Particle Design for Antidiabetic Drugs by the Spherical Crystallization Technique. IV.   Assessment of Compressibility of Agglomerated Tolbutamide Crystals Prepared by Crystallization Technique

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Three different crystallization methods, *i.e.*, the solvent change (SC) method, neutralization (NT) method and quasi-emulsion solvent diffusion (QESD) method, were employed to prepare agglomerated tolbutamide crystals (referred to as SC-A, SC-B, NT and QESD). Each of the agglomerated crystals or unagglomerated tolbutamide crystals (abbreviated as bulk) alone (single formulation), magnesium stearate (MgSt; a lubricant)-added single formulation sample (formulation A), and Kollidon CL (a disintegrating agent)-added formulation A samples (formulation B) were compacted into tablets by the direct tableting method. With the objective of elucidating the compressibility of these samples, the following parameters were analyzed: (1) the course of change in the powder bed volume as a function of the applied compression pressure, (2) the pressure–transmission ratio from the upper punch to the lower punch, (3) the course of decompression (ejection force) and (4) the tensile strength of the tablets determined by the diametric compression method. The results of each sample were compared.

For each of the single-formulations, formulation A and formulation B, Kawakita's equation was able to be applied to each stage of the compaction process over the tested compression pressure range of 50—1500 kg/cm². The limiting value of the compaction ratio of the samples was higher in the order of SC-B > NT > SC-A > QESD > bulk, and each agglomerate showed much higher compressibility than the bulk. Although the agglomerates and bulk showed the same pressure–transmission ratio from the upper punch to the lower punch, the bulk showed a smaller ejection force during decompression. The agglomerates, whose primary crystal diameter is small, showed much larger tensile strength of the compacted tablet than the bulk. The addition of MgSt improved the compaction process, but it weakened the tensile strength of the compacted tablets, especially in the case of the bulk. The addition of Kollidon CL decreased the ejection force due to a decrease in the adhesion force of the tablet to the surface of the die wall. Because Kollidon CL suppressed the effect of MgSt, the tensile strength of the compacted tablets was increased.

The above results revealed that the compressibility of the agglomerates, especially SC-B and NT, is much superior to that of the bulk, and that these agglomerates have the properties necessary for direct tableting. Moreover, formulation B was suggested to be useful as a practical formulation for direct tableting.

Keywords compressibility; compaction process; Kawakita's equation; transmission ratio; ejection force; tensile strength; tolbutamide; particle design; spherical crystallization technique

Introduction

Among drug products, the most frequently employed drug form is tablets. In recent years, regarding the methods employed for tablet manufacturing, from the viewpoint of both factory automation and good manufacture practice (GMP), the direct tableting method is being re-evaluated. This method presents advantages over the widely-employed conventional granule-compaction method (indirect method) in that (1) the number of processes involved is smaller, (2) it is more economic and (3) it can ensure good stability to moisture and heat. Generally, tablets are comprised of and shaped from a mixture of the active ingredient, vehicle, lubricant, disintegrating agent, *etc.* Therefore, it is important to elucidate the compaction performances of this tablet mixture, such as its compressibility and the course of compaction. Especially in the direct tableting method, it is necessary to increase the "flowability" and compressibility of the bulk drug powder in order to ensure a steady supply of the powder mixture to the tableting mechine and sufficient mechanical strength of the compacted tablets. In this regard, many studies have reported on the influences of the vehicle type and particle size on compressibility,[1–6] the compressibility of a powder mixture of the active ingredient, vehicle, *etc.*,[7–9] and more. In addition to the efforts to increase the efficiency of the manufacturing process, it is also important to increase the bioavailability of the drug by improving the solubility of the bulk drug powder. That is, it has become necessary to increase the added value by endowing the drug particle itself with high functionality.

The authors have been studying the particle design of tolbutamide (TBM), a poorly soluble drug, by applying spherical crystallization techniques such as the solvent change (SC) method, neutralization (NT) method, quasi-emulsion solvent diffusion (QESD) method, *etc.* The goals have been to increase the efficiency of the manufacturing process (unification of the crystallization and agglomeration processes and improvement of the "flowability") and to endow TBM agglomerates with high functionality. We have demonstrated that TBM agglomerates prepared by these methods are much superior to the bulk in terms of such micromeritic characteristics as "flowability" and solubility, and we reported that it is possible to endow TBM agglomerates with high functionality.[10,11]

In the present study, (1) TBM agglomerated crystals (abbreviated as agglomerates) produced by three spherical crystallization methods, *i.e.*, the SC method, NT method and QESD method, (2) a mixture of an agglomerate and a lubricant magnesium stearate (MgSt) (formulation A) and (3) a mixture of an agglomerate, MgSt and a disintegrating agent (Kollidon CL: polyvinyl-pyrrolidone cross-linked, BASF Japan) (formulation B) (formulations A and B were prepared supposing the actual tableting process) were shaped into tablets by the direct tableting method. The micromeritic characteristics of each of the tablets thus prepared were assessed, and comparative analysis was made

of the course of the powder bed volume change, the change in the ratio of transmission of the applied pressure from the upper punch to the lower punch, the ejection force during the decompression process and the tensile strength of the compacted tablets. The feasibility of these agglomerates as crystals for direct tableting was thus investigated and evaluated.

Experimental

Method of Preparation of TBM Agglomerated Crystals The following methods were employed to prepare TBM agglomerates by each of the SC, NT and QESD methods. Further details are provided in the authors' earlier reports.[10-12]

SC-A Method[12]: 250 ml of a 0.025% sucrose fatty acid ester aqueous solution was placed in a cylindrical vessel. During stirring with a turbine-type agitator at 600 rpm, a mixture consisting of 50 ml of ethanol containing 5 g of TBM and 15 ml of isopropyl acetate (bridging liquid) was added. The TBM was crystallized out, followed by agglomeration of the crystals at 25 °C for 40 min.

SC-B Method[11]: 50 ml of ethanol containing 5 g of TBM was placed in a cylindrical vessel. While stirring with a turbine-type agitator at 600 rpm, 250 ml of a 0.025% sucrose fatty acid ester aqueous solution was added to crystallize out the TBM. Two min later, 22 ml of an isopropyl acetate–ethanol mixture (bridging liquid) was added dropwise at a rate of 10 ml/min, and agglomeration was performed at 25 °C for 40 min.

NT Method[10]: 25 ml of 1 N sodium hydroxide in which 5 g of TBM had been dissolved was placed in a cylindrical vessel. During stirring with a turbine-type agitator at 600 rpm, 250 ml of 2% hydroxypropyl-methylcellulose aqueous solution and 25 ml of 1 N hydrochloric acid were added to neutralize the NaOH solution of TBM and crystallize out the TBM. Then 29 ml of ether (bridging liquid) was added dropwise at a rate of 10 ml/min, followed by agglomeration of the TBM crystals at 25 °C for 40 min.

QESD Method[11]: 275 ml of a 0.025% sucrose fatty acid ester aqueous solution was placed in a cylindrical vessel with baffle plates. During stirring with a propeller-type agitator at 300 rpm, 5 ml of dimethylformamide in which 2.7 g of TBM had been dissolved was added, followed by agglomeration of the TBM crystals at 25 °C for 15 min.

The form of the TBM crystals thus obtained was A-form for SC-A, NT, QESD and bulk, while it was B-form for SC-B.

Determination of Micromeritic Characterisics of TBM Agglomerated Crystals and Bulk The equation $\rho = 6 w/n\pi d^3$ was used to calculate particle density (ρ) from a circle equivalent diameter (d) and the number (n) of the known weight (w) of the particle dispersed on a slide glass with a microscope and an image analyzing processor (Nikon, Luzex 3U). The circle equivalent diameter of the agglomerate-constituting primary crystal was measured after uniform dispersion in liquid paraffin by sonification.

The specific volume of the agglomerates was determined on the basis of the weight and volume of the agglomerates packed in a 10-ml graduated cylinder. The surface of the agglomerates was observed with a scanning electron microscope (JEOL; JMS-25SIII).

Method of Preparation of Compacted Tablets The particle size of the SC-A, SC-B, NT and QESD agglomerated crystals and the bulk was adjusted to 250—500 μm (60—30 mesh) using a JIS sieve shaker. Then powder mixtures (61—65 mg) were prepared in accordance with the formulations shown in Table I and compacted into tablets using a single punch machine (Okada Seiko; Model N-30) with flatfaced punches (6-mm diameter) at a compression pressure of 50—1500 kg/cm² and a punch speed of 2.4 cm/s.

Method of Assessment of Compacted Tablets The porosity (ε) of the compacted tablets was calculated using the equation of $\varepsilon = 1 - (\rho_{app}/\rho_t)$, where ρ_{app} is the apparent density of the tablet, which was obtained by measuring the diameter and thickness of an accurately-weighed tablet using a micrometer, and ρ_t is the true density measured using an air comparison pycnometer (Beckman Japan; Model 930).

The tensile strength[13] (kg/cm²) required to split the compacted tablets was calculated in accordance with Eq. 1 below, using the hardness F (kg) which was measured by splitting the tablet along its diameter using a tablet hardness tester (Erwerk; Model TBH 28).

$$T = 2F/\pi dl \qquad (1)$$

where, d and l are the diameter (cm) and thickness (cm) of the tablet. The split surface of the tablet was observed with a scanning electron microscope.
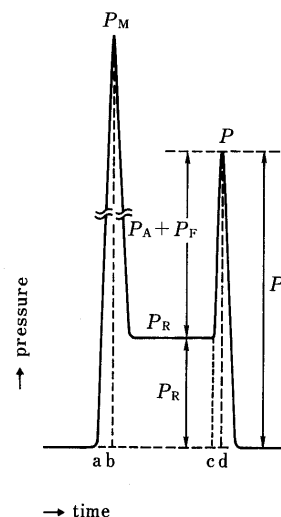

Fig. 1. Lower Punch Pressure during the Decompression Process

P, ejection force; P_A, adhesion pressure; P_F, friction pressure; P_R, residual pressure; P_M, maximum pressure during compression process.

TABLE I. Formulation of Compacted Tablets

Component	Single formulation (TBM alone)	Formulation A	Formulation B
Tolbutamide (agglomerate or bulk)	62 mg	61.7 mg	49.3 mg
Magnesium stearate (lubricant)	—	0.3 mg	0.3 mg
Kollidon CL (disintegrating agent)	—	—	12.4 mg

The pressure–transmission ratio (lower punch pressure/upper punch pressure) and the ejection force during decompression were measured using a compression pressure displacement tester (Okada Seiko; Model N-30E) equipped with a strain gauge of the upper and lower punch.

Figure 1 shows the change in the pressure in the lower punch during compaction and decompression. The compaction process was begun and point a by the upper punch, the maximum pressure (P_M) was reached at point b, the decompression process (detachment of the upper punch from the upper surface of the compacted tablet) was begun at the point b, and, simultaneously with the decrease in the pressure, the elastic recovery force of the compacted tablet acted on the die wall and ramained as the residual pressure (P_R). Thereafter, lifting of the compacted tablet by the lower punch began at point c. The decompression process was completed when the pressure decreased to zero after having reached P, which was necessary to lift the lower punch against the adhesion pressure P_A between the lateral surface of the compacted tablet and the die wall and the friction pressure P_F due to the residual pressure P_R. Therefore, the ejection force P is expressed as the sum of P_R, P_A and P_F.

Results and Discussion

Analysis of Process of Volume Change in Agglomerate Bed Due to Compaction. 1. Application of Heckel's Equation to Compaction Process Heckel's equation (Eq. 2) is frequently used in the analysis of the compaction process of a powder bed.[14,15]

$$\ln(1/1-D_r) = KF + A \qquad (2)$$

Where, F is the compression pressure (kg/cm²), D_r is the relative density of the tablet (ratio relative to the tablet density at a porosity of 0) at compression pressure $= F$, and K and A are constants. $1-D_r$ can be substituted by porosity ε. Heckel[14,15] assumed that the linear region of the curve
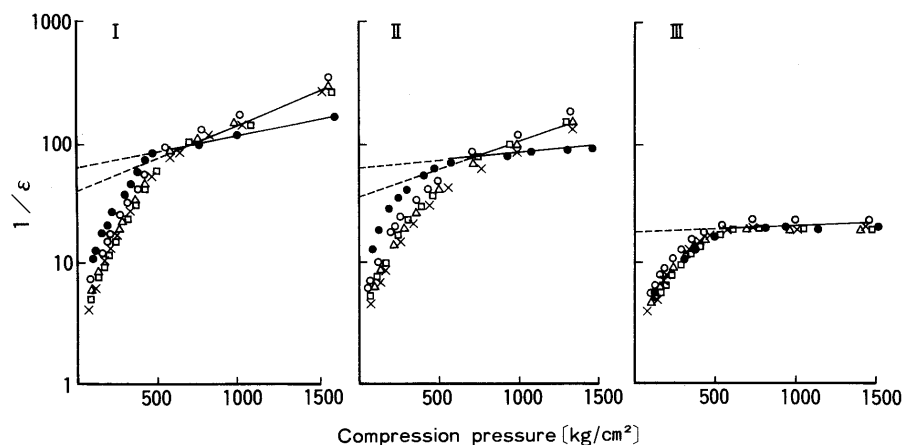
Fig. 2. Relationship between $1/\varepsilon$ and Compression Pressure

I, single formulation; II, formulation A; III, formulation B. ○, SC-A; ×, SC-B; □, NT; △, QESD; ●, bulk.
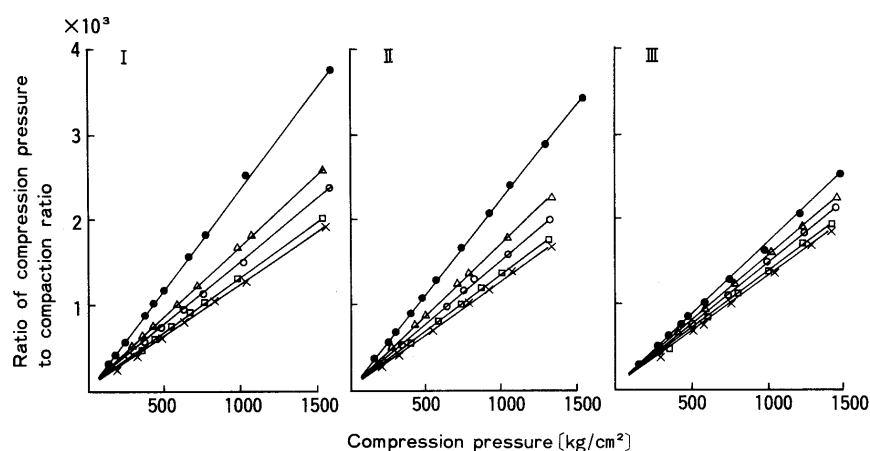

Fig. 3. Relationship between Ratio of Compression Pressure to Compaction Ratio and Compression Pressure

I, single formulation; II, formulation A; III, formulation B. ○, SC-A; ×, SC-B; □, NT; △, QESD; ●, bulk.

prepared by plotting ln $1/\varepsilon$ against F indicates the stage where interparticle bonding is proceeding. As plotted in Fig. 2, for all formulations, each sample showed a straight line at 500 kg/cm² or higher, indicating that desification of the tablet was proceeding by means of particle deformation in the late stage of compaction.

In the case of single-formulation and formulation A, the slope of the line was nearly the same for each agglomerate, but it was larger for the agglomerates than the bulk. Heckel described that the slope is proportional to the ease of particle deformation; that is, the greater the plasticity of the sample, the larger the slope. It was found that in the late stage of compaction, since the agglomerates were more plastic than the bulk, the agglomerates more readily underwent deformation and were thus easier to be densified compared with the bulk.

In the case of formulation B, the slopes of the agglomerates and bulk were almost the same, and thus the degree of their densification was equal. This is because the characteristics of the bulk and agglomerates are not expressed in the compaction process due to the low plasticity of Kollidon CL (added as a disintegrating agent) as a result of its fibrous structure.

In order to analyze the particle behavior during the compaction process from the early stage through the middle

stage, to which Heckel's equation could not be applied, Kawakita's equation[16] was applied.

2. Application of Kawakita's Equation to the Compaction Process

$$C=\frac{V_0-V}{V_0}=\frac{abF}{1+bF} \tag{3}[16]$$

$$F/C=\frac{1}{ab}+\frac{1}{a}F \tag{4}[16]$$

$$C_\infty=\frac{V_0-V_\infty}{V_0}=a \quad \text{(limiting value of compaction ratio)} \tag{5}[16]$$

$$\varepsilon_\infty=\frac{V_\infty-V_t}{V_\infty} \quad V_t: \text{true specific volume} \tag{6}$$

$$\varepsilon_0=\frac{V_0-V_t}{V_0} \tag{7}$$

Where C is the compaction ratio calculated from the powder specific volumes (V_0 and V) measured before compaction and after compaction (F), respectively, and a and b are constants. Figure 3 shows the result of settlement of the whole compaction process from the early stage through the late stage of compaction using Eq. 4, obtained by modification of Eq. 3. For all formulations, a linear

Table II. Micromeritic Properties of TBM Agglomerated Crystals, Bulk and Compacted Tablets

Sample		SC-A	SC-B	NT	QESD	Bulk
Single formulations	C_∞	0.671	0.800	0.752	0.595	0.417
(TBM alone)	V_0	2.50	4.12	3.33	2.04	1.43
	ε_0	0.672	0.801	0.754	0.598	0.427
	ε_∞	0.004	0.005	0.007	0.007	0.016
	ε	0.022	0.028	0.028	0.028	0.020
Formulation A	C_∞	0.662	0.793	0.746	0.588	0.447
	V_0	2.45	4.00	3.25	2.00	1.50
	ε_0	0.666	0.795	0.748	0.590	0.450
	ε_∞	0.010	0.010	0.007	0.007	0.012
	ε	0.030	0.040	0.033	0.033	0.020
Formulation B	C_∞	0.685	0.775	0.752	0.671	0.599
	V_0	2.72	3.83	3.44	2.63	2.15
	ε_0	0.697	0.784	0.750	0.686	0.616
	ε_∞	0.036	0.042	0.032	0.045	0.042
	ε	0.056	0.060	0.060	0.060	0.060

C_∞: Limiting value of compaction ratio. V_0: Specific volume of particle bed without compaction (cm^3/g). ε_0: Porosity of particle bed without compaction. ε_∞: Porosity of compacted tablet under compression pressure of infinity. ε: Intercept A in Heckel's equation.

correlation was obtained for each sample, indicating that Eq. 4 is applicable. As shown in Eq. 5, Kawakita[16] found that the constant a is equal to C_∞, which is the compaction ratio when the compression pressure F is infinity in Eq. 3. Thus, the limiting value of the compaction ratio was calculated from the slope of each straight line and presented in Table II. In the case of the single-formulations and formulation A, the limiting value of the compaction ratio of the bulk was about 40%, while the ratios of the agglomerates were 60—80%, indicating higher compressibility of the agglomerates than the bulk.

In the case of formulation B, on the other hand, the limiting value of the compaction ratios of agglomerates were almost the same as those obtained for the single-formulations and formulation A, while the limiting value of the compaction ratio of the bulk increased and showed an asymptotic approach to that of the agglomerates. This finding suggested that the bulk is more susceptible to the influence of Kollidon CL than the agglomerates, thereby resulting in an increase in the densification ratio (Table II).

The differences in the compressibility between each agglomerate sample could not be demonstrated when using Heckel's equation, whereas they could with Kawakita's equation. That is, for each agglomerate sample of each formulation, the degree of densification was found to be higher in each compaction stage in the order of SC-B > NT > SC-A > QESD.

Next, the porosity (ε_0) of each sample under no compression pressure was calculated from Eq. 7 (Table II). For each formulation, the value of ε_0 was nearly equal to the respective limiting value of the compaction ratio. This indicates that densely compacted tablets with almost no void were formed. Next, the limiting value of the compaction ratio (C_∞) and specific volume under no compression pressure (V_0) were substituted in Eq. 5 to obtain the specific volume under a compression pressure of infinity (V_∞). Equation 6 was used to calculated the porosity of the compacted tablet (ε_∞) under those same conditions, and the value of ε_∞ was compared with the porosity of actually-

obtained compacted tablets. The porosity of tablets compacted at $1500\,kg/cm^2$ and 0.01—0.05, which was close to ε_∞. From this data, as well, the compaction ratio of actually-obtained tablets was found to have reached the limiting value.

Next, ε was calculated by extrapolating the linear region of the plots of $\ln 1/\varepsilon$ vs. F in Fig. 2 to $F=0$. Here, ε is the porosity at the time the highest packing due to particle movement and rearrangement before interparticle bonding becomes appreciable.[15] As shown in Table II, ε_∞ of each sample was smaller than ε. This indicates that Kawakita's equation is applicable to each compaction stage from the early through late compaction stages.

The compaction process of samples prepared using the single-formulations of formulation A was analyzed on the basis of the results obtained using Heckel's equation and Kawakita's equation. Compared with the bulk of a flat shape, the agglomerates with a spherical shape had superior flowability and were therefore easier to densify in all formulations at the early stage of compaction.

Due to the differences in the limiting value of the compaction ratio, densification was easier in the order of SC-B > NT > SC-A > QESD. The V_∞ of each sample obtained from the relationship expressed in Eq. 5 was nearly equal (0.82—0.83 cm^3/g). These results indicated that the limiting value of the compaction ratio increases with larger V_0.

From this result, it was found that the larger the V_0 of the agglomerate, the higher the compressibility of the agglomerate.

On the other hand, the agglomerates had a small particle density of 0.7—0.9 g/cm^3 because they were made up of aggregated fine primary crystals (Fig. 4), and their inner void (inter-primary-crystal void) was markedly larger than that of the bulk. These facts are presumed to be responsible for the formation of tablets with a smaller relative density than those from the bulk in the early compaction stage where packing of the interparticle void proceeds predominantly.[17]

On the other hand, the plastic agglomerates were also easier to densify than the bulk from the middle through the late compaction stages, where the intraparticle void packing and the breakage and deformation of the particles predominantly occurred, though there was no difference among the agglomerates of each formulation.

Formulation B formed, in each compaction stage, compacted tablets with a smaller relative density than those obtained from the single-formulations and formulation A. This is surmised to have been due to the fact that Kollidon CL (mean particle size: 20 μm) attached to the surface of particles of the bulk and agglomerates and increased the interparticle adhesion force, thereby decreasing the flowability. The large porosity of the tablet from the bulk was presumed to be caused by the increased amount of Kollidon CL attached to the bulk, which has a small specific surface area owing to its smooth surface (Fig. 4) in contrast to the agglomerates, which have a rough surface.

In order to analyze the above-described compaction process in more detail, the relationship between the compression pressure and pressure–transmission ratio was studied.

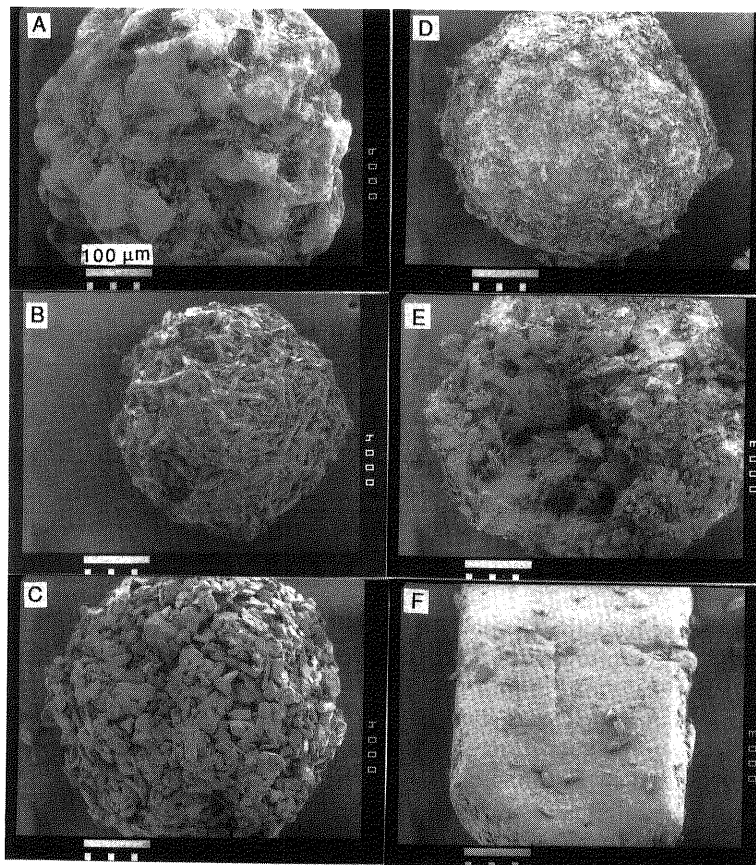**Relationship between Compression Pressure and Pressure–**

Fig. 4. Scanning Electron Microphotograph of TBM Agglomerated Crystals and Bulk

A, SC-A; B, SC-B; C, NT; D, QESD; E, Cross-section of QESD; F, bulk.
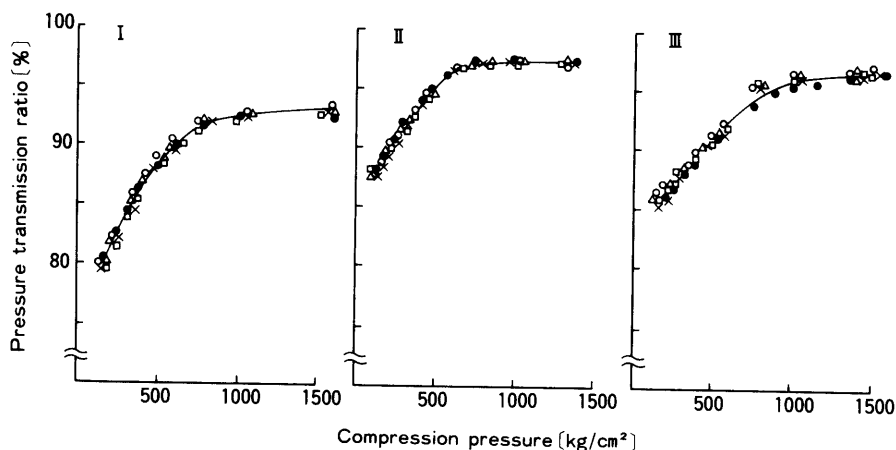

Fig. 5. Relationship between Pressure Transmission Ratio and Compression Pressure

I, single formulation; II, formulation A; III, formulation B. $\bigcirc$, SC-A; $\times$, SC-B; $\square$, NT; $\triangle$, QESD; $\bullet$, bulk.

Transmission Ratio Each sample was compressed only with the upper punch (compression pressure), and the ratio of the compression pressure transmitted from the upper punch to the lower punch (pressure–transmission ratio; P_L/P_U) was plotted against various upper punch compression pressures. The results are presented in Fig. 5. For each sample prepared by each formulation, the P_L/P_U increased and reached an equilibrium as the compression pressure increased, and their compression pressure–P_L/P_U curves showed the same pattern. The P_L/P_U at equilibrium was larger in the order of formulation A > formulation B > single-formulations. The P_L/P_U of formulation A is larg-

est because of reduced friction on the die wall surface due to the lubricating effect of the added magnesium stearate (MgSt). For formulation B, the lubricating effect of MgSt was countered to some extent as a result of adsorption of Kollidon CL to the particle surface.

Next, Janssen's equation[18] (Eq. 8), which expresses the relationship between the P_L/P_U and friction force on the die wall surface, was applied. Logarithmic conversion of both sides gives Eq. 9.

$$P_L/P_U = \exp.(-4\mu KH/D) \tag{8}$$
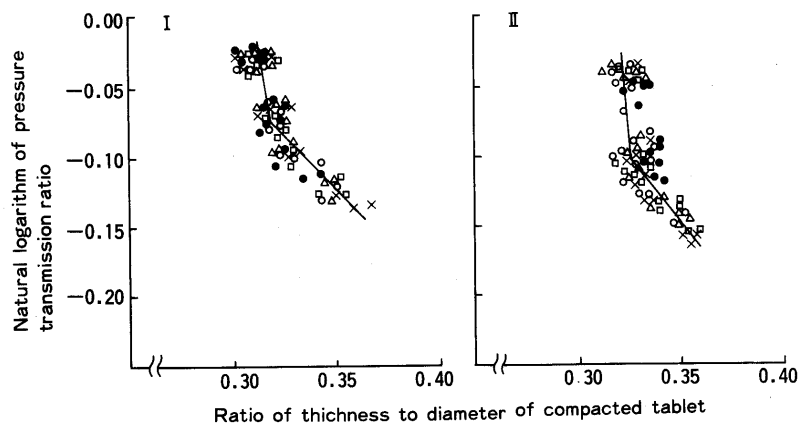
$$\ln P_L/P_U = -4\mu KH/D \tag{9}$$

Fig. 6. Relationship between Pressure Transmission Ratio and Ratio of the Thickness to the Diameter of Compacted Tablets

I, formulation A; II, formulation B. ○, SC-A; ×, SC-B; □, NT; △, QESD; ●, bulk.

Where P_L/P_U is the pressure–transmission ratio (PTR) from the upper punch (P_U) to the lower punch (P_L), 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 depth of the particle bed, and D is the diameter of the die. Formulations A and B were analyzed in relation to the correlation between the logarithm of PTR and H/D, and the results are plotted in Fig. 6. For both formulations, there were no marked differences between the bulk and the agglomerates. There was a linear correlation having a point of inflection between the logarithm of P_L/P_U and H/D, although some data deviated from the line. Okada et al.[19] studied the correlation between the logarithm of P_L/P_U and H/D using potassium chloride, and reported that the plots were linear when the tests were performed over a wide range of sample weights, but the linearity was poor when a very narrow range of sample weights was employed. In the present study, nearly a constant amount of sample (61—65 mg) was employed, and thus our result was the same as their result when using a very narrow range.

In Janssen's equation, μK is constant. Thus, the value of μK was qualitatively assessed based on the slopes of the lines in Fig. 6. The results indicated that μK was increased in the region with a small H/D ratio, that is, under a high compression pressure. Under a high compression pressure, the porosity of the compacted tablet is small, resulting in an increase in the number of interparticle contact points and the number of contact points between the die wall and particles. Accordingly, it is surmised that K (ratio of the horizontal pressure to the vertical pressure) and μ (coefficient of friction) with increase.

Adhesion to Die Wall Surface during Decompression Process In addition to elucidation of the densification performance during the compaction process of particles, it is also important—from the aspect of the actual tablet manufacturing process—to elucidate the particle performance, such as ejection of the tablet from the die, which may cause tableting failure. Therefore, formulations A and B were studied regarding the relationship between the compression pressure and the ejection force against the resistance between the sample and die wall surface during the decompression process. Here, the ejection force is the sum of (1) the adhesion force between the die wall surface and particles, (2) residual pressure (elastic recovery force)
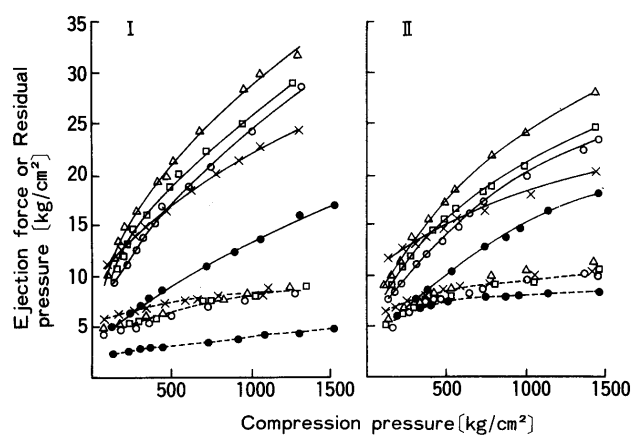

Fig. 7. Relationship between Ejection Force or Residual Pressure and Compression Pressure

I, formulation A; II, formulation B. —, ejection force; ---, residual pressure. ○, SC-A; ×, SC-B; □, NT; △, QESD; ●, bulk.

and (3) friction force due to the residual pressure.

Figure 7 shows the correlation between the compression pressure and ejection force and between the compression pressure and residual pressure for formulations A and B. In the case of formulation A, the ejection force increased strikingly as the compression pressure increased, but the residual force increased only slightly under a high compression pressure. These results suggest that the contribution of the adhesion force to the ejection force becomes large if tableting is performed under a high compression pressure. That is, when the compression pressure was small (early stage of compaction), the elastic recovery force of the compacted tablet was nearly equal to the adhesion force of the tablet to the die wall, but the adhesion force increased as the compression pressure increased because the particles underwent deformation, which resulted in a increase in the number of contact points with the die wall and the area of contact with the die wall. The reason for the ejection force of the bulk being lower than for the agglomerates is surmised to have been due to the fact that the bulk does not undergo deformation as readily as the agglomerates. Among the various kinds of agglomerates, SC-B showed the smallest ejection force. As seen from the SEM photographs in Fig. 4, SC-B has a needle-like shape, unlike the flat shape of the primary

particle of the other agglomerates, and its area of contact with the die wall is therefore surmised to be smaller than the areas of the other agglomerates; this is through to be the reason for SC-B showing the smallest ejection force.

In the case of formulation B, on the other hand, the elastic recovery force was larger than the adhesion force when the compression pressure was low, and the ejection force decreased in each compaction stage compared with formulation A. This is surmised to have been due to elastic deformation of Kollidon CL, which has a fibrous structure. Moreover, because Kollidon CL does not readily undergo plastic deformation and thus causes a decrease in the adhesion force, the ejection force of formulation B agglomerates is surmised to have decreased in each compaction stage. That is, the adhesion force is surmised to have decreased due to the agglomerates being covered with Kollidon CL, which caused a decrease in the number of contact points and the contact area between the crystalline particles and the die wall.

Tensile Strength of Compacted Tablets Figure 8 depicts the correlation between the tensile strength and compression pressure of compacted tablets on the basis of the data obtained by the diametric compression test. The tensile strength of the compacted tablets prepared from the single-formulations increased rapidly over a compression pressure range of 50—400 kg/cm^2 but slowly thereafter (Fig. 8-I). The agglomerates showed a markedly larger tensile

strength than the bulk for all compression pressures tested. The slope of the line plotted for the compression pressure *vs.* tensile strength, which indicates the case of forming interparticle bonding, was larger for the agglomerates than for the bulk up to a compression pressure of 400 kg/cm^2; the compressibility of the agglomerates was excellent. This is due to an increase in the number of interparticle contact points and the interparticle contact area. That is, since the agglomerates consisted of fine primary crystalline particles, the number of contract points per unit contact area is large. In addition, the agglomerates more readily undergo plastic deformation than the bulk, and thus the increase in the interparticle contact area due to the deformation is larger than that for the bulk. As a result, the interparticle bonding force of the agglomerates became larger than that of the bulk. The patterns of graphs plotted for the tensile strength *vs.* the compression pressure for formulations A and B were similar to those for the single-formulations. However, the addition of MgSt and Kollidon CL affected the compressibility of the samples. That is, as shown in Fig. 8-II, the tensile strength of formulation A, to which MgSt, a lubricant, had been added, was decreased to lower than that of the single-formulations, and this effect was especially remarkable for the bulk: its tensile strength became 0. This is a result of weakening of the interparticle bonding force caused by a decrease in the interparticle contact area due to the adhesion of MgSt to the surface of the crystalline
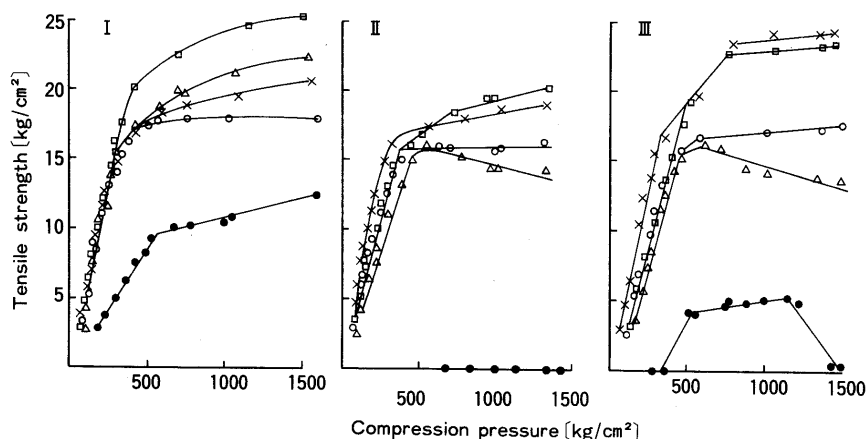

Fig. 8. Relationship between Tensile Strength and Compression Pressure

I, single formulation; II, formulation A; III, formulation B. ○, SC-A; ×, SC-B; □, NT; △, QESD; ●, bulk.
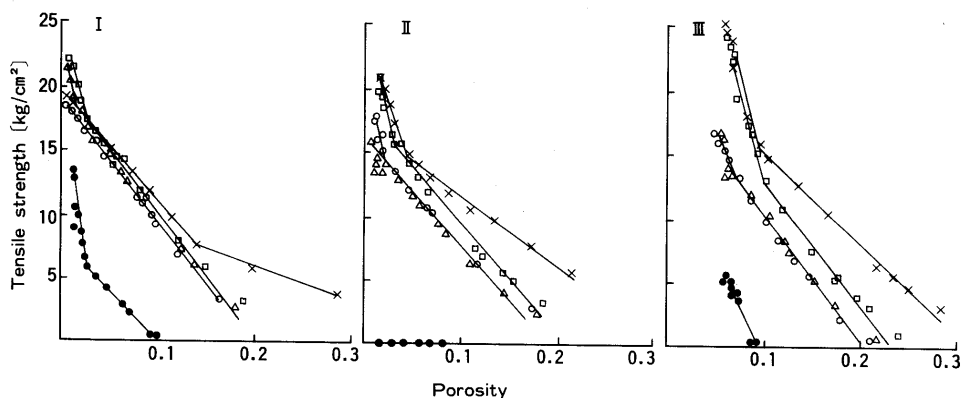

Fig. 9. Relationship between Tensile Strength and Porosity

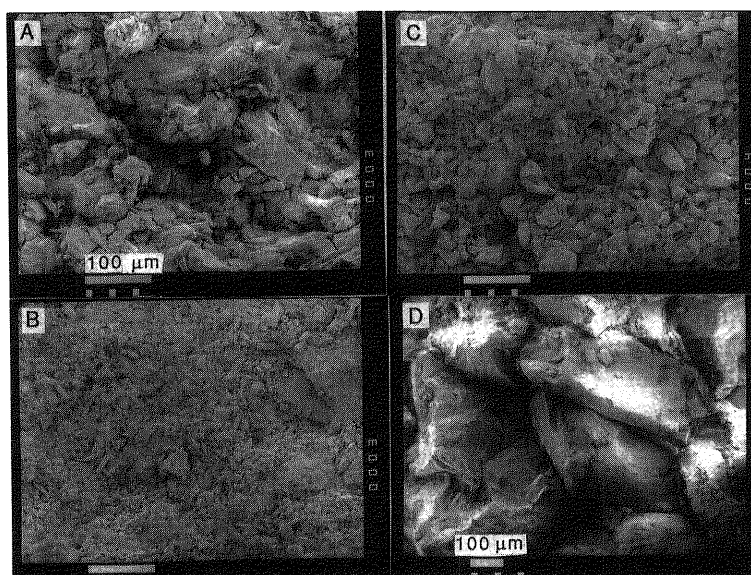I, single formulation; II, formulation A; III, formulation B. ○, SC-A; ×, SC-B; □, NT; △, QESD; ●, bulk.

Fig. 10. Scanning Electron Microphotograph of Split Surface of Compacted Tablet

Compacted into tablets under compression pressure of about 80 kg/cm². A, SC-A; B, SC-B; C, NT; D, bulk.

particles. That is, compared with the agglomerates, whose specific surface area is large due to their rough surface, the specific surface area of the bulk is small due to its smooth crystal surface, and thus the adhesion of MgSt to the bulk particles becomes large.

In the case of formulation B, to which both MgSt and Kollidon CL (20%) had been added, the tensile strength of the agglomerates increased to some extent, while that of the bulk increased strikingly. This is surmised to indicate the following: the interparticle bonding force of Kollidon CL particles is stronger than that of MgSt particles, and thus the number of Kollidon CL particles adhering to the particle surface of the agglomerates or bulk is larger than the number of MgSt particles. In other words, it is thought that, for formulation A, the interparticle bonding force of the bulk decreased due to the influence of MgSt, while for formulation B, due to the adhesion of a larger number of Kollidon CL particles, the influence of MgSt was blocked. The tensile strength was dampered under a high compression pressure of 500 kg/cm² or more for QESD and 1 250 kg/cm² or more for the bulk. When the compression pressure was increased to higher than those values, cracks occurred inside the compacted tablet, causing capping.

Finally, the relationship between tensile strength and porosity was studied. As depicted in Fig. 9, for each formulation, under each compression pressure tested, the tensile strength was larger in the order of SC-B ≥ NT > SC-A = QESD ≫ bulk when the porosity was the same. This result indicates that, since the tensile strength of compacted tablets is dependent on the interparticle bonding force per unit area, the number of contact points was different for each sample. As seen in the SEM photographs (Figs. 4 and 10), the size of the agglomerates was, approximately, 15 μm for SC-B, 20 μm for NT, 30 μm for SC-A and 300 μm for the bulk. Thus, the smaller the particle size, the larger the tensile strength. That is, it is through that even when the porosity of the tablets is the same, the number of interparticle contact points per unit cross-sectional area is larger and the interparticle bonding force is stronger when

the primary particle size is smaller. Therefore, it was found that the tensile strength of a compacted tablet is dependent on the size of the primary particles constituting the crystalline agglomerates.

Conclusion

For each of the single-formulations, formulation A and formulation B, densification of the agglomerates, whose inner void was large, was much easier than that of the bulk during each stage of the compaction process. However, the ejection force during the decompression process was smaller for the bulk than for the agglomerates. The tensile strength of the compacted tablets was markedly larger for the agglomerates, whose primary particle size is small, than for the bulk.

Addition of MgSt and Kollidon CL affected the compressibility of the samples. Addition of MgSt (formulation A) increased the pressure–transmission ratio but markedly decreased the tensile strength of compacted tablets prepared from the bulk. Addition of Kollidon CL together with MgSt (formulation B) decreased the ejection force but increased the tensile strength of the compacted tablets.

On the basis of the above results, the compressibility of the agglomerated crystals, especially SC-B and NT, was found to be much superior to that of the bulk, and the agglomerates were found to have the properties necessary for direct tableting as crystalline particles. The present study suggested that formulation B for TBM agglomerated crystals may be useful as a practical formulation for direct tableting.

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