Studies on the Granulation Process of Granules for Tableting with a High Speed Mixer. I. Physical Properties of Granules for Tableting

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Several kinds of theophylline granules were prepared by monitoring the power consumption of a high speed mixer while compressing them into tablets. The physical properties of the granules and their tablets were evaluated in order to investigate the optimal physical properties and granulation conditions for tableting. As a result, the granule consisting of a mixture of small agglomerates and bulk powder of similar sizes demonstrated the most favorable physical properties for tableting. Its granulation end point was at the end above the first small peak of the power consumption curve.

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

Many studies have been done on the granulation process regarding manufacting the granule preparations using high speed mixers. Reportedly, the amount of binder solution and the rotation speed of a main blade affect the growth rate and densification of granules,[1-3] and the necessary amount of binder solution depends on the solubility of the materials in water.[4] The granulation process can be monitored based on the consumed electric power of a main motor, which changes depending on the added amount of binding solution.[5] Terashita *et al.* have reported that the granulation end point can be decided by monitoring the power consumption in the mixing granulation of dense spherical granules.[6]

On the other hand, little has been reported on the manufacturing process of granules for tableting, such a process might differ from the manufacturing process of granule preparation. With the aim of finding the suitable physical properties of granules for tableting, the present study was undertaken to decide the end point in the granulation process from a physical mixture until coarse lumps of wet mass were formed in a high speed mixer by monitoring the power consumption of a main motor.

Materials and Methods

Materials Theophylline (Kanto Chemical Co., Inc.) 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 I.

Methods Granulation: The preparation flow is shown in Fig. 1. Theophylline (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. The mixture was kneaded under the same conditions with the addition of purified water at a rate of 15 ml/min. Six batches of granules were prepared up to different end points by monitoring the power consumption.

The granules thus obtained were dried with a fluid bed dryer, passed through an 850 μm sieve to remove coarse lumps, and mixed with croscarmellose sodium and magnesium stearate in a vinyl bag.

Tableting: The granules were compressed into tablets of 200 mg in weight at four compression levels of 500, 1000, 1500, 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: During the kneading process, the power consumption was monitored over time with a power converter (Elphy Automation Japan, GS-VFD Co., Ltd.) and an analyzing recorder (Yokogawa, AR 1100A).

Measurement of Physical Properties Particle Diameter and True Density of Ingredients: The particle diameter and true density of each

TABLE I. Formulation of Theophylline Tablet

Ingredient	Amount (mg/tablet)
Theophylline	80.0
Lactose monohydrate	70.6
Corn starch	35.4
Hydroxypropyl cellulose	6.0
Croscarmellose sodium	6.0
Magnesium stearate	2.0
Total weight	200.0

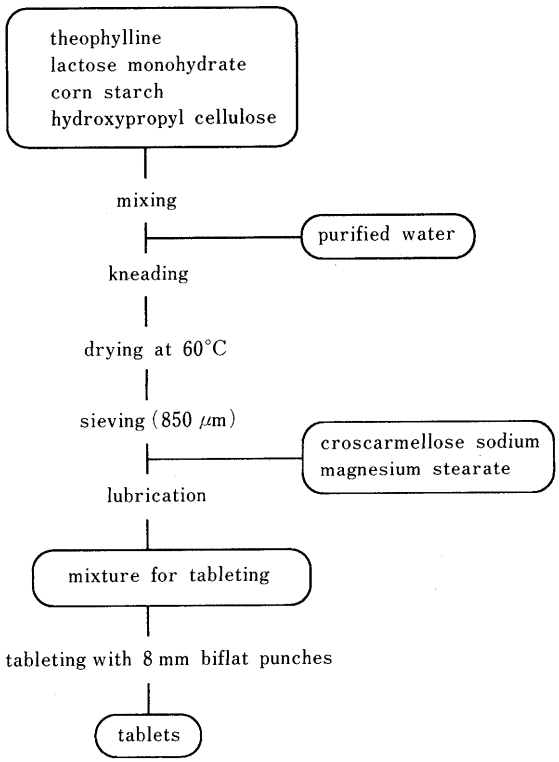

Fig. 1. Preparation Method for Theophylline Tablets

ingredient were measured with a laser diffraction analyzer (Sympatec, H & R Rodos-SR) and an air comparison pycnometer (Toshiba-Beckman Co., Ltd., model 930), respectively.

Evaluation of Physical Properties Angle of Repose: The poured angle of repose was measured with a Powder tester® (Hosokawa Micron Co.) using a disk 80 mm in diameter.

Apparent Density: The apparent density was also measured with a Powder tester® using a 100 ml cup.

Water Content: The water content was measured by the JP XII loss on drying method.

Particle Size Distribution of the Granules: The particle size distribution of the granules was measured by the sieve method (Seishin Enterprise Co., Ltd., Robot shifter, RPS-85). The mean particle diameter, D_{50}, and standard deviation, σ_g, were calculated from the accumulated weight on the sieve and the particle diameter.

Hardness of Tablets: The hardness of 10 tablets of each kind was measured with a tablet hardness tester (Erweka, TBH28) at a loading speed of 0.5 mm/s.

Friability: Friability was determined by the method of Funakoshi *et al.*[7] using 20 tablets of each kind.

Disintegration Time: The disintegration time was measured according to the JP XII.

Pore Size Distribution of Granules and Tablets: The pore size distribution of the granules and the tablets was measured with a mercury porosimeter (Quantachrome Co., Autoscan-33) and calculated by Washburn's equation[8]:

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

where P is the pressure; r, the pore radius; φ, the surface tension of mercury, and θ, 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 a room temperature of 23—26 °C, 42—54% relative humidity.

Results and Discussion

Preparation of Granules The particle size and true density of the ingredients are summarized in Table II.

The power consumption curve during the kneading is depicted in Fig. 2. It was divided into 4 stages by the shape of the curve: the initial steady stage (I), the stage showing a small peak (II), the next steady stage (III) and the final stage (IV) where the power consumption rose steeply and then fell. According to the power consumption curve, the points of A from initial steady stage, B at the first small peak, C from the 2nd steady stage and D, E and F from the final stage were chosen as the end points to evaluate the suitability of the granules for tableting. Table III shows the amount of purified water added and the kneading time up to each end point.

Physical Properties of the Tablets The hardness, friability and disintegration time of the tablets compressed from the granules obtained at each end point are shown in Figs. 3—5, respectively. Granules E and F were not compressed into tablets because they could not pass through an 850 μm sieve due to their large particle diameters (2—4 mm).

The maximum tablet hardness and minimum friability were obtained with tablets B, and the disintegration time was the shortest for tablets A and B at each compression force. The disintegration time was delayed for tablets C and D when the compression force was raised, but tablets A and B were hardly affected by compression force. The tablets compressed at 500 kg/cm^2 disintegrated within an extremely short time and were supposed to be poor in mechanical strength, such as hardness and friability.

Table IV shows the weight deviation of tablets A to D. All tablets met the requirement of the JP XII weight variation test and the deviation was very small particularly, for tablets B and C.

TABLE II. Particle Diameter and True Density of Ingredients

Ingredient	Particle diameter (μm ($\pm$S.D.))	Density (g/ml)
Theophylline	37.7 (2.38)	1.48
Lactose monohydrate	26.0 (6.08)	1.52
Corn starch	13.5 (1.55)	1.48
Hydroxypropyl cellulose	74.5 (2.44)	1.22
Croscarmellose sodium	41.7 (1.96)	1.59
Magnesium stearate	3.5 (2.57)	1.08

$n=3$.

TABLE III. Kneading Time and Added Purified Water at Each End Point of Kneading

	A	B	C	D	E	F
Kneading time (s)	38	139	197	240	293	307
Purified water added (ml)	9	34	48	58	71	75

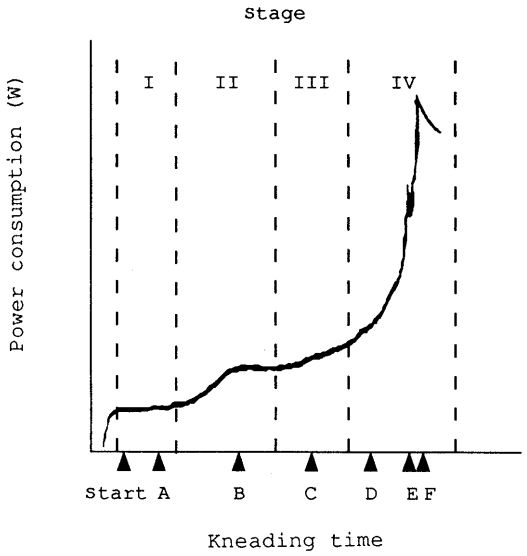

Fig. 2. Power Consumption Curve during Kneading

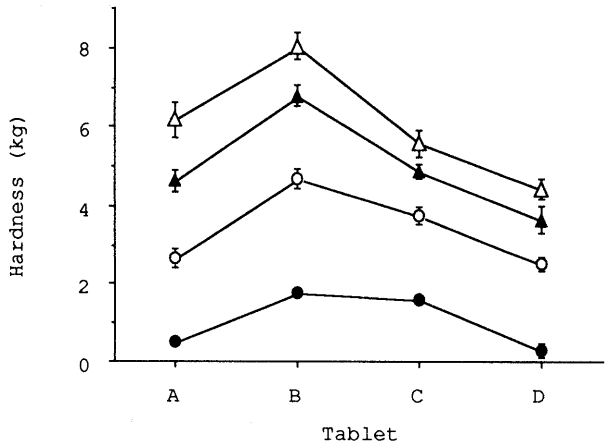

Fig. 3. Hardness of Tablets Compressed at 4 Compression Levels
●, 500 kg/cm^2; ○, 1000 kg/cm^2; ▲, 1500 kg/cm^2; △, 2000 kg/cm^2.

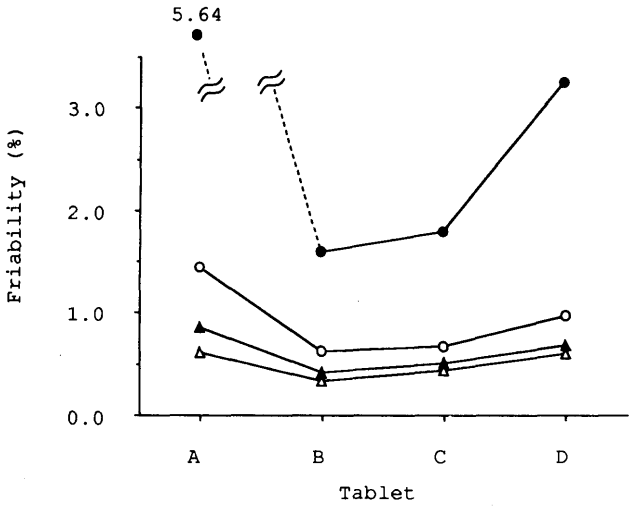

Fig. 4. Friability of Tablets Compressed at 4 Compression Levels
●, 500 kg/cm²; ○, 1000 kg/cm²; ▲, 1500 kg/cm²; △, 2000 kg/cm².

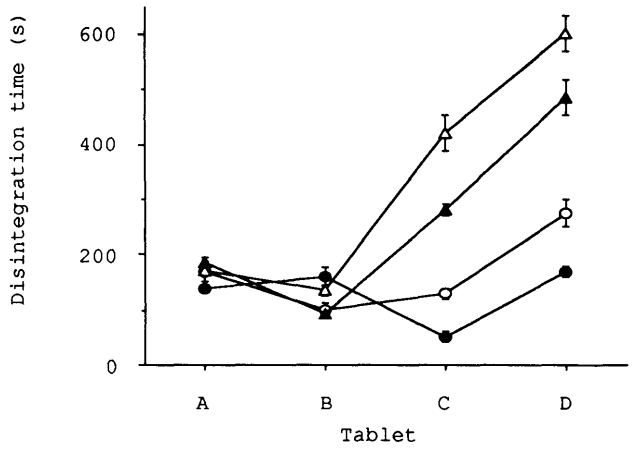

Fig. 5. Disintegration of Tablets Compressed at 4 Compression Levels
●, 500 kg/cm²; ○, 1000 kg/cm²; ▲, 1500 kg/cm²; △, 2000 kg/cm².

According to the mechanical strength and disintegration time of the tablets, granule B was considered to be most suitable for tableting in the present formulation. Since the mechanical strength of tablets is considered to be closely related with the internal structure of the tablets, the internal structure of the tablets and the physical properties of the granules were examined to confirm the suitability of granule B to tableting.

Physical Properties of Granules and Internal Structure of Tablets Figure 6 shows the scanning electron micrographs of the physical mixture before kneading, and granules A to F. Agglomeration of the particles was hardly

TABLE IV. Standard Deviation of Tablet Weight

	500 kg/cm²	1000 kg/cm²	1500 kg/cm²	2000 kg/cm²
A	1.847	1.429	2.039	2.417
B	0.812	0.750	0.952	0.564
C	0.929	0.579	0.587	0.942
D	1.426	0.922	1.306	1.226

$n = 20$.

TABLE V. Physical Properties of Physical Mixture before Kneading and Granules

	D_{50} (μm ($\pm\sigma_g$))	Angle of repose (degree)	Apparent density (g/ml)	Water content (%)
Mixture	28 (2.0)	50.4	0.501	2.43
A	58 (2.4)	49.3	0.477	2.11
B	115 (4.4)	42.9	0.503	2.33
C	210 (3.3)	38.7	0.565	2.27
D	440 (4.9)	36.9	0.628	2.74
E	2100 (1.9)	—	—	3.03
F	3700 (1.8)	—	—	3.87

$n = 3$.

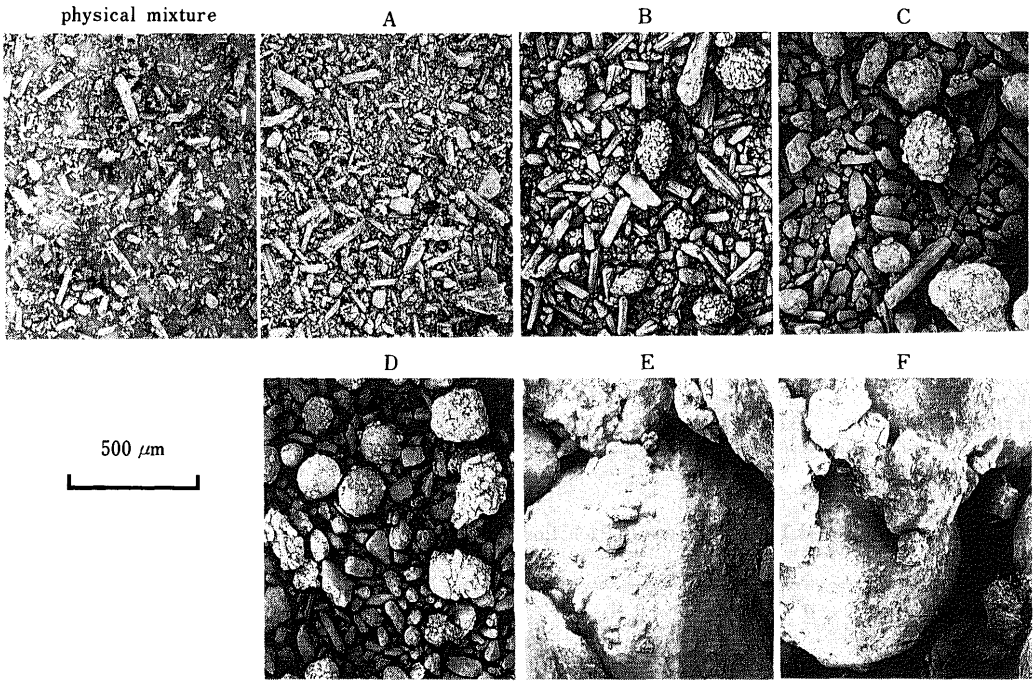

Fig. 6. Scanning Electron Micrographs of Physical Mixture and Kneaded Materials

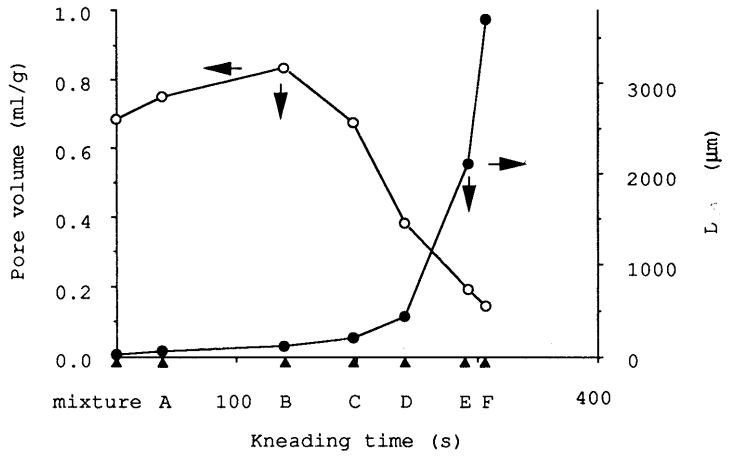

Fig. 7. Transition of Pore Volume and D_{50} of Physical Mixture and Kneaded Materials
○, pore volume; ●, particle size.

observed at point A due possibly to a lesser amount of added purified water. Granule B consisted of about 100 μm of agglomerates of fine particles and a bulk powder of similar sizes. Granule growth was observed from point C to point D as the amount of binder solution increased. Furthermore, coarse lumps were formed due to the secondary agglomeration of the granules at points E and F.

Table V shows the particle size distribution, angle of repose, apparent density and water content of the physical mixture and granules A to F. The D_{50} value increased with prolongation of the kneading time, and in particular, granules E and F showed higher D_{50} values due to the formed coarse lumps. The angle of repose decreased as the kneading continued, which is presumed to be attributed to the increasing particle diameter and ongoing spherical-lization of the granules by wet massing. The apparent density decreased in the granules at point A, but then, increased when the kneading time was expanded. This decreasing of apparent density at point A was considered to be caused by the formation of a loose agglomeration of part of the ingredients at the beginning of the kneading. The water content of granules A to D used for tableting was almost equal.

Figure 7 shows the transition in pore volume (mercury intrusion method) and D_{50} of granules A to F. The longer the kneading time, the larger the D_{50} value of the granules. On the other hand, the pore volume increased in the order of the physical mixture, granule A and granule B, and decreased in the subsequent granules. The increase in pore volume at points A and B was considered to be caused by the formation of loose agglomerates with part of ingredients, and the effect of the densification by tumbling was not yet revealed at this stage.

The pore size distribution of the physical mixture and granules A to F is shown in Fig. 8 to further investigate the change in the pore volume. In the physical mixture, the pores of about 2—10 μm in diameter, thought to be interparticle pores, accounted for 90% of the total pore volume. As the kneading went on, pore of about 10 μm in diameter increased in granules A and B. The pore size decreased remarkably by further kneading to points C, D, E and F, owing possibly to densification by tumbling during the kneading.

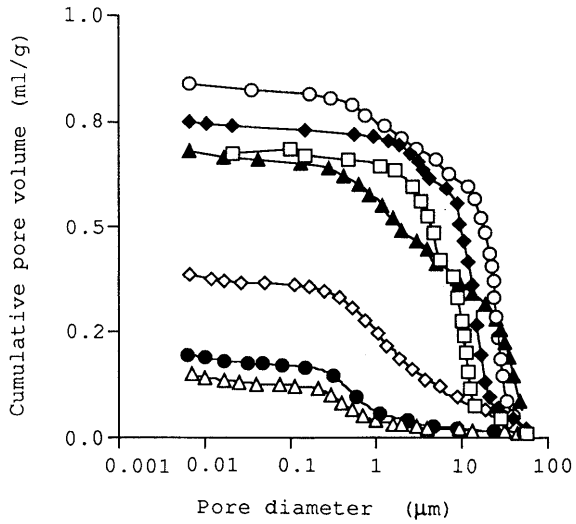

Fig. 8. Pore Size Distributions in Physical Mixture and Kneaded Materials
□, mixture; ◆, A; ○, B; ▲, C; ◇, D; ●, E; △, F.

TABLE VI. Pore Diameter and Cumulative Percentage of Pore Volume at the Point of Inflection

Compression force	Diameter percentage	A	B	C	D
500 kg/cm^2	μm	4.0	3.2	3.4	4.1
	%	4.9	3.0	3.8	8.2
1000 kg/cm^2	μm	2.2	1.6	1.3	2.0
	%	9.3	3.1	6.6	15.5
1500 kg/cm^2	μm	1.2	1.0	1.0	1.3
	%	13.0	3.9	6.3	16.5
2000 kg/cm^2	μm	0.8	0.9	0.4	0.2
	%	5.0	2.6	1.3	9.3

The pore size distribution of the tablets compressed under varied compression forces is shown in Fig. 9. At each compression force, the point of inflection of the pore distribution curve was observed with pore diameters of about 1—4 μm.

Maekawa *et al.* reported that the cracking of tablets

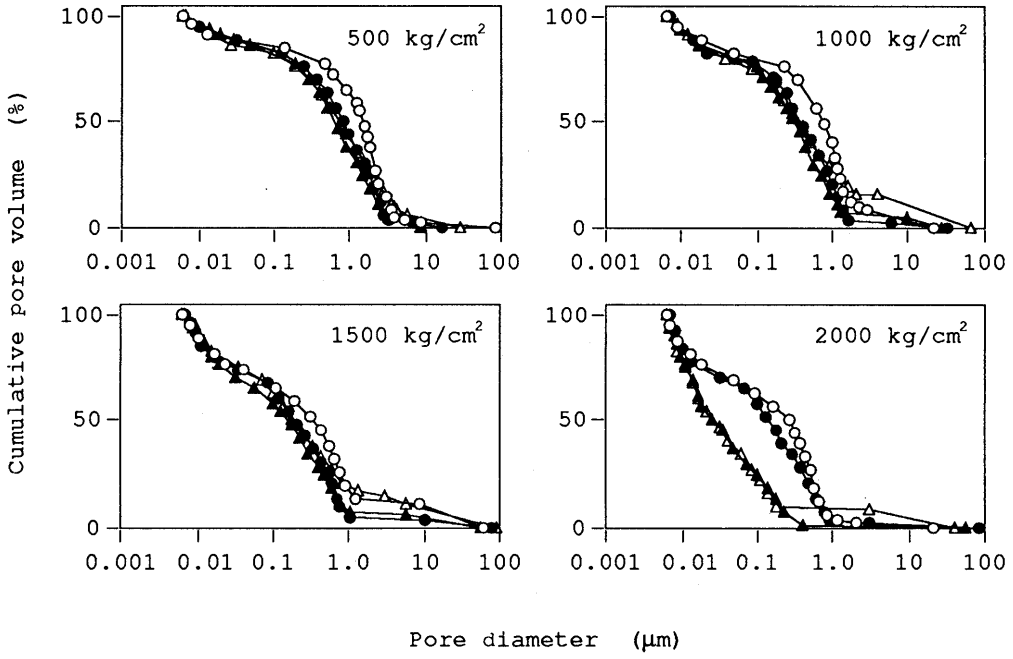

Fig. 9. Pore Size Distribution in Tablets Compressed at 4 Compression Force Levels
○, A; ●, B; ▲, C; △, D.

occurred at a weak part of the internal structure.[10] Funakoshi *et al.* also stated that the capping of tablets was closely related to the relaxation of stress due to relatively large pores in tablets.[11] In our previous study,[12] a conjecture similar to Funakoshi's was held that the decline in mechanical strength of the tablets might be caused by large pores, ranging from 4—10 μm. Table VI shows the pore diameter and the cumulative percentage of pore volume at the point of inflection given in Fig. 9. In tablets A and D, pores larger than those at the point of inflection occupied a larger part than in tablets B and C. Compared with tablets B and C, tablets A and D contained many pores, which might result in cracks, and had high structure sensitivity. These results suggested that mechanical strength was diminished in tablets A and D.

Conclusion

The granules obtained at point B, the first peak in the power consumption curve, is supposed to be most suitable for tableting, since the tablets compressed from granule B indicated better properties in weight variation, tablet hardness, friability and disintegration time. These granules consisted of not the agglomerates alone, but a mixture of small agglomerates and bulk powder of similar sizes. The mechanical strength of the tablet was favorable because of a smaller quantity of large pores which cause cracks in tablets.

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