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EFFECT OF AMOUNT OF ADDED WATER DURING EXTRUSION-SPHERONIZATION PROCESS ON PHARMACEUTICAL PROPERTIES OF GRANULES

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ABSTRACT

In order to clarify mechanism of spherical granulation using a spheronizer and its pharmaceutical properties, crystalline lactose, corn starch and theophylline were used as pharmaceutical powders, with an aqueous solution of hydroxypropylcellulose as a binder. The granules were prepared by extruding wet masses containing various amounts of water (150, 200 and 250 ml/kg). They were treated in a spheronizer for 0-10 min, and dried at 60°C for 12 min in a fluidized-bed dryer. The elongation ratio was used as an index of spheronization, and the arithmetic mean granules diameter were used as mean daimeter. The elongation ratio of the granules decreased from 5-8 to around 1.5 after 2-min spheronization. The angle of repose of spheronized granules was lower than that of the intact granules, suggesting that they had better flowability. The yield of granules obtained from addition of 250 ml/kg of water was much higher than that by adding 150 ml/kg of water, indicating that the former had a larger mean particle size than the latter. The result of mercury porosimetry

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showed that the amount of water in the binder solution affected the internal porosity of the spherical granules; it increased with decreasing internal porosity. The friability test suggested that the weight loss after the test was affected by the amount of water added, and it increased with decreasing amounts of water. Therefore, the quantity of water added to the granules influenced the mechanical strength of the granules. On the other hand, the hardness of tablets prepared by using a compressor at 2500 kg/cm^2 seemed to increase with a decrease in the mechanical strength of intact granules. And, tablets prepared from harder granules showed a capping tendency. Practical tabletting simulation using an eccentric type tabletting machine yielded the same results as those obtained by static compression.

INDRODUCTION

Granulation is a key process in the production of many pharmaceutical dosage forms. Various techniques and equipment have been developed to obtain granular materials. The preparation of spheronized granules offers a number of potential advantages to the pharmaceutical industry in the production of beads or granules as either finished or intermediate products. Some of these advantages include accurate control of dosage, speed of production, and a choice of batch or continuous flow production. The operation of a spheronizer (Marumerizer) in combination with an extruder has been reported[1,2] as follow: Processing of the pharmaceutical formulation involves extruding wetted material into cylindrical segments, breaking the segments, and rolling them into solid spheres on a spinning friction plate. To produce a solid sphere, the extruded substance must be plastic enough to be rolled into a spherical shape. Woodruff and Nuessle[3] reported that different kinds of spheronized granules can be obtained by alternating the plate rotational speeds during extrusion-spheronization. Miyake et al.[4] reported the relationship between the degree of spheronization of granules and the mechanism. Therefore, the relationship between tablet compressibility and granule strength have attracted the interest of many formulation

scientists,[5] and the effects of binder concentration,[6] types and viscosity[7] of binders and kinds of solvents[8] on the mechanical properties of granules have been investigated. These granules contained different amounts and types of binder, therefore, it was not so easy to understand the mechanism of interparticle binding after tabletting. Therefore, in this study, we prepared spheronized granules with various degrees of mechanical strength which contained a constant amount of binder, by means of extrusion-spheronization. We then investigated the effect of the physical characteristics of the granules on such pharmaceutical properties as tablet compressibility and flowability.

EXPERIMENTAL

Materials A bulk powder (J.P. grade; lot No. 11085) of theophylline anhydrate was obtained from Nakarai Co., Osaka, Japan. Crystalline α-lactose monohydrate (De Melkindustrie Veghel Co., Netherlands.) and corn starch (Mitsubishi Co. Japan) were used as a diluent and a disintegrator. Hydroxypropylcellulose (HPC) (Nihon Soda Co. Japan) and magnesium stearate (Kishida Chem. Co. Japan) were used as a binder and a lubricant, respectively. All other chemicals were of analytical grade.

Granulation process

Forty grams of theophylline powder, 252 g of crystalline lactose and 108 g of corn starch were mixed in a twin-shell type mixer (Model 5DMr, Sanei Ind. Co., capacity: 4.7 l, mixing speed 240 rpm) for 20 min. After adding various concentrations of aqueous HPC binder (6g/60ml, 6g/80ml and 6g/100ml), the mixed powder was kneaded in for 10 min, and the wet mass was immediately transferred to a side screen extruder equipped with a 0.5-mm mesh (Type EXKS-1, Fuji Powdal Co., Japan) where the wet mass was extruded at 16 rpm. A charge of 330 g of wetted extrudate was immediately placed in the spheronizer (Q-230, Fuji powdal Co., Japan) and treated at 430 rpm for 0-20 min. Completed, processed granules were dried in a fluidized-bed dryer (MD-A-200, Fuji Powdal Co., Japan) for 12 min at 60°C. Sample granules were passed though a 10 mesh screen (1680 μm).

Micrometric characterization

1) True density measurement: The true density of the crystals was determined using an air comparison pycnometer (model 930; Beckman-Toshiba Co., Tokyo, Japan).

2) The specific surface area (Sw) measurement: The Sw of the powder was measured by the air permeability measurement instrument (SS-100; Shimadzu Co., Kyoto, Japan), assuming the particles to be spherical. The specific surface area diameter was calculated from the Sw value.

3) Measurements of particle size distribution and average particle diameter: The particle size of granules was estimated as a nomianl diameter, and their size distribution and average particle diameter were evaluated in 200 granules on the photomicrograph using a microparticle counter (TGZ-3, Carl Zeiss Co., Germany).
The average particle size was estimated as a median diameter from the count base cumulative curve.

4) Measurement of the elongation ratio of the granule: The length and width of a granule were measured in the photomicrograph, and the elongation ratio was evaluated in 70 granules.

5) Measurement of angle of repose: The angle of repose was measured using a Miwa type rotary drum angle of repose tester (Tutui Sci. Co., Japan).

Measurement of drying rate of granules

The drying process of wet granules was evaluated using an electronic moisture balance (Libor EB-280, MDC, Shimadzu Co., Japan). After 7 g of sample was put on the sample plate, the weight loss during drying was measured at 60°C.

Scanning electron microscopy (SEM) SEM photographs of samples were taken with a scanning electron microscope (model JSM-T20, Jeol Datum Co., Tokyo, Japan) at a magnification of 200x or 1500x.

Measurement of the tapping rate constant The tapping rate constants were measured as follows: Sample powder (5 g) was placed in a graduated cylinder (1 cm in diameter and 20 ml in volume) and the apparent volume was measured during tapping (RHK-type tapping

instrument, Konishi Co., Osaka, Japan). The tapping rate constant was calculated from Kuno's equation[9] (eq. 1) by the least-squares method.

$$\rho f - \rho n = (\rho f - \rho o) \exp(-kn) \qquad \text{eq. 1}$$

ρf is the bulk density of the sample powder after infinite tapping, ρn is the bulk density at tapping number n, ρo is the bulk density at the initial packing, k is the tapping rate constant and n is number of taps.

Friability test Ten grams of sample granules remaining on 150- mesh screen (105 μm) were put in the chamber, which was rotated for 20 min at 25 rpm. After the sample was sieved on the 150 mesh screen for 1 min, the sample granules remaining on the screen were weighed. Friability (F) was calculated using the following equation.

$$F = [(W1 - W2)/W1] \times 100\ (\%) \qquad \text{eq. 2}$$

F is friability, W1 is the weight of the total sample granules and W2 is the weight of sample granules on the screen.

Tabletting compression process

Sample granules, 280 g were mixed with 1% magnesium stearate in a twin-shell mixer (Tokujyu Ind. Co., Model V-1, capacity: 2 l, mixing speed 28 rpm) for 2 min.

Static compression: Granules (300 mg) were compressed in a 1.3-cm diameter punch and die by a compressor for IR-spectrophotometry at 2500 kg/cm^2 for 5 min.

Tabletting compression: Granules (about 300 mg) were compressed using a 0.8-cm diameter punch and die sets on a single punch tabletting machine (6B type, Kikusui Co., Japan) at 28 spm.

Tablet hardness The tablet hardness was measured 3 times using a hardness tester (Erweka Co.).

Micropore distribution measurement Micropore distribution of the tablet was measured by means of mercury porosimetry (type 2000, Carlo Erba Strumentazione, Italy). The pore size ranged from 300 to 6×10^{-3} μm.

RESULTS AND DISCUSSION

Particle Shape and Average Diameter of Granules After Spheronization

Figure 1 shows the effect of spheronizing time on the average diameter of the granules. The average diameter of all granules rapidly decreased at the initial spheronization process, and after treatment for 3 min, and were a constant at around 600 μm. Howevr, the average diameter of the granules added 150 ml/kg water decreased to 460 μm after 13 min treatment.

Figure 2 shows the effect of spheronizing time on elongation ratio of granule. The elongation ratio rapidly decreased at initial spheronization process, simlar to the results of the average diameter in Fig. 1, indicating that the granules were spheronized with the elapse of time. The granules prepared by adding 250 ml/kg water had the lowest elongation ratio. These results suggested that granular spheronization could be divided into two processes, the initial being segmentation, when the long cylindrical segments broke into short segments as reported by Conie and Hadley.[1] In the latter process the short cylindrical segments were transformed into spherical granules.

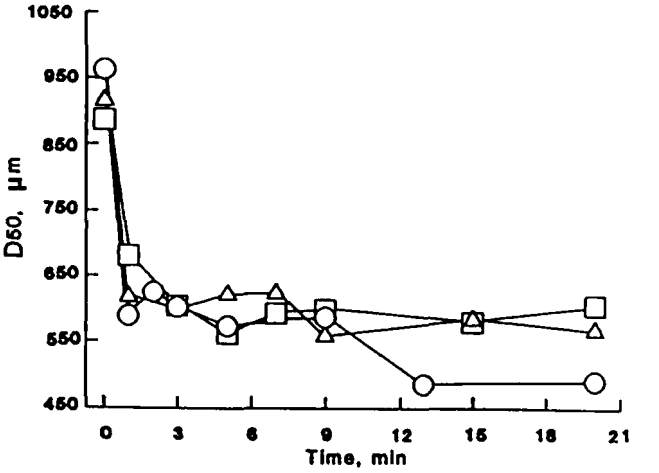

Fig. 1. The Effect of Spheronizing Time on the Average Diameter of the Granules
○ , 150 ml/kg; △ , 200 ml/kg; □ , 250 ml/kg.

Drying Process of Spheronized Granules

Figure 3 shows the drying processes of the granules after spheronization under various conditions. The initial water content of granules depended on the amount of water added, but the time required for drying was almost the same.

Figure 4 shows the relationship between the drying rate and the moisture content of the granules. Since the

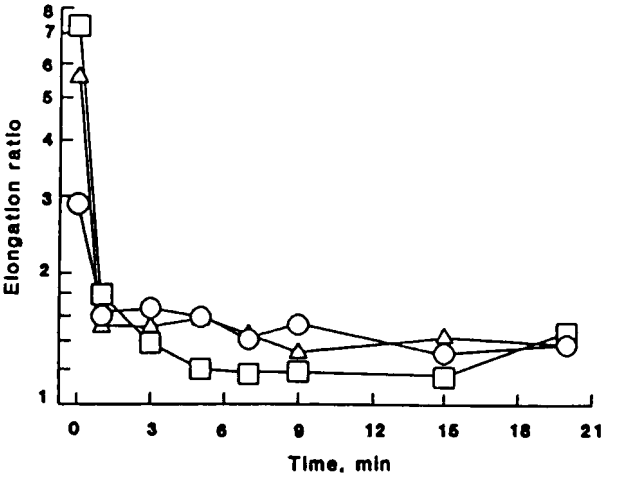

Fig. 2. The Effect of Spheronizing Time on the Granular Elongation Ratio
○ , 150 ml/kg; △ , 200 ml/kg; □ , 250 ml/kg.

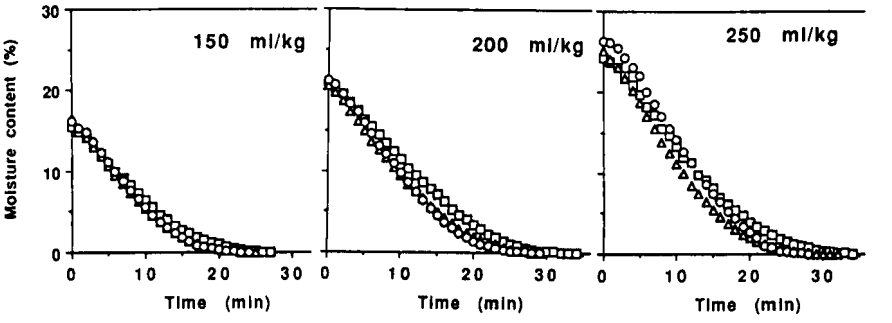

Fig. 3. Drying of Various Granules after Spheronization under Various Conditions
○ , spheronized for 0 min; △ , 5 min; □ , 10 min.

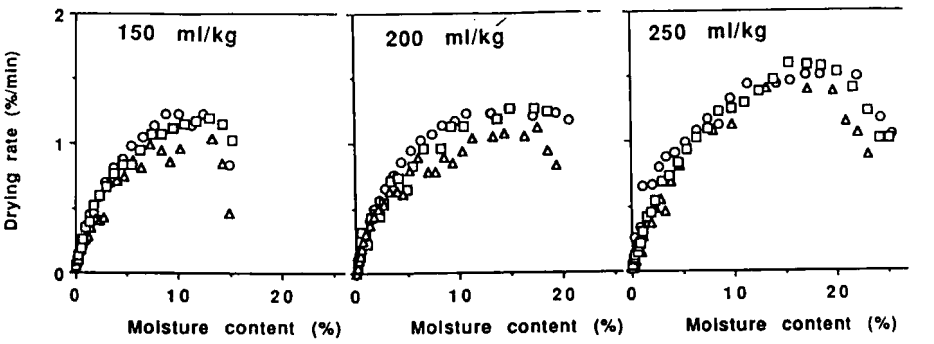

Fig. 4. The Relationship between the Drying Rate and the Moisture Content of the Granules
○ , spheronized for 0 min; △ , 5 min; □ , 10 min.

drying process was divided into three, namely decreasing rate, constant rate and initial periods, the critical moisture contents were evaluated from the drying process analysis and are summarized in Table I. The critical moisture content of all granules increased with increasing spheronization time and the amount of water added. The constant drying rate increased with increasing added water, but that of the granules spheronized for 5 min was the lowest in each formulation.

Physical Properties of Spheronized Granules

Figure 5 shows the relationship between the porosity of granules and spheronization time. The porosity of granules contained 200 and 250 ml/kg water decreased with elapsed spheronized time, but that contained 150 ml/kg increased. Since the average diameter of the latter decreased after spheronization for 10 min, the granules were destroyed, having several cracks.

Figure 6 shows the results of the friability test. The percent friability of granules contained 200 and 250 ml/kg water decreased with elapsed spheronized time, but that of granules contained 150 ml/kg water did not. The percent friability of the latter after spheronization for 5 min was minimal. These results of Figs 5 and 6 suggested a relationship between the mechanical strength of granulates and the inside granule structure. Since the granules were compressed by a

Table I Kinetic parameters for drying of spheronized granules

Amount of Added water (ml/kg)	Time[a] (min)	C.M.C.[b] (w/w%)	CR[c] (w/w%/min)
150	0	9	1.22
150	5	10	0.97
150	10	11	1.18
200	0	12	1.22
200	5	13	1.12
200	10	15	1.23
250	0	13	1.45
250	5	14	1.36
250	10	15	1.55

a, spheronization time; b, critical moisture content; c, constant drying rate.

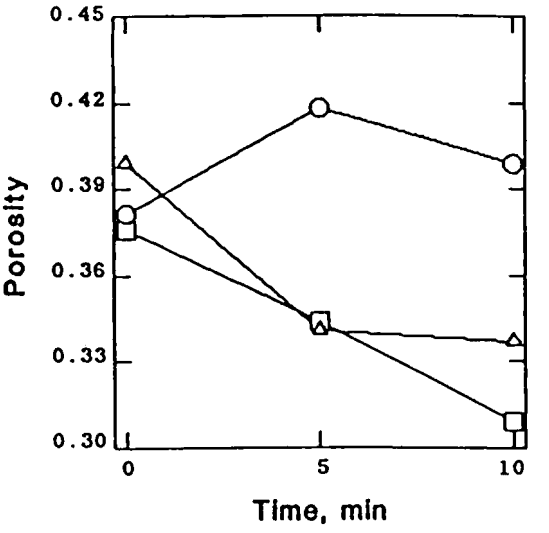

Fig. 5. The Relationship between the Porosity of the Granules and Spheronization Time

○ , 150 ml/kg; △ , 200 ml/kg; □ , 250 ml/kg.

centrifugal force during the spheronization process and the porosity decreased, the following mechanism was considered: When the particles in the granule were rearranged by the centrifugal force during spheronization, the granules containing sufficient water became a fluid wet mass. The less porous products had higher mechanical strength since the bonding surface area

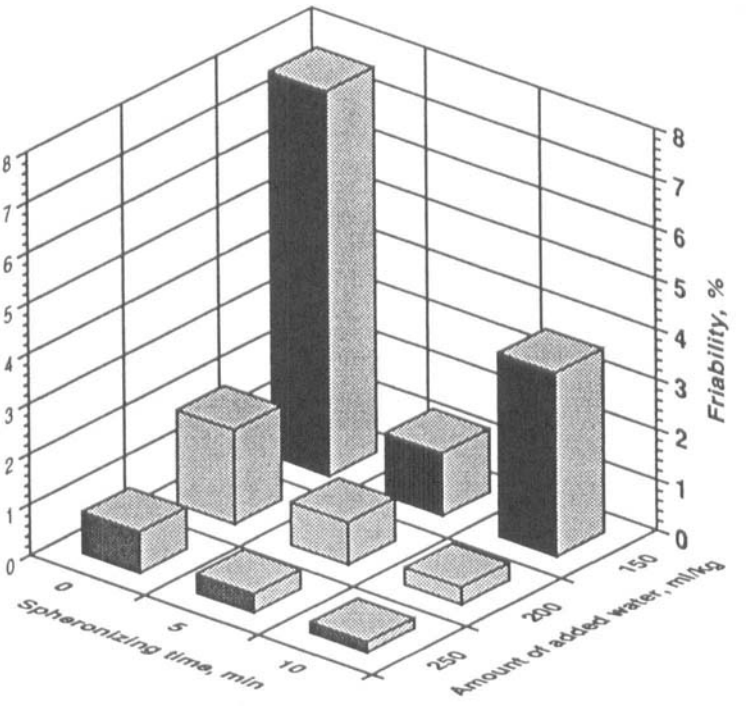

Fig. 6. Effect of the Amount of Added Water on the Friability of the Granules and Spheronization Time

between particles was larger.

Flowability of spheronized granules

Figure 7 shows Kuno's plots of granules contained 200 ml/kg water. The tapping rate constants (k) were estimated from these plots. Figure 8 shows the relationship between the k and spheronized time. The k of the granules contained 200 and 250 ml/kg water increased compared with that of non-spheronized granules, but that of granules contained 150 ml/kg water did not.

This suggested that fine particles in the granules contained 150 ml/kg water increased with increase of spheronized time, since the mechanical strength was weak.

Figure 9 shows the relationship between the angle of repose and spheronized time. The angle of repose of all granules decreased to

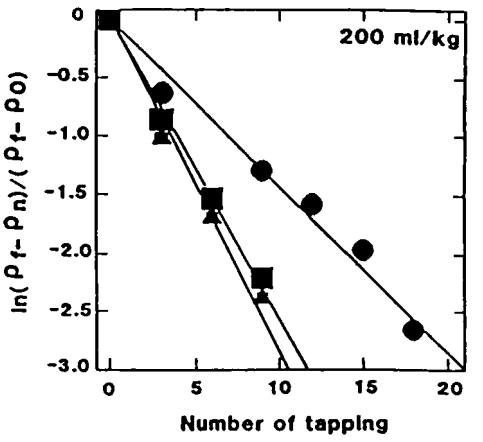

Fig. 7. Kuno's Plots of Various Spheronized Granules Contained ml/kg water
● , spheronized for 0 min;
▲ , 5 min; ■ , 10 min.

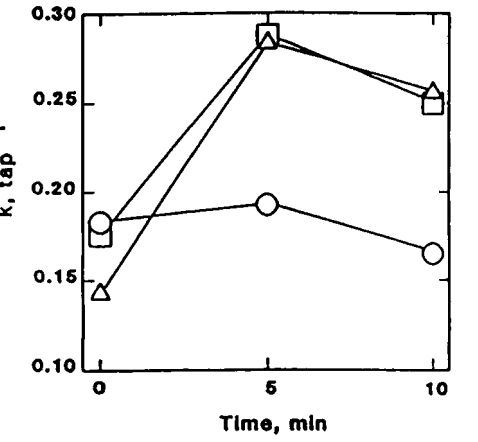

Fig. 8. The Relationship between the Tapping Rate Constant and 200 Spheronized Time
○ , 150 ml/kg; △ , 200 ml/kg;
□ , 250 ml/kg.

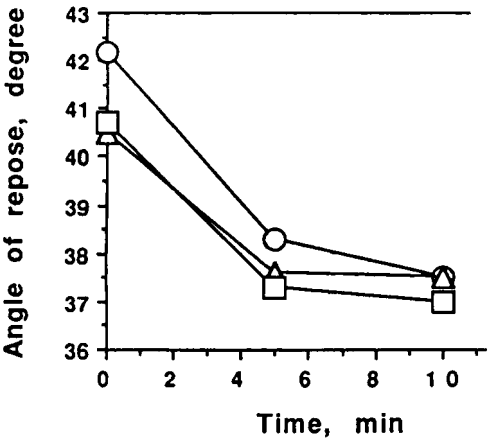

Fig. 9. The Relationship between of Repose and Spheronized Time.
○ , 150 ml/kg; △ , 200 ml/kg;
250 ml/kg.

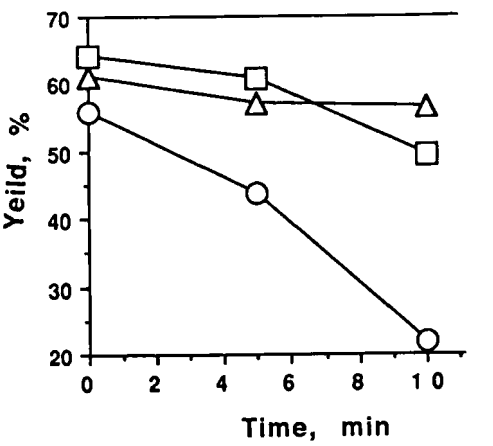

Fig. 10. The Relationship the Angle between the Yield and Spheronized Time.
○ , 150 ml/kg; △ , 200 ml/kg; □ ,
□ , 250 ml/kg.

about 37° with elapsed spheronized time, and that of 150 ml/kg was relatively higher than that of the others.
Since the tapping rate and the angle of repose related to the powder flowability, these results suggested that the flowability of the extruded granules was improved by spheronization for more than 5 min.

Figure 10 shows the relationship between the yield and spheronized time. The yield of the granules contained 200 and 250 ml/kg water slightly decreased with elapsed spheronized time, but that of granules contained 150 ml/kg decreased considerably. Since the granules were dried in fluidized-bed dryer, the small particles were removed during drying. Therefore, the results suggested that the granules contained 150 ml/kg water were destroy by too long spheronization treatment.

Morphology of Spheronized Granules

Figure 11 shows the SEM photographs of the granule surfaces before and after the spheronization. All granules before spheronization were long cylindical segments, but those contained 150 and 200 ml/kg water became an irregular ellipse after treatment and that of granules contained 250 ml/kg water was close to that of spherical granules. The untreated granules had several cracks on the surface, but it became smooth and elaborate after spheronization.

Tabletting Compression of Spheronized Granules

Figure 12 shows the tablet hardness obtained from various kinds of spheronized granules by static compression. The tablet hardness obtained from the granules before spheronization was statistically significantly higher than that after treatment. The decreasing order of hardness after treatment was 150 < 250 < 200 ml/kg, indicating that the amount of added water affected tablet hardness. The spheronized granules 150 ml/kg contained water had the highest tablet hardness. Since these granules had larger porosity (Fig. 5) and higher friability (Fig. 6), indicating that the mechanical strength of the granules was lower than that of granules contained 200 and 250 ml/kg water, the physical characteristics of the tablet made from the spheronized granules contained 150 ml/kg water were similar to those of non-spheronized granules.

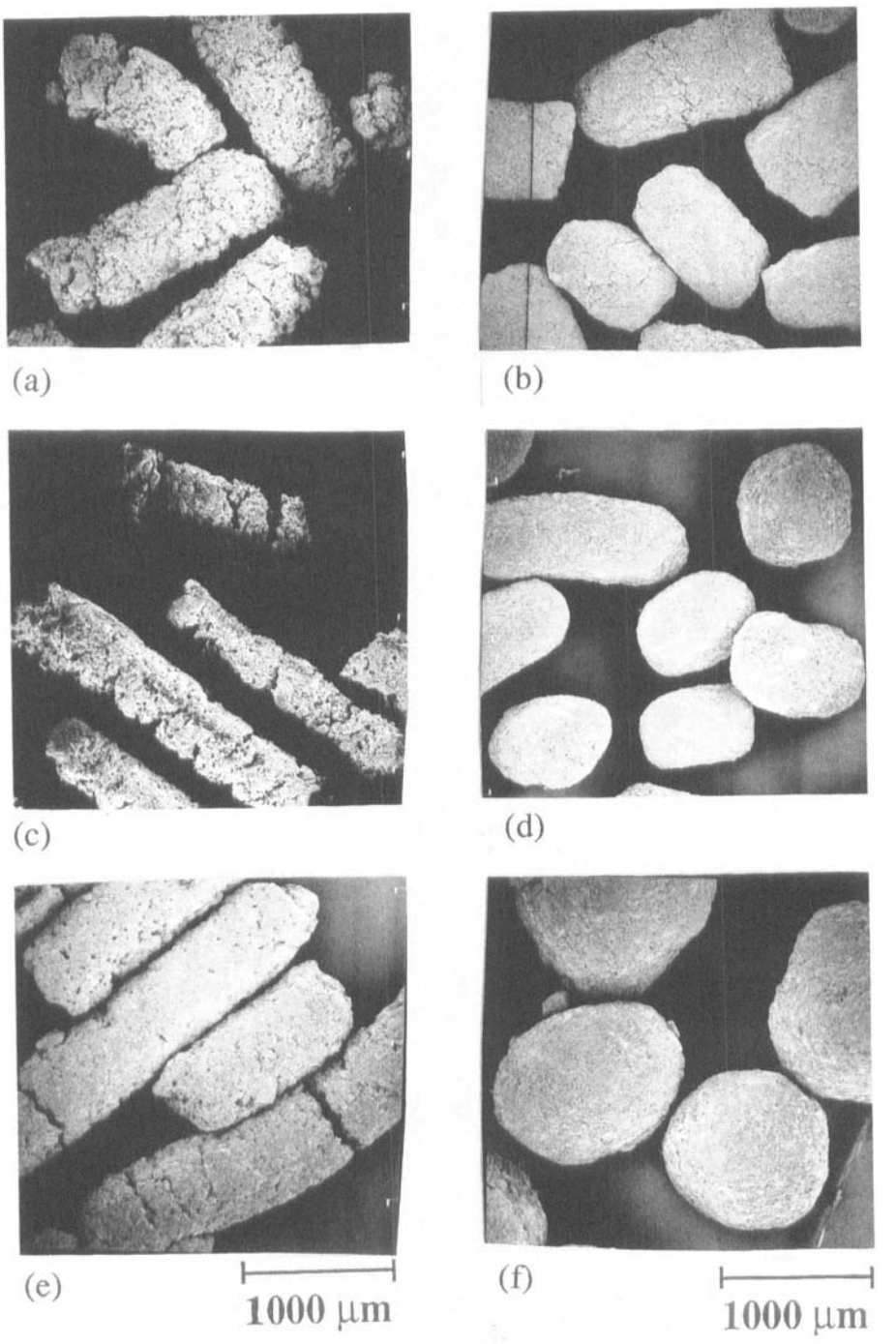

Fig. 11. SEM Photographs of Granules before and after Spheronization (2000X)
(a), (c), (e), intact granules; (b), (d), (f), spheronized for 5 min; (a), (b), 150 ml/kg; (c), (d), 200 ml/kg; (e), (f), 250 ml/kg.

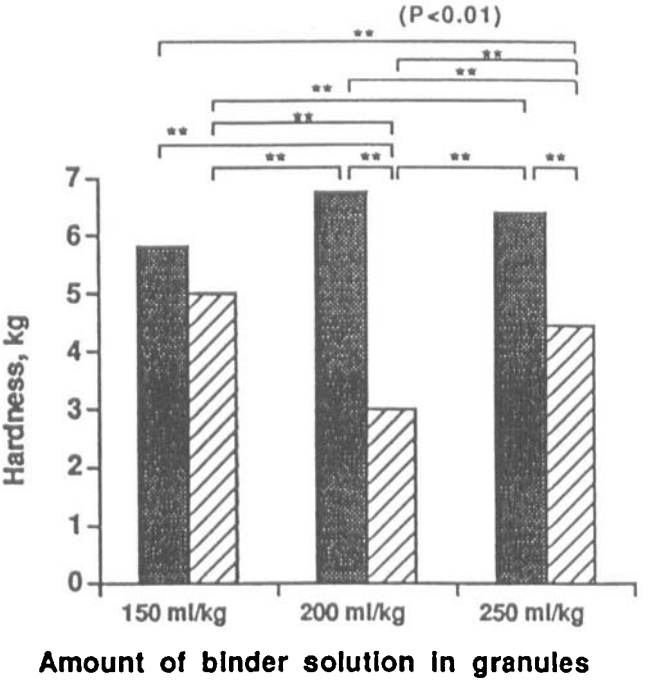

Fig. 12. The Tablet Hardness obtained from Various Spheronized Granules by Static Compression The shadowed and slashed bars represent spheronizing for 0 and 5 min, respectively.

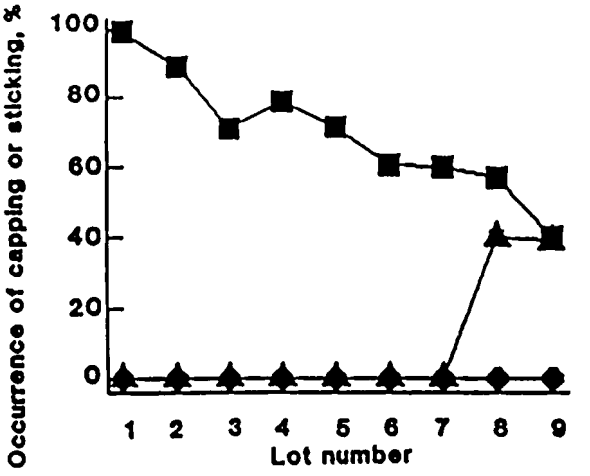

Fig. 13. The Capping Frequency during Tabletting from Spheronized Granules for 5 min (One lot was 20 tablets)
● , 150 ml/kg;
▲ , 200 ml/kg;
■ , 250 ml/kg.

Figure 13 shows the capping frequency during tabletting from spheronized granules for 5 min. During tabletting granules contained 250 ml/kg water, there was a very high capping frequency. During tabletting those contained 200 ml/kg capping appeared in the final process, but that of granules contained 150 ml/kg water did not show capping. Toyoshima et al.[10] reported that the granule number per unit weight decreased with increasing of added water. In this study, the number of granule per 100 mg containing 150, 200 and 250 ml/kg of added water were 609, 532 and 483, respectively. This result suggested that the intergranules contact area decreased with decreasing the granule number, indicating that the mechanical strength of the tablet decreased. Therefore, it seems that the decreasing tablet hardness was caused as follow: Since the high mechanical strength granules was not so much deformed by tabletting compression, the tablet had high intergranule porosity and a lower intergranule contact area. A high ratio of spheronized granules had a lower intergranular contact area.

CONCLUSION

Spheronized granules obtained using extrude-spheronization had good flowability and mechanical strength. The amount of water added to the formulation during the granulation process affected the pharmaceutical properties of the granules. Thus, since the spheronized granules have high mechanical strength, those were useful as raw materials for coated granules. However, too hard granules were unsuitable as a raw materials for tablet preparation.

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