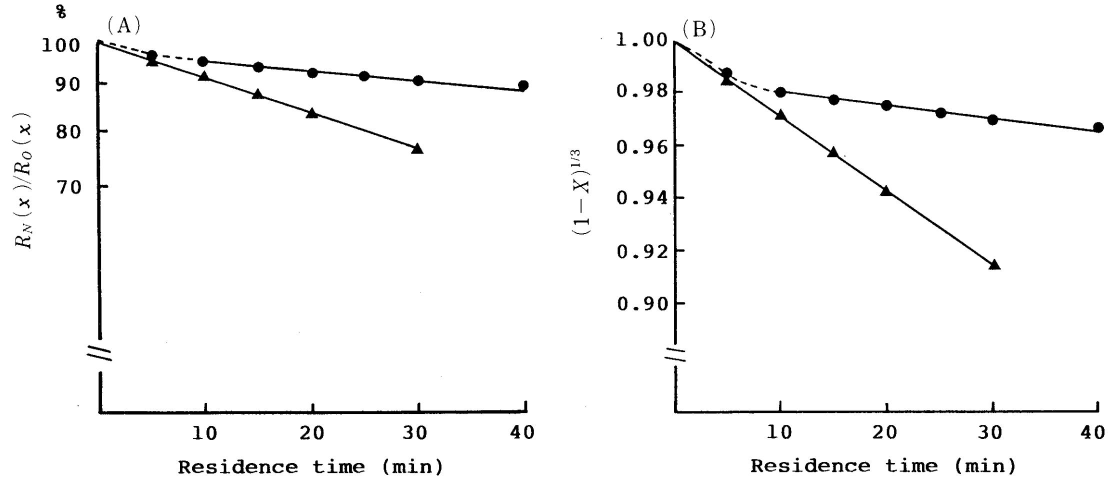

Fig. 9. Friability Test of Agglomerates

●, QESD method (loading weight of TBM 2.5 g; particle diameter, 500 μm); ▲, SC method (amount of bridging liquid, 21.9 ml; particle diameter, 390 μm).

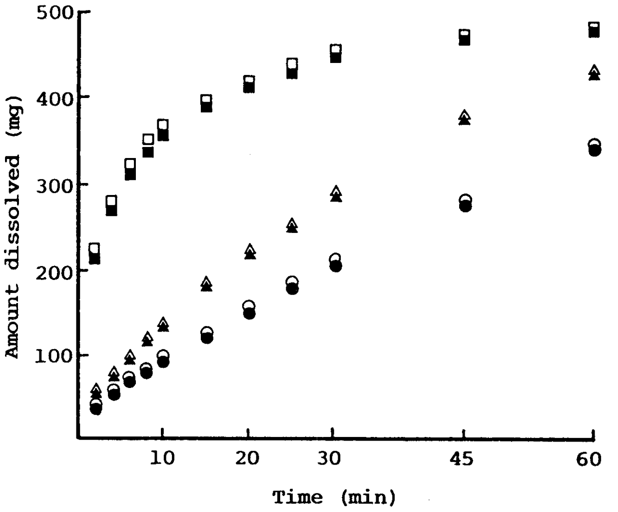

Fig. 10. Dissolution Profiles of Agglomerates and Physical Mixture with Kollidone CL® (SC Method)

Crystallization solvent: 0.025% sucrose fatty acid ester DK-F70. Particle diameter: ○, 1100 μm; △, 650 μm; □, 350 μm. Solid symbols, physical mixture with Kollidone CL®; open symbols, without Kollidone CL®.

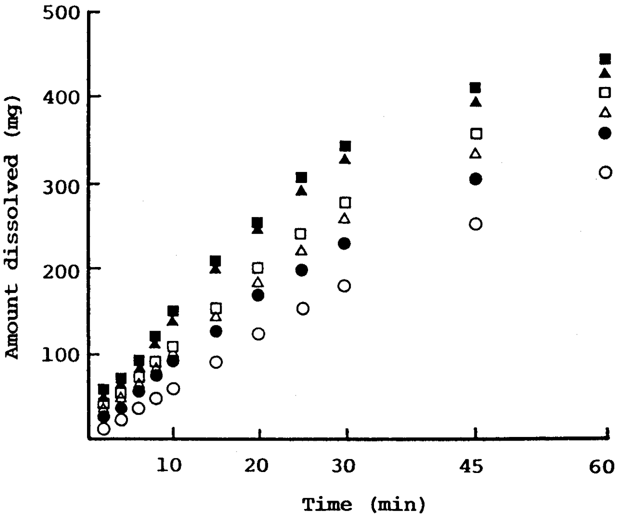

Fig. 11. Dissolution Profilels of Agglomerates and Physical Mixture with Kollidone CL® (SC Method)

Crystallization solvent: water. Particle diameter: ○, 1000 μm; △, 420 μm; □, 360 μm. Solid symbols, physical mixture with Kollidone CL®; open symbols, without Kollidone CL®.

method, quasi-emulsion droplets crystallize out instantaneously from their surface inward, thus making the formed agglomerates very dense in texture; the surface of these particles appears smooth under a microscope. It is thought that these differences in the physical properties of the crystalline agglomerates influence the mechanical strength of the agglomerates.

Mechanical Strength of the Crystalline Agglomerates To investigate the mechanical strength of the crystalline agglomerates obtained by the QESD and SC methods, they were subjected to the friability test, and the results were then treated by means of Eq. 4[12)]

$$R_N(x) = Ro(x)\cdot(1-Pr)^N \qquad (4)$$

where Pr is the probability of breakage of the agglomerates per impaction, N is the number of impactions (or the residence time), and R_N (x) is the cumulative percent in excess of size X, determined with a sieve having a mesh size of 125 μm. In addition, assuming that the abrasion rate is proportional to the surface area of the agglomerates in the case of the friability test on spherical agglomerates, the relationship between the friability (X) and the time (t) can be expressed by Eq. 5,[12)]

$$(1-X)^{1/3} = 1 - \frac{2\kappa\phi}{\rho_{\mathrm{app}}X_0}t \qquad (5)$$

$$\theta = \frac{2\kappa\phi}{\rho_{\mathrm{app}}X_0} \qquad (6)$$

where κ is the abrasion rate constant, X_0 is the agglomerate particle diameter prior to the test, ρ_{app} is the apparent density of the agglomerates, and ϕ is the specific surface shape factor. As shown in Figs. 9A and 9B, the agglomerates obtained by the SC method showed friability in accordance with Eqs. 4 and 5. In view of this finding, it is understood that the damage to the agglomerates prepared by the SC method proceeds from the surface inward, and the aggregation force working between constitutive particles within the agglomerates in uniform within the crystalline agglomerates. On the other hand, the agglomerates prepared by the QESD method deviated from Eq. 5 during

Table II. Dissolution Rate Constants of Agglomerates Prepared by the QESD Method[a] and SC Method[b] and Physical Mixture with Kollidone CL®

	QESD method				SC method					
Crystallization solvent	0.025% DKF[c]				0.025% DKF			Water		
Mean particle size (μm)	1050	800	580	450	1100	650	350	1000	420	360
Dissolution rate constant ($\times 10^{-2}$)	3.08	4.46	5.91	8.30	4.36	6.61	34.4	3.68	5.34	5.83
Physical mixture with Kollidone CL®	—	—	—	—	4.20	6.45	—	4.74	8.03	8.43

a) Quasi-emulsion solvent diffusion method. *b*) Solvent change method. *c*) 0.025% Sucrose fatty acid ester DK-F70. —; not determined.

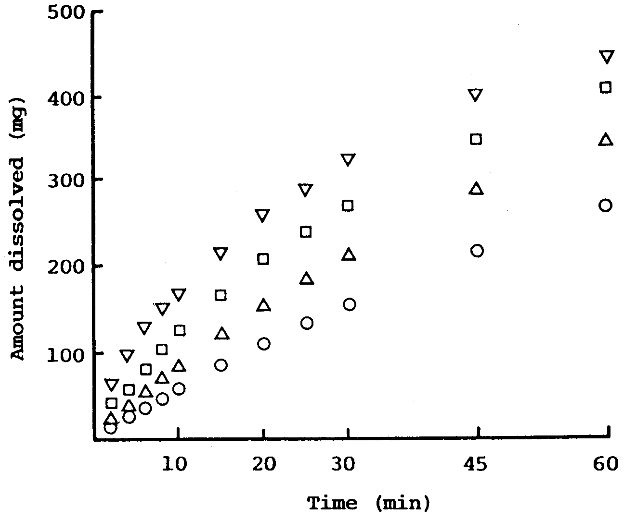

Fig. 12. Dissolution Profiles of Agglomerates Obtained by the QESD Method

Crystallization solvent: 0.025% sucrose fatty acid ester DK-F70. Particle diameter: ○, 1050 μm; △, 800 μm; □, 580 μm; ▽, 450 μm.

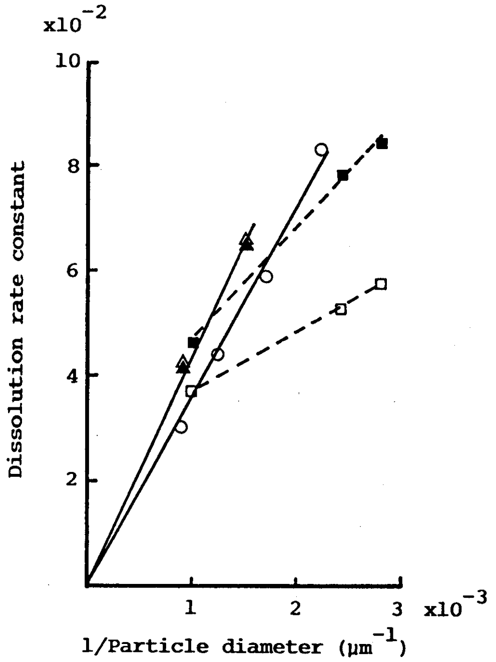

Fig. 13. Relation between Dissolution Rate Constant and Reciprocal of Particle Diameter of Agglomerates and Physical Mixture with Kollidone CL®

○, QESD method; △, SC method (crystallization solvent: 0.025% sucrose fatty acid DK-F70); □, SC method (crystallization solvent: water); solid symbols, physical mixture with Kollidone CL®; open symbols, without Kollidone CL®.

the initial 10 min of testing, but they subsequently underwent abrasion in accordance with the equation. That is, during the early period they readily underwent damage, but later on they were not easily damaged (Fig. 9B). These findings indicate that the surface layer of the agglomerates formed by the QESD method is comparatively soft, while the core is hard. Next, θ, the slope determined from Fig. 9B, was substituted into Eq. 6 and the values for the abrasion rate constant, κ, of the agglomerates prepared by the SC and QESD methods were calculated. They were 7.1×10^{-6} and 2.4×10^{-6} g/cm^2/min, respectively. On the basis of these data, it is understood that the agglomerates prepared by the QESD method are more resistant to abrasion and have greater mechanical strength than the agglomerates prepared by the SC method.

Dissolution Rates of Crystalline Agglomerates Figures 10—12 present the data on the dissolution profiles of the agglomerates. Assuming that the particles dissolve isotropically under sink conditions in a monodispersed polyparticle system, the dissolution rate constants were calculated from the slope (κ) by applying the Hixson–Crowell equation (Eq. 7)[13] (Table II). In the SC method, the dissolution rate of the agglomerates formed upon addition of DKF was more rapid than when DKF was not added. Because of poor wettability of the agglomerates formed without any addition of DKF, most of the agglomerates did not disperse in the test fluid and instead floated at the fluid surface. On the other hand, the agglomerates formed with the addition of DKF, which is a hydrophilic compound, had DKF adhered to the surface of the crystals and thus showed good wettability. As a result, these DKF-containing agglomerates are considered to have a greater effective surface area.

$$W_0^{1/3}-W_t^{1/3}=\left(\frac{\pi N\rho}{6}\right)^{1/3}\frac{2DC_s}{h\rho}t=\frac{1}{d}W_0^{1/3}\frac{2DC_s}{h\rho}t \qquad (7)$$

$$N=\frac{W_0}{\pi/6d^3\rho} \qquad \kappa=\frac{1}{d}W_0^{1/3}\frac{2DC_s}{h\rho} \qquad (8)$$

where W_0 is the initial weight, W_t is the weight after t hours, N is the number of particles, t is the time, ρ is the density, C_s is the solubility, D is the diffusion constant, h is the thickness of the diffusion layer, and d is the diameter.

In addition, it was found that the dissolution rate of the agglomerate obtained by the SC method without any addition of DKF was strikingly increased when it was mixed with Kollidone CL® (Fig. 11). In consideration of the SEM findings for these agglomerates, showing adherence of numerous dense particles of the Kollidone CL® to the microscopic pores on the surface of the agglomerate particles, it is deduced that this improved dissolution was brought about because the hydrophilic Kollidone CL® formed capillaries which acted as conduits for water[14] and thus improved the wettability of the particles. On the other hand, the agglomerates formed in the presence of DKF already were endowed with good wettability, and their dissolution rate was thus not further improved when mixed with Kollidone CL®. These results and our deduction were also supported by the result that the contact angle with water was smaller in the case of the agglomerates containing DKF or mixed with Kollidone CL® in comparison with the agglomerates prepared without DKF addition.

Next, we investigated the relationship between the dissolution rate constant and $1/d$, as represented by Eq. 8. As shown in Fig. 13, it was found that the agglomerates formed in the presence of DKF obeyed the Hixson–Crowell equation, whereas the plot of the data for the agglomerates formed without DKF did not pass through the point of origin and thus deviated from the equation. This phenomenon is supposed to be due to a decrease of the effective surface area of aggregated floating particles, which increase in number as the particle diameter becomes smaller because of the poor wettability of TBM.[15,16] In addition, it is thought that the difference in dissolution rates between the DKF-containing agglomerates prepared by the SC method and by the QESD method can be explained on the basis of the SC agglomerates having a smaller apparent density, which results in a larger effective surface area.

Conclusion

It was found that the QESD method was suitable for the manufacture of TBM crystalline agglomerates which are dense and have great mechanical strength (*i.e.*, resistant to abrasion), while the SC method was appropriate for production of TBM crystalline agglomerates having a large apparent specific surface area and a high dissolution rate. Both of these agglomeration processes were able to endow crystalline agglomerates of tolbutamide with improved functional properties.

References

1) T. Kawashima, M. Okumura and H. Takenaka, *Science*, **216**, 1127 (1982).
2) Y. Kawashima, M. Okumura, H. Takenaka and A. Kojima, *J. Pharm. Sci.*, **73**, 1535 (1984).
3) Y. Kawashima, T. Handa, H. Takeuchi and M. Okumura, *Funtaikogaku Kaishi*, **20**, 759 (1983).
4) Y. Kawashima, H. Takeuchi, T. Niwa, T. Hino, M. Yamakoshi and K. Kihara, *Funtaikogaku Kaishi*, **26**, 659 (1989).
5) Y. Kawashima, T. Handa, H. Takeuchi, M. Okumura, H. Katou and O. Nagata, *Chem. Pharm. Bull.*, **34**, 3376 (1986).
6) Y. Kawashima, T. Niwa, T. Handa, H. Takeuchi, T. Iwamoto and K. Itoh, *J. Pharm. Sci.*, **78**, 68 (1989).
7) Y. Kawashima, T. Niwa, T. Handa, H. Takeuchi, T. Iwamoto and Y. Itoh, *Chem. Pharm. Bull.*, **37**, 425 (1989).
8) A. Sano, T. Kuriki, T. Handa, H. Takeuchi and Y. Kawashima, *J. Pharm. Sci.*, **76**, 471 (1987).
9) A. Sano, T. Kuriki, Y. Kawashima, H. Takeuchi and T. Niwa, *Chem. Pharm. Bull.*, **37**, 2183 (1989).
10) T. Itoh and M. Koishi, *Shikizai*, **50**, 488 (1977).
11) Y. Kawashima, T. Handa, H. Takeuchi and M. Okumura, *Chem. Pharm. Bull.*, **34**, 3403 (1986).
12) I. Sekiguchi, *Seiyaku Kouzyo*, **3**, 19 (1983).
13) A. Hixson and H. Crowell, *Ind. Eng. Chem.*, **23**, 923 (1931).
14) Y. Matsuda, S. Kawaguchi, K. Usuki and N. Eguchi, *Yakugaku Zasshi*, **102**, 76 (1982).
15) P. Finholt, H. Kristiansen, O. C. Schmidt and K. Wold, *Medd. Norsk. Farm. Selsk.*, **28**, 17 (1966).
16) H. Nakagawa, K. Mohri, K. Nakashima and I. Sugimoto, *Yakugaku Zasshi*, **100**, 1111 (1980).