Studies on the Granulation Process of Granules for Tableting with a High Speed Mixer. II. Influence of Particle Size of Active Substance on Granulation[1,2]

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In the process of granulation for tableting using theophylline as a model drug, the power consumption pattern and the physical properties of the granules were examined with varied particle sizes of theophylline. During kneading of the physical mixtures containing these varied particle sizes into granules for tableting, the first peak of the power consumption curve declined with decreasing particle size of the physical mixtures and a second peak appeared for physical mixtures with smaller particle sizes. The optimal kneading end point for granules was at the end of the first peak for mixtures with larger particles and at the beginning of the second peak for those with smaller particles. The best granules for tableting prepared from individual physical mixtures at different end points had maximum pore volume and consisted of a mixture of similar size of porous loose agglomerates and bulk powder as reported previously. This inner structure of granules is assumed to induce plastic deformation and particle movement upon compression and to result in high mechanical tablet strength.

Key words granulation; granulation end point; power consumption; compression; pore size; high speed mixer

In the process of tablet preparation, the physical properties of granules and their compressibility into tablets in model experiments using lactose have been reported by Wikberg and Alderborn[3–6] and Zuurman *et al.*[7] However, little has been studied using a high speed mixer in the granulation process, the physical properties of granules or the compressibility of those granules into tablets. In our previous study[2] using theophylline as a model drug, we investigated the granulation process in a high speed mixer and reported that granules most suitable for tableting consisted of a mixture of small agglomerates and bulk powder having similar sizes to agglomerates and that such granules could be obtained by kneading up to a small first peak in the power consumption curve. The present paper reports the influence of different theophylline particle sizes on the pattern of a power consumption curve and on the physical properties of the resulting granules.

Materials and Methods

Materials Theophylline (Kanto Chemical Co., Inc., TH) was used as a model drug. The excipients included lactose monohydrate (DMV), corn starch (Nihon Shokuhin Kakou Co., Ltd.), hydroxypropyl cellulose (Nihon Soda Co., Ltd., HPC-SL®), croscarmellose sodium (Asahi Chemical Industry Co., Ltd., Ac-Di-Sol®) and magnesium stearate (Sakai Kagaku Co., Ltd.). Purified water was used as a binder medium. The formulation of theophylline tablets is shown in Table 1.

Preparation of TH Powders of Different Particle Sizes TH powders of 5 different particle sizes were prepared from small to large: TH-I, milled in a jet mill (Seisin Enterprise Co., Ltd., Co-Jet) milling air pressure of 3.5 kg/cm^2 and at a feeding rate of 100 g/min; TH-II, milled at a different feeding rate of 300 g/min; TH-III, that passed through sonic sieving equipment of 45—20 μm (Seishin Enterprise Co., Ltd., P-60); TH-IV, that passed through a 75—45 μm sieve; and TH-V, that passed through a 106—75 μm sieve. The mean particle diameter (D_{50}) and standard deviation (σ_g) of these powders and their physical mixtures (PM) before kneading are given in Table 2. Though TH-II and TH-III had the same D_{50} value, both powders were evaluated in the present experiment because of the large difference in σ_g value, *i.e.* particle size distribution.

Methods The overall procedure is schematized in Fig. 1.

Granulation TH (120 g), lactose monohydrate (106 g), corn starch (53 g) and hydroxypropyl cellulose (9 g) were mixed in a high speed mixer (Fukae Industrial Co., Ltd., LFS-GS-1J) for 30 s at 800 rpm of the main blade and 1000 rpm of the chopper. Each PM was kneaded under the same conditions with the addition of purified water at a rate of 15 ml/min. The whole granules thus obtained at individual end points were dried in a fluid bed dryer (Aeromatic AG, STREA-1), passed through an 850 μm sieve to remove coarse lumps, and mixed with croscarmellose sodium and magnesium stearate in a vinyl bag. Their water content was confirmed to be within the range of 2 ± 0.3% by JP loss on drying method (5 g, 90 °C, 5 min, Mettler, PM480).

Tableting The granules were compressed into tablets weighing 200 mg at four compression levels of 500 kg/cm^2, 1000 kg/cm^2, 1500 kg/cm^2, and 2000 kg/cm^2 with a single type tableting machine equipped with a pair of load cells (Okada Seiko Co., Ltd., N30E) using 8 mm biflat punches.

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

Table 1. Formulation of Tablet

Ingredient	Amount	
	mg/tab.	%
Theophylline	80.0	40.0
Lactose monohydrate	70.6	35.3
Corn starch	35.4	17.7
Hydroxypropyl cellulose	6.0	3.0
Croscarmellose sodium	6.0	3.0
Magnesium stearate	2.0	1.0

Table 2. Mean Particle Diameter and Standard Deviation for Physical Mixture and Theophylline

	PM		TH	
	Mean (μm)	S.D.	Mean (μm)	S.D.
PM-I	16.6	3.4	3.0	2.2
PM-II	19.7	3.6	30.8	5.7
PM-III	20.4	3.0	30.8	2.5
PM-IV	28.8	2.7	37.1	2.7
PM-V	29.9	2.8	39.8	2.8

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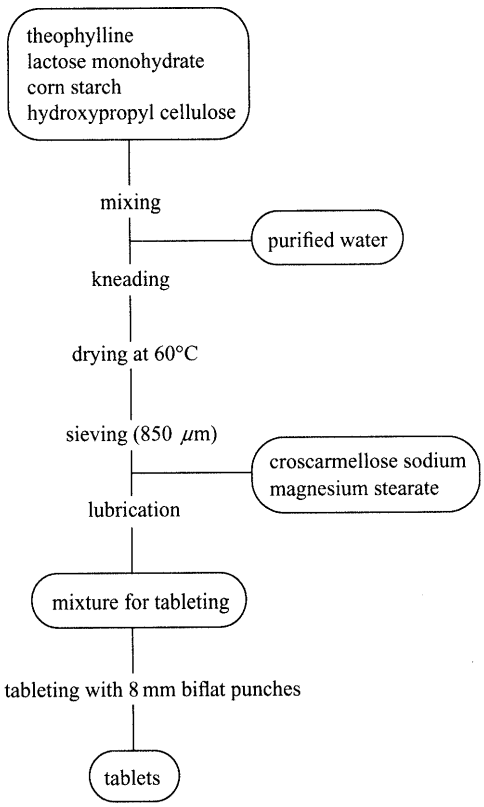

Fig. 1. Method of Preparation for Theophylline Tablets

recorder (Yokogawa, AR 1100A).

Measurement of Physical Properties The angle of repose was measured with a Powder Tester® (Hosokawa Micron Co.) using a disk 80 mm in diameter. The apparent density was also measured with the Powder Tester® using a 100 ml cup. The particle size distribution of the TH, PM and granules was determined with a laser diffraction analyzer (Sympatec, H & R RODOS-SR), and D_{50}, σ_g, and correlation coefficient, r, were calculated by fitting to the logarithmico-normal distribution using logarithmico-normal probability paper. Tablet hardness was measured for 10 tablets with a tablet hardness tester (Erweka, TBH28) at a loading speed of 0.5 mm/s. Friability of tablets was determined by the method of Funakoshi *et al.*[8] using 20 tablets. Disintegration time of tablets was measured according to the JP XII. Pore volume of the granules was measured with a mercury porosimeter (Quantachrome Co., Autoscan-33) and calculated by Washburn's equation[9]:

$$Pr = -2\varphi\cos\theta$$

where P is the pressure, r is the pore radius, φ is the surface tension of mercury and θ is the contact angle of mercury with the solid material. φ and θ were regarded as 480 dyn/cm and 140°, respectively.[9] All of these experiments were done at room temperature (25±2 °C) and 50±5% RH.

Results and Discussion

Influence of Power Consumption Curve As shown in Fig. 2, the power consumption curves for 5 kinds of PM showed almost the same pattern; *i.e.*, the power consumption value increased gradually from the start of kneading and at the final stage rose steeply, then fell. The first peak became smaller as the particle size decreased from PM-V to PM-I, and the second peak appeared for PM-I and II with smaller particle sizes. Then, four end points of kneading were designated to evaluate the suitability of the granules for tableting: A, the rising point of the first peak (granule A); B, end of the first peak (granule B); C, rising point of the second peak (granule C); and D, end of the second peak (granule D). Table 3 shows the kneading time and the amount of purified water added up to each end point.

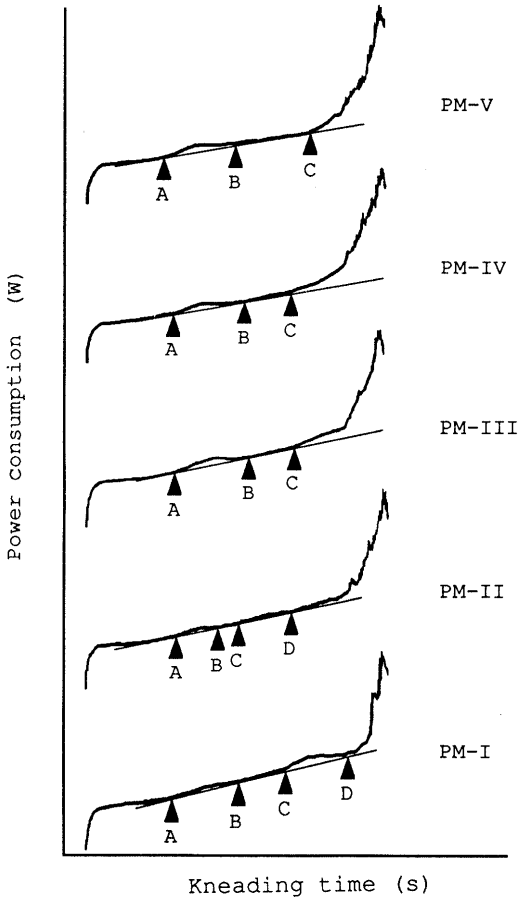

Fig. 2. Power Consumption Curve During Kneading

Table 3. Kneading Time and Purified Water Added up to Each End Point of Kneading

		A	B	C	D
PM-I	Kneading time (s)	70	131	206	262
	Added purified water (ml)	18	33	52	66
PM-II	Kneading time (s)	75	137	173	228
	Added purified water (ml)	19	35	43	57
PM-III	Kneading time (s)	74	144	251	—
	Added purified water (ml)	19	36	63	—
PM-IV	Kneading time (s)	55	157	228	—
	Added purified water (ml)	14	39	57	—
PM-V	Kneading time (s)	62	126	241	—
	Added purified water (ml)	16	32	60	—

Influence on Tablet Properties The hardness of the tablets compressed from the granules obtained at each end point is shown in Fig. 3. In PM-I, granules A and B were not compressed due to poor flowability. The maximum hardness was obtained with tablets C from PM-I and II and tablets B from PM-III, IV and V at each compression force. The friability of the tablets compressed from the granules obtained at each end point is shown in Fig. 4. Tablets A exhibited high values at individual compression forces, indicating that little agglomeration had occurred at end point A. Friability was minimum for tablet C from

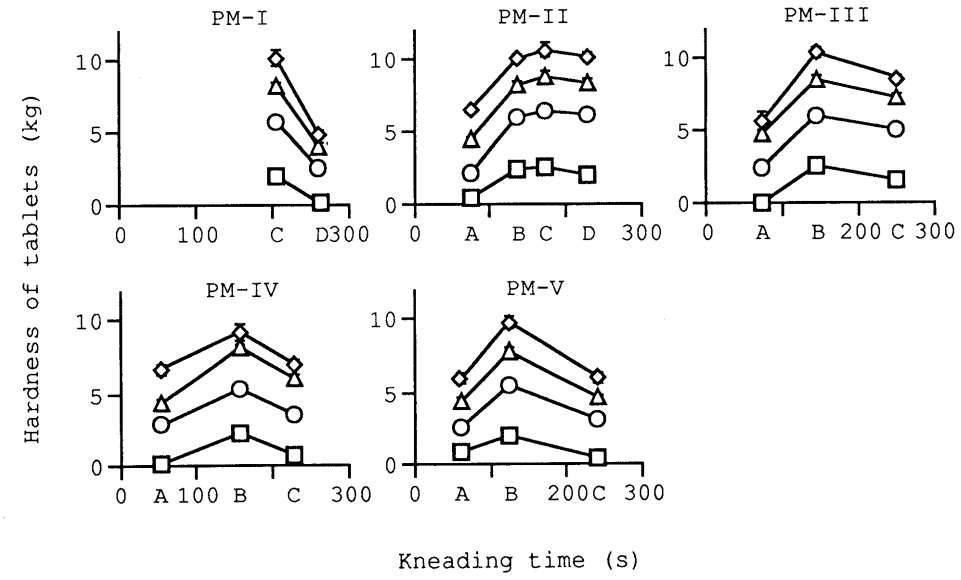

Fig. 3. Hardness of Tablets Compressed at 4 Compression Levels

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

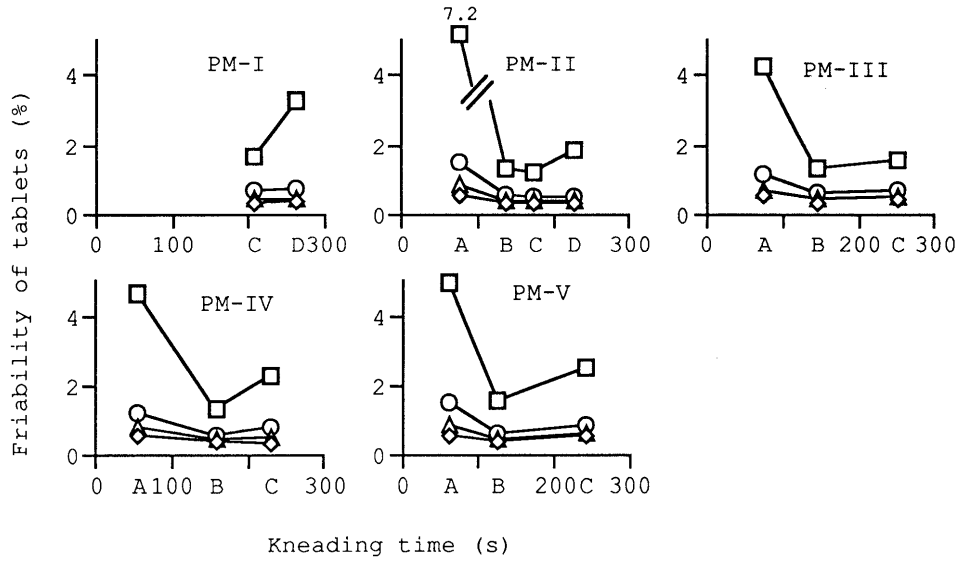

Fig. 4. Friability of Tablets Compressed at 4 Compression Levels

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

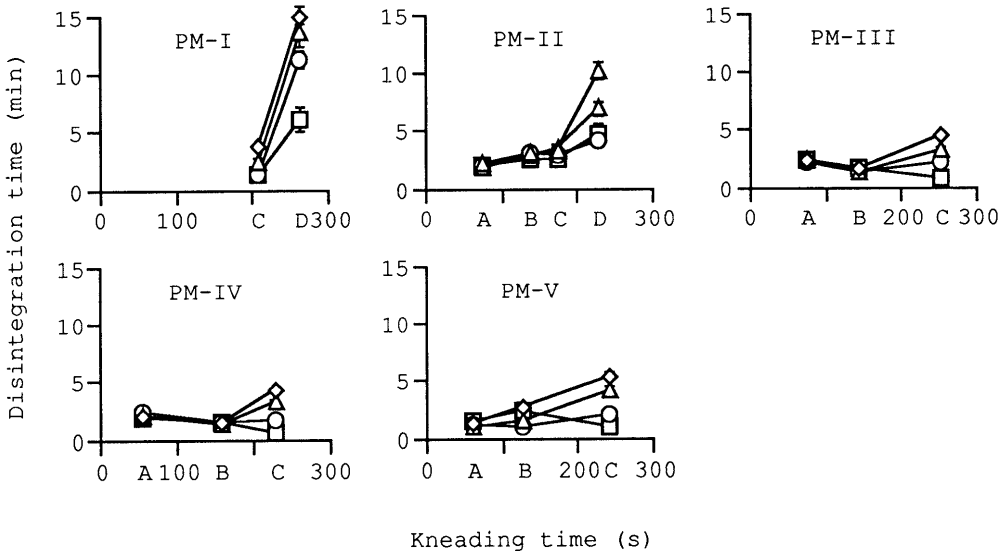

Fig. 5. Disintegration Time of Tablets Compressed at 4 Compression Levels

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

PM-I and II and for tablet B from PM-III, IV and V at 500 and 1000 kg/cm^2. Influence of varied particle sizes of PM on tablet friability was not obvious for the tablets compressed at 1500 and 2000 kg/cm^2. As mentioned above, high mechanical strength of tablets in hardness and friability was observed at point C for PM-I and II with smaller particles and point B for PM-III, IV and V with larger particles.

The disintegration time of tablets is shown in Fig. 5. Tablets A—C disintegrated within 5 min irrespective of compression force or granulation end point. However, tablets D from PM-I and II consisting of smaller particles exhibited longer disintegration times than tablet C of PM-III, IV and V which had been kneaded for similar period. This difference was thought to be due to tablets generally consisting of smaller particles requiring many more disintegrators, as reported in our previous paper on

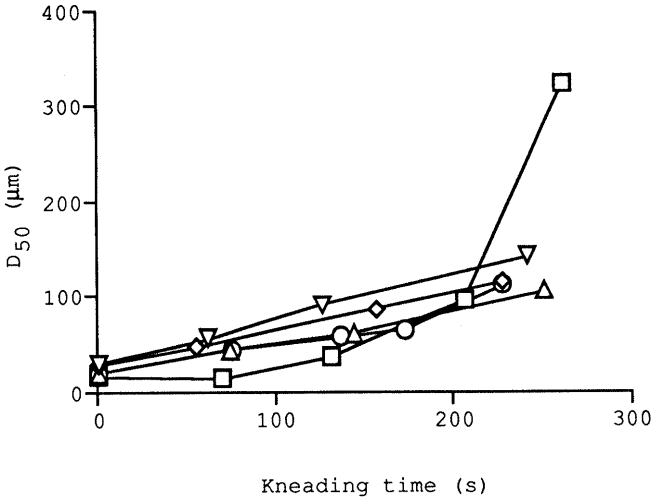

Fig. 6. Changes of D_{50} during Kneading
□, PM-I; ○, PM-II; △, PM-III; ◇, PM-IV; ▽, PM-V.

Table 4. Mean Particle Diameter, Standard Deviation and Correlation Coefficient of Particle Size Distribution against the Logarithmico-Normal Distribution of Physical Mixtures and Granules

		D_{50} (μm)	σ_g	r
PM-I	PM	14	3.0	0.992
	A	17	3.6	0.990
	B	36	4.8	0.985
	C	95	3.3	0.998
	D	324	2.0	0.971
PM-II	PM	20	3.6	0.984
	A	44	2.7	0.998
	B	57	2.7	0.994
	C	64	2.7	0.995
	D	112	2.8	0.987
PM-III	PM	20	3.0	0.969
	A	44	2.4	0.998
	B	60	2.3	0.997
	C	106	2.8	0.994
PM-IV	PM	29	2.8	0.970
	A	47	2.8	0.997
	B	86	2.5	0.994
	C	115	2.5	0.989
PM-V	PM	30	2.8	0.977
	A	55	3.0	0.996
	B	90	2.2	0.990
	C	142	2.2	0.978

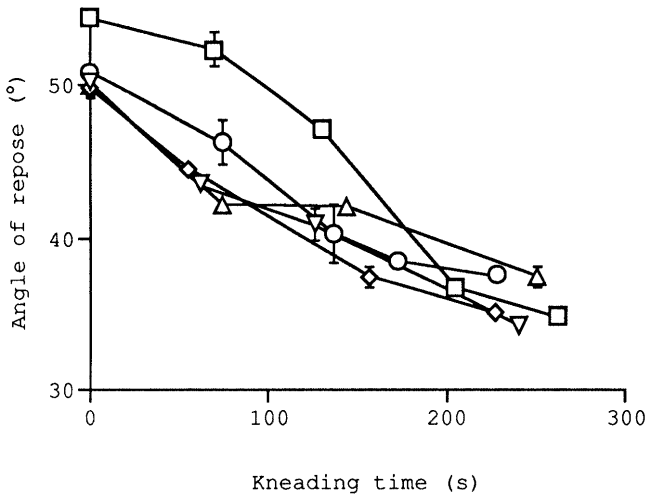

Fig. 7. Changes of Angle of Repose during Kneading
□, PM-I; ○, PM-II; △, PM-III; ◇, PM-IV; ▽, PM-V.

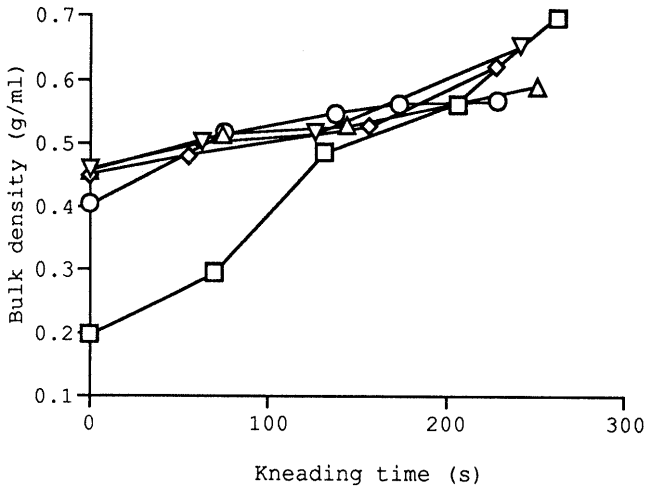

Fig. 8. Changes of Bulk Density during Kneading
□, PM-I; ○, PM-II; △, PM-III; ◇, PM-IV; ▽, PM-V.

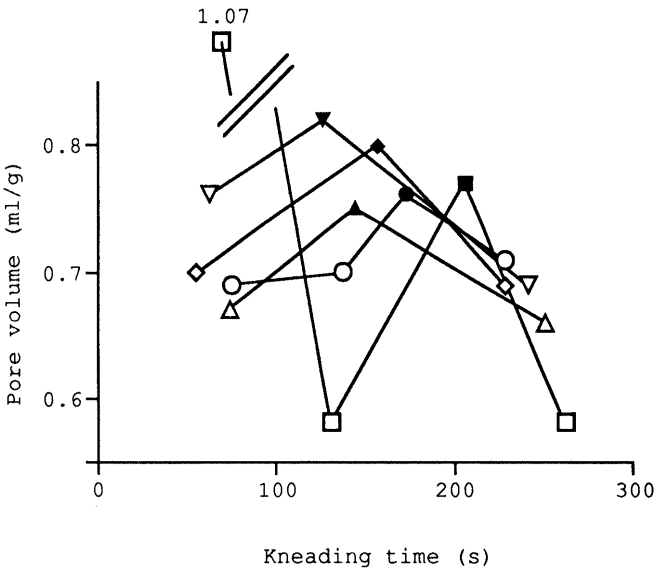

Fig. 9. Changes of Pore Volume during Kneading
□, PM-I; ○, PM-II; △, PM-III; ◇, PM-IV; ▽, PM-V. ■, PM-I C; ●, PM-II C; ▲, PM-III B; ◆, PM-IV B; ▼, PM-V B.

critical disintegrator amount.[10]

Based on these results, the granules C of PM-I and II and granules B of PM-III, IV and V were considered preferable for tableting. The physical properties of these granules were then examined to confirm their suitability.

Influence on the Physical Properties of Granules Figure 6 shows the D_{50} value transition for each PM during kneading. This D_{50} value increased when kneading time was lengthened and when the amount of added purified water increased. The increasing ratio in D_{50} value for PM-I of the smallest particle size, during the early stage of kneading was lower than other PM. It was supposed that the added binding solution was inadequate to cover the large specific and total surface areas of all small particles as Lindberg and Joensson[11] and Paris and Stamm[12] reported. The D_{50}, σ_g and r values for all PM and granules obtained by fitting to the logarithmico-normal distribution are shown in Table 4. The particle size distribution of the PM and granules showed very good approximations to the logarithmico-normal distribution. The granule best suited to tableting, *i.e.* granule C of PM-I and II and granule B of PM-III, IV and V, had about 60—

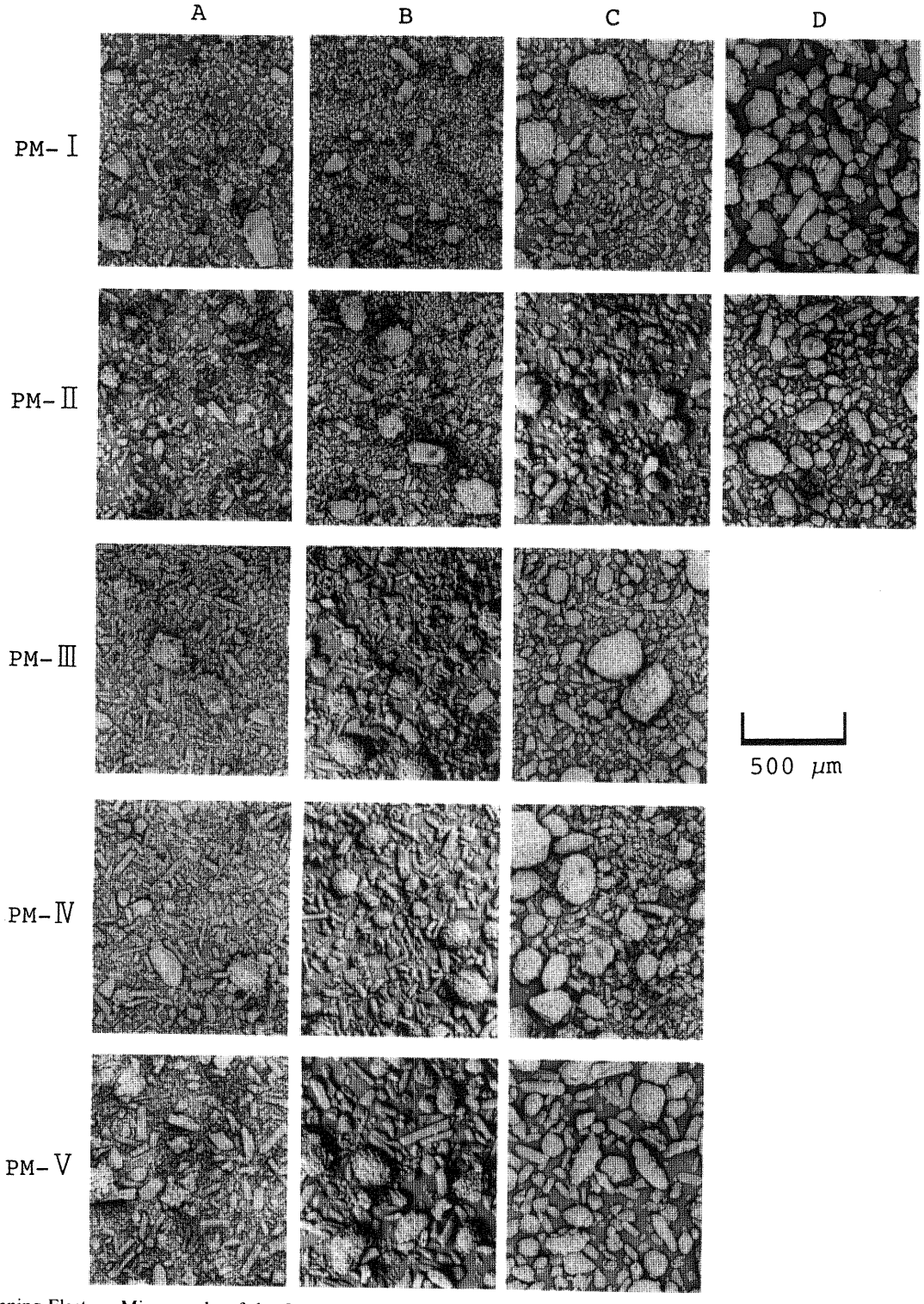

Fig. 10. Scanning Electron Micrographs of the Grenules from Individual PM

100 μm of D_{50} with a tendency toward small σ_g values. The angle of repose decreased with the passage of kneading time, and the decrease was remarkable for PM-I (Fig. 7). Presumably this can be attributed to the increase in granule diameter by ongoing kneading. The apparent density of the PM increased as kneading went on and a marked increase was observed with PM-I (Fig. 8). The pore volumes of the individual granules are shown in Fig. 9. In the present granulation process, the pore volume was thought to undergo the following transition: at the initial stage of kneading, the extragranular pores accounted for most of the pore volume; with successive kneading, the intragranular pore volume increased by the aggregation of particles in parallel with a decrease of the extragranular pores; with further kneading, the pore volume rose to a maximum value of intragranular pores by formation of loose agglomerates of smaller particles; and then the pore volume decreased by densification. Granule A of PM-I consisting of fine particles appeared to have the highest pore volume; however, it was suggested that extragranular pores were involved in the calculation of pore volume because there was little agglomeration at this stage. As it is the intragranular pore volume that affects compressibility, maximum pore volume was obtained with the granules at end point C for PM-I and II and at end point B for PM-III, IV and V. These granules, B and C, showed the highest mechanical strength upon tableting as stated in the previous paragraph. Increased intragranular porosity reportedly provokes higher tablet hardness[7] and it is desirable that granules for tableting be mechanically locked together and easily deformed during the compression process.[13] It is speculated that high mechanical tablet strength would be obtainable with granules having large pore volume and a loose structure, because they easily undergo plastic deformation which results in formation of a uniform internal tablets structure during compression. Figure 10 shows scanning electron micrographs of the granules from the individual PM kneaded until the individual end points in the present experiment. The granules most appropriate for tableting were granules C of PM-I and II and granules B of PM-III, IV and V, all of which consisted of a mixture of similar sizes of agglomerates with loose structures and bulk powder. Poor agglomeration of smaller particles and formation of densified large granules were observed before and after these optimal times, respectively.

Conclusion

During kneading of physical mixtures containing theophylline particles of various sizes into granules for tableting, the first peak of the power consumption curve declined with decrease in particle size of the physical mixtures and a second peak appeared for the physical mixtures of smaller particle sizes. The optimal kneading end point for granules to be tableted was at the end of the first peak for the mixture of larger particles and at the beginning of the second peak for that of smaller particles. The best granules for tableting at each kneading end point from the individual physical mixtures had maximum pore volume and consisted of a mixture of similar size of porous loose agglomerates and bulk powder as reported previously.[2] This inner structure of granules is supposed to induce plastic deformation and particle movement upon compression and to result in high mechanical tablet strength.

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