Studies on the Granulation Process of Granules for Tableting with a High Speed Mixer. III. Analysis of the Compression Process

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Several kinds of theophylline granules were prepared in a high speed mixer by varying the kneading time, and their compression processes were analyzed by Heckel and by Cooper and Eaton equations. The compressibility of those granules was also examined comparatively by analyzing the compression energy applied to the powder layer to determine the relation between the compression behavior, compression energy, tablet hardness and internal structure of the tablet.

The granules having the largest pore volumes were found to have high tablet hardness and tended to show larger ratios of compression loss energy to compression energy. It was suggested that in the granules having the largest pore volumes, the pores were easily filled by particle movement, rearrangement, plastic deformation and brittle fracture upon compression and the energy applied to the powder layer upon tableting was consumed efficiently.

Key words granulation; granulation end point; pore volume; high speed mixer; compression; energy

Many studies have been reported on the compression process of powders. Heckel[1] classified the compression process of metal powders into 3 stages: 1) densification by die filling, 2) densification by movement and rearrangement of individual particles before particle binding takes place and 3) densification by deformation and fragmentation of particles during particle binding at high compression pressure, by analyzing the relation between density and pressure during the compression process. The Heckel equation is reportedly applicable to the powders and granules for medicinal use.[2-5] On the other hand, Cooper and Eaton[6] reported equations concerning the probability of density increase in two filling processes: one is filling of the pores of the same size as those of original particles by particle sliding and the other is filling of such voids which are substantially smaller than those of the original particles through plastic deformation and fragmentation.

In previous papers[7,8] on the granulation process for tableting using a high speed mixer, the authors reported that this process could be monitored by power consumption changes of the blade of the mixer, that the pattern of power consumption curves and suitable granulation end points varied depending on the particle size of formulated powder, and that the granules most suitable for tableting had large pore volume. In the present study, the compression process of several kinds of theophylline granules prepared by varying the kneading time was analyzed by Heckel[1] and by Cooper and Eaton[6] equations and the compressibility of those granules was compared by analyzing the compression energy applied to the powder layer.

Materials and Methods

The materials, formulation, tablet manufacturing method and physical characterization method for granules and tablets were reported previously.[7]

Monitoring of Power Consumption The power consumption was monitored throughout the kneading process with a power converter (Elphy Automation Japan, GS-VFD Co., Ltd.) and an analyzing recorder (Yokogawa, AR 1100A). The power consumption curve and each granulation end point are shown in Fig. 1.

Evaluation of Compression Process Analysis of Compression Curve Heckel[1] and Cooper and Eaton[6] equations can be written as follows:

$$\ln\left[\frac{1}{1-D}\right]=KF+A \tag{1}$$

where F is the applied pressure, D is the relative density of powder compact, and K and A are determined analytically from the slope and intercept, respectively, of the extrapolated linear region of a plot of $\ln(1/1-D)$ *vs.* F. Slope K and intercept A are identified, respectively, as the reciprocal yield pressure of the material and the movement of particle during the initial stage of compaction,

$$\frac{[V_0-V]}{[V_0-V_\infty]}=a_1\exp[-k_1/F]+a_2\exp[-k_2/F] \tag{2}$$

where V_0 is the initial volume at zero pressure, V is the compact volume, V_∞ is the compact volume at infinite pressure calculated from the true density and F is the applied pressure; a_1 and a_2 are coefficients indicating the fraction of theoretical compression that would be achieved at infinite pressure by each particular process; k_1 and k_2 are coefficients with units of pressure indicating the magnitude of the pressure where the particular

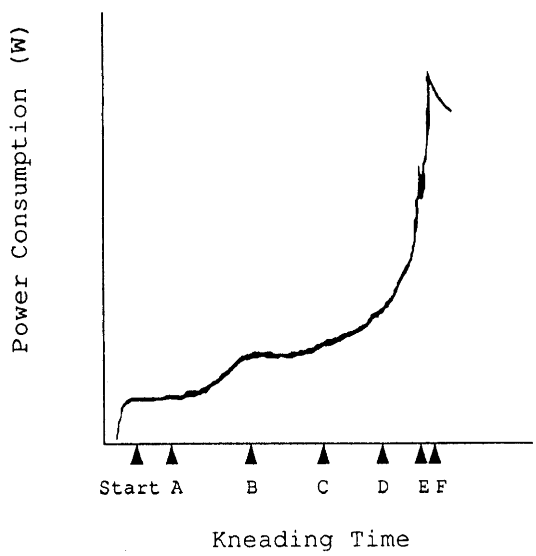

Fig. 1. Power Consumption Curve During Kneading

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process has the greatest probability density. a_1, a_2, k_1 and k_2 were calculated by the nonlinear least squares method[9] to equation (2).

Measurement of Compression Energy Granules were compressed into tablets each weighing 400 mg using biflat punches having a cross section of 1 cm^2 with a universal testing machine (Minebea Co., Ltd., Model TCM-5000C) at a compression speed of 2 mm/min. Compression energy (CE), compression loss energy (LE) and elastic energy (EE) were calculated from the compression pressure–displacement plot (Fig. 2) according to the report of Kaneniwa *et al.*[10]

Results and Discussion

Physical Properties of Granules and Tablets Figure 3 shows scanning electron micrographs of the physical mixture and granules obtained at individual granulation end points. Agglomeration of the particles was hardly observed at point A due to a shorter kneading time and lesser amount of added purified water. Granules B were found to be a mixture of small agglomerates (about 100 μm in mean particle diameter) of fine particles and the bulk powder of similar sizes. As observed in granules C and D, granule growth was noted with prolonged kneading time and an increased amount of added purified water. Furthermore, coarse lumps were formed due to secondary agglomeration of granules at points E and F. Table 1 shows D_{50}, σ_g, the angle of repose and bulk density of the physical mixture and granules obtained at individual granulation end points. D_{50} value increased with ongoing kneading time, and in particular, granules E and F indicated high D_{50} value with formed coarse lumps as mentioned above. With the passage of kneading time, the angle of repose was decreased and the bulk density was increased. These phenomena were believed attributable to the increasing particle diameter and the densification of granules by wet massing. The pore volume of granules was increased from the start of kneading through point A to point B, and decreased thereafter as shown in Fig. 4. It was speculated that loose agglomerates formed as the kneading progressed increased the pore volume and then further kneading accelerated granule densification through tumbling.

The hardness of the tablets compressed from the granules A—D is shown in Fig. 5. Tablets from granules B showed the maximum hardness at every compression pressure.

Evaluation of the Compression Process Figure 6 shows the stress of the upper and lower punches at compression into tablets. The force transmission ratio from the upper punch to the lower punch for granules A—D exceeded 90%, but there was no difference in the force transmission due to varied particle diameters and kneading times.

The Heckel plots[1] for tableting of granules A—D are given in Fig. 7 and the parameter and lower limit pressure of linearity in Table 2. Slope k in the table was calculated by the method of least squares, and the lower limit pressure

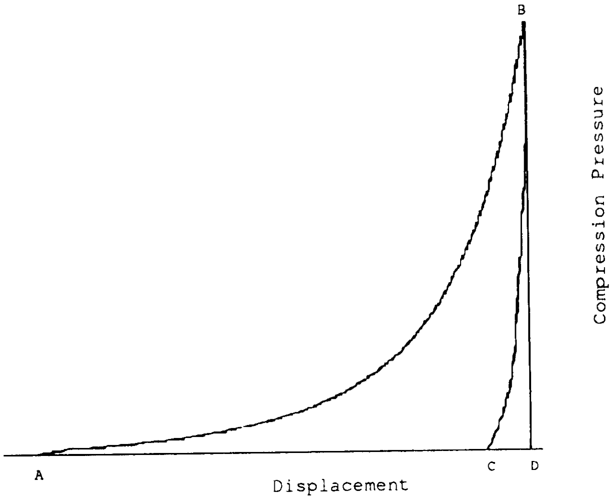

Fig. 2. Schematic Diagram of Pressure Displacement Plot in the Energy Analysis

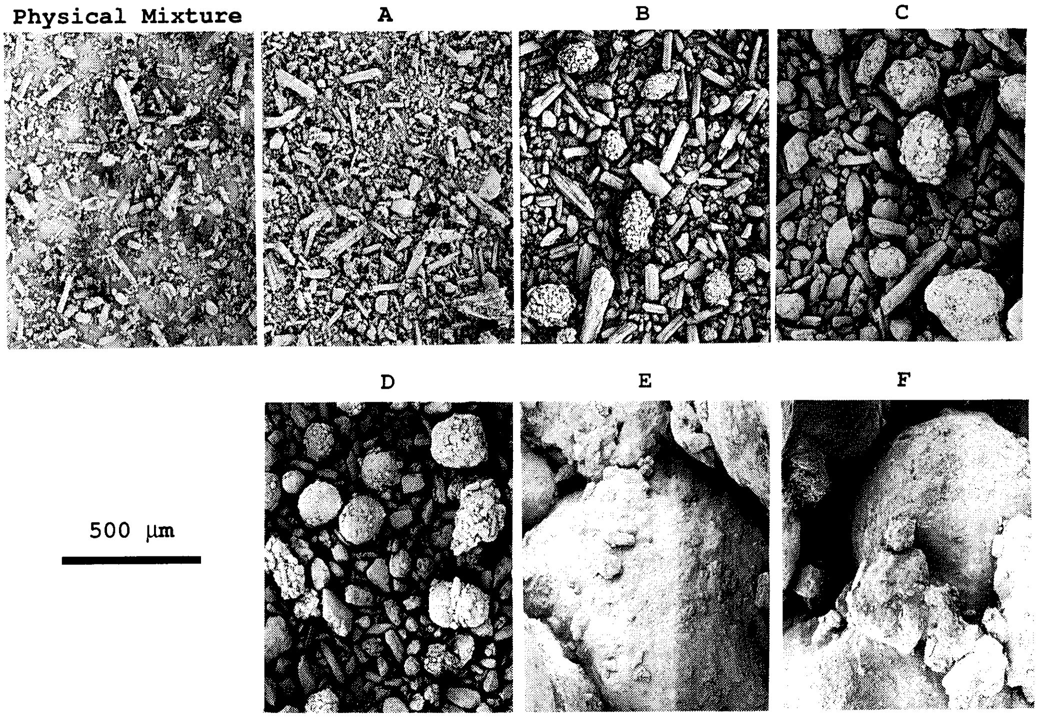

Fig. 3. Scanning Electron Micrographs of Physical Mixture and Granules Obtained at Each Granulation End Point

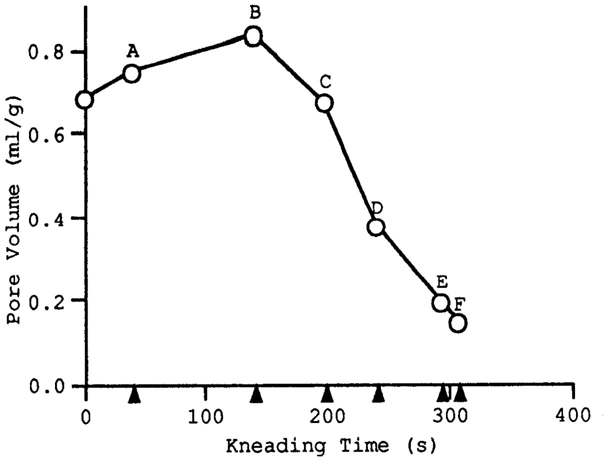

Fig. 4. Pore Volume of Granules Obtained at Each Granulation End Point

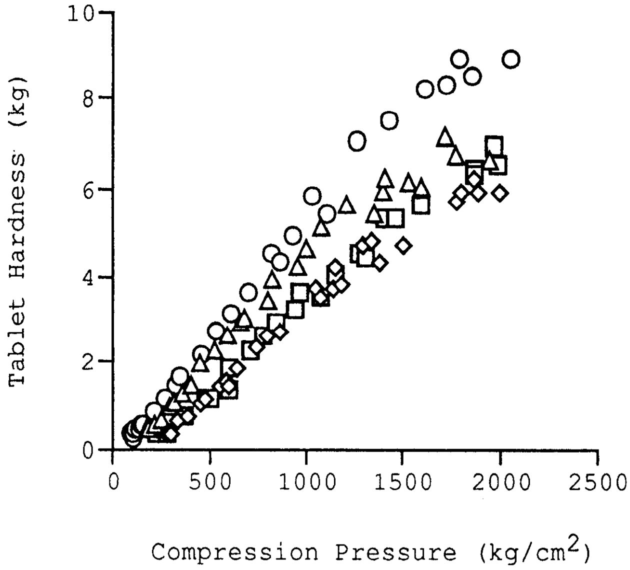

Fig. 5. Hardness of Tablets Compressed from Granules Obtained at Each Granulation End Point

□, A; ○, B; △, C; ◇, D.

Table 1. Physical Properties of Granules Obtained at Each Granulation End Point

	D_{50} μm (±σg)	Angle of repose (degrees)	Bulk density g/ml
Mixture	28 (2.0)	50.4	0.501
A	58 (2.4)	49.3	0.477
B	115 (4.4)	42.9	0.503
C	210 (3.3)	38.7	0.565
D	440 (4.9)	36.9	0.628
E	2100 (1.9)	—	—
F	3700 (1.8)	—	—

$n=3$.

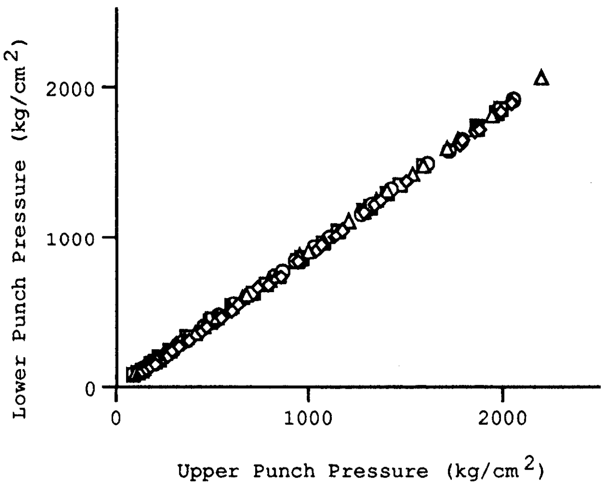

Fig. 6. Compression Pressure Plot of Upper Punch *vs.* Lower Punch

□, A; ○, B; △, C; ◇, D.

of linearity was designated as the maximum value of the correlation coefficient. D_0, D_a and D_b show the measured initial filling density, densification due to die filling and particle slippage and rearrangement, and the density contribution owing to particle movement and rearrangement before appreciable interparticle bonding takes place, respectively. D_a and D_b were calculated by the following equations,

$$D_a = 1 - e^{-A} \quad (3)$$

$$D_b = D_a - D_0 \quad (4)$$

With longer kneading times, D_0 became larger and D_b decreased. The initial filling was believed to be improved by the decreased amount of fine powder and increased particle diameter in the granules, both of which occurred as kneading progressed. The slope k indicated a pronounced change between granulation end points B and C. As the scanning electron micrographs in Fig. 3 show, granules A and B were composed of bulk powder and agglomerates, whereas granules C and D consisted of agglomerated granules alone. Thus, the compression process was considered to be greatly different between granules A and B and granules C and D. Generally the k value indicates the reciprocal yield pressure of material, so the materials showing higher k values are said to gain high consolidation strength by undergoing plastic deformation at relatively low pressure.[11] In the present study, however, granules B showing a minimum k value had the greatest tablet hardness after compression. It was assumed that agglomerates contained in these granules were fractured at relatively low compression pressure before the linear region of the Heckel plots and that plastic deformation and fragmentation of primary particles of bulk powder took place, because 1) granules B have the largest pore volume (Fig. 4), 2) the particles in these granules are coarsely bound together (Fig. 3), and 3) the lower limit of linearity is the highest (Table 2). In granules C and D, on the other hand, the agglomerates were densified and strengthened by longer kneading times, which led to plastic deformation and fragmentation of the agglomerates during the linear region of the Heckel plots. Thus, it was suggested that lower yields of granules than primary particles of drug powder might lead to larger k values for granules C and D.

The Cooper plots during tableting of granules A—D are shown in Fig. 8. The experimental values represented by symbols accorded well with theoretical ones indicated by solid lines, suggesting that the application of Cooper's equation was valid.

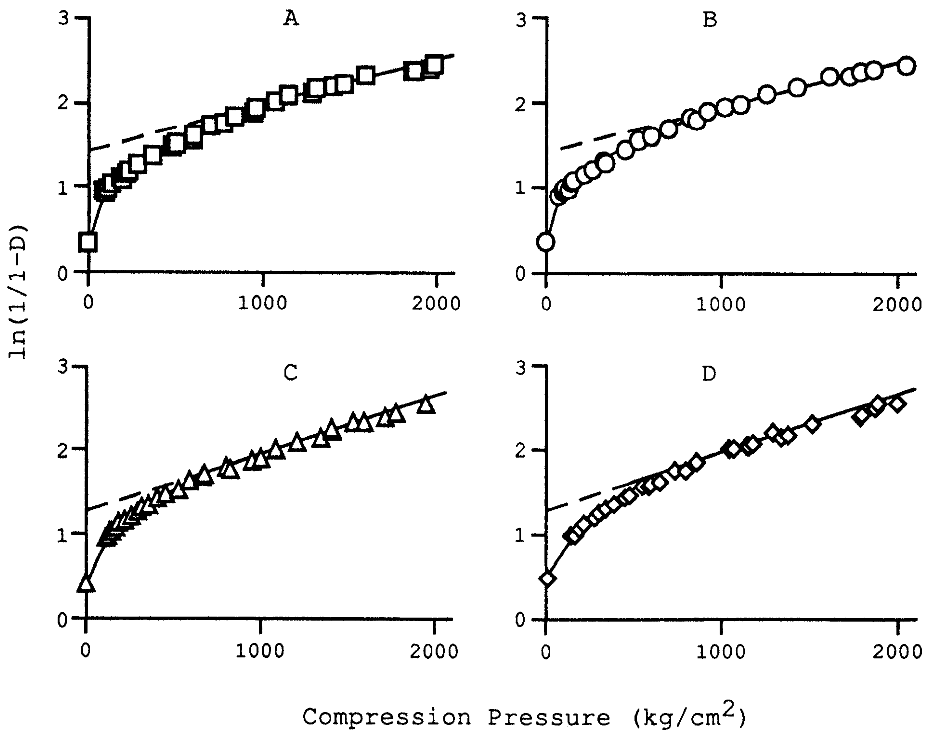

Fig. 7. $\ln(1/1-D)$ *vs.* Pressure for Granules.
□, A; ○, B; △, C; ◇, D.

Table 2. Values of k, A, D_0, D_a, D_b and Lower Limit of Linearity

Granule	k (kg/cm^2)$^{-1}$	A	D_0	D_a	D_b	Lower limit of linearity, kg/cm^2
A	5.56×10^{-4}	1.413	0.313	0.757	0.444	706.6
B	5.45×10^{-4}	1.414	0.330	0.757	0.427	822.1
C	6.78×10^{-4}	1.281	0.371	0.722	0.351	585.2
D	6.91×10^{-4}	1.281	0.413	0.722	0.309	521.5

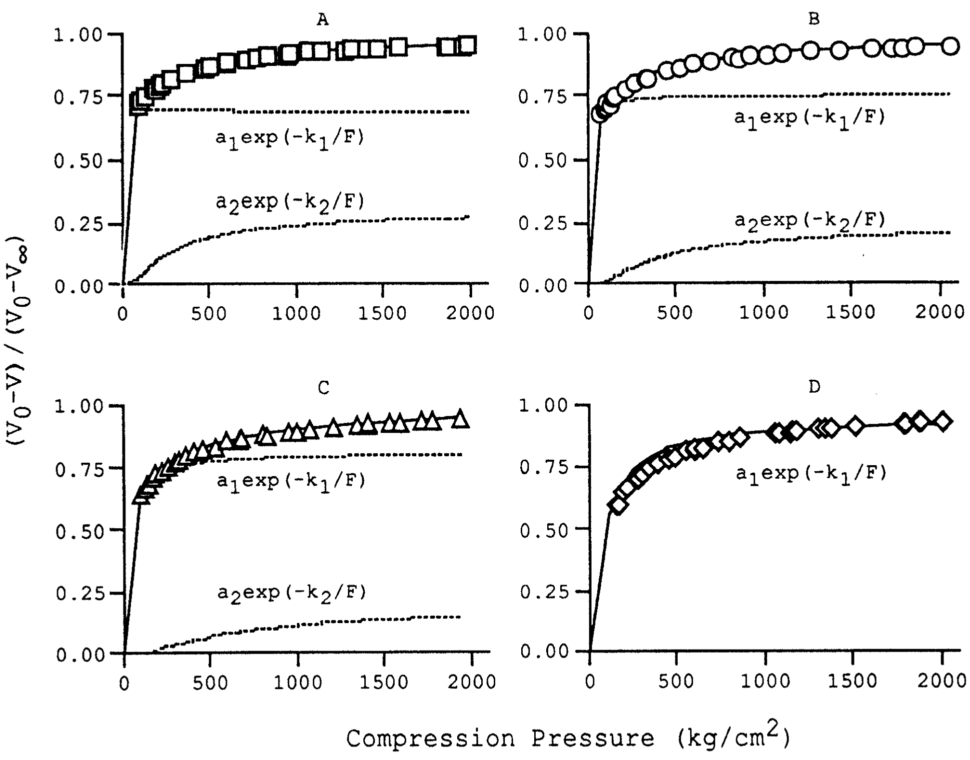

Fig. 8. Fractional Volume of Compression of Granules *vs.* Pressure Plots
□, A; ○, B; △, C; ◇, D.

Table 3. Values of Coefficients a_1, a_2, k_1 and k_2 of Granules Obtained at Each Granulation End Point

	a_1	a_2	a_1+a_2	k_1	k_2
A	0.68	0.30	0.98	−1.84	226.19
B	0.75	0.24	0.99	8.08	330.16
C	0.81	0.19	1.00	23.99	537.41
D	0.95	0.00	0.95	63.94	−0.56

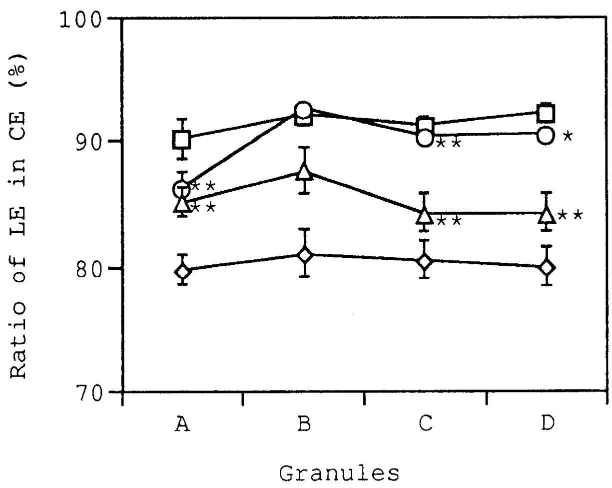

Fig. 9. Ratio of LE in CE

□, 500 kg/cm²; ○, 1000 kg/cm²; △, 1500 kg/cm²; ◇, 2000 kg/cm².

The coefficients of Cooper's equation are summarized in Table 3. As the kneading time became longer, the proportion of the large holes filled with particles by particle sliding became larger and that of small pores filled by deformation and fragmentation of particles became smaller. In addition, such processes were not observed with granules D, and the compression pressure at which such processes occur at the maximum probability was also higher. These results suggested that the voids were easily filled by particles through particle movement, plastic deformation and fragmentation at relatively low compression pressures in granules A and B. In granules C and D, in contrast, little plastic deformation and fragmentation took place because of large and compact agglomerates, though large holes tended to be filled. Thus, the filling of small voids is believed difficult. Next, the compressibility of the individual granules were compared by analyzing the compression energy applied to the powder layer. The ratio of the compression loss energy (LE) to the compression energy (CE) of granules B tended to have larger values and was statistically significant at 1000 and 1500 kg/cm² as shown in Fig. 9. It was suggested that the compression energy was efficiently consumed in the plastic deformation of granules giving the greatest tablet hardness.

Conclusion

The results of the present study demonstrated the following. In the granules prepared in a high speed mixer, densification due to particle rearrangement, plastic deformation and fragmentation tends to take place in those having larger pore volumes at lower compression force. Thus, the compression force is consumed efficiently for tablet formation, which results in high mechanical strength of tablets.

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