Determination of Optimal Formulation for Extrusion Granulation by Compression Test of Wet Kneaded Mass

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The purpose of this study is to propose the application of a compression test to the determination of an optimal formulation for extrusion granulation. The electric current during extrusion was measured and the characteristics of the wet kneaded mass in the compression test were analyzed under various operating conditions, with different types of extruders and several formulations of kneaded mass. It was found that addition of a binder (HPC-L) to pharmaceutical powders lowered the load of a high-compressing type extruder, since the binder reduced the friction among the wet mass during extrusion. Also, the support stress was found to be proportional to the compression pressure without a binder, although an inflection point appeared on the support stress curve when a binder was present. This inflection point suggested large water retention of the wet kneaded mass, at which the medium of pressure was changed from a discontinuous solid powder to a continuous liquid, and large water retention contributed to the low friction of the wet mass. The friction of the wet kneaded mass and the aptitude of the formulation for extrusion were understood by using the compression test. The compression test is a very useful procedure at the first stage of a formulation study.

Key words compression test; formulation study; extrusion; wet mass; friction; water retention

Extrusion granulation has widely been used in pharmaceutics, agriculture, foods, ceramics, chemicals and various industries, since the construction and operation are simple, mass production is easy with low operating costs, and uniform physical properties can be easily obtained. In the process of extrusion granulation, powder materials are kneaded with a liquid, then the wet kneaded mass is extruded through a punched or mesh screen. If the condition of the kneaded mass is unfavorable for extrusion, a lot of power is required. In the worst case, the screen or other parts may be broken. This condition depends on the characteristics of the kneaded mass, friction, plasticity *etc.*, and not every material is suitable for extrusion. Therefore, extensive and detailed formulation studies are necessary for stable manufacturing. However, in the formulation study of extrusion granulation, a large quantity of materials is required (several kilograms for one formulation) and also there is a risk of breaking the screen. If the characteristics of the material for extrusion are previously understood at the first stage of the formulation study, much time and cost can be saved.

Many investigators have used simple equipment like a ram extruder to understand the extrusion process.[1—3] Also, many scientists have studied the compression of powders.[4—7] As a result, some characteristics of pressure transmission have been made clear. The compression behavior of pharmaceutical powders was also examined[8—10] and compression of a wet mass has been investigated as well.[11] Watano *et al.* evaluated the water dispersion of a wet kneaded mass using a compression test and predicted the properties of the final extruded products.[12] They also analyzed the rheo-mechanical properties of wet powder.[13,14] Meanwhile, several studies on the prediction of optimal formulations have been made.[15] The compression test is suited to a pharmaceutical formulation study since it is simple and it requires only a small amount of sample (a few grams), which is normally very expensive at the first stage of development. However, there is no major publication on the application of compression tests to the formulation studies.

In this study, a compression test was applied to a pharmaceutical formulation study for extrusion granulation. The electric current during extrusion was measured and the characteristics of the wet kneaded mass in the compression test were analyzed under various operating conditions, with different types of extruders and several formulations of kneaded mass. Based on the results, a method for determining the optimal formulation for extrusion granulation was proposed.

Experimental

Powder Materials Table 1 lists the materials used. The excipient consisted of lactose monohydrate (Pharmatose 200M), cornstarch (W) and microcrystalline cellulose (Avicel PH-101). Hydroxypropyl cellulose (HPC-L) was adopted as a binder. These materials were mixed in a polyethylene bag for 3 min. Purified water was fed into the mixture and then kneaded in a planetary mixer (25AM-02-rr, DALTON Corporation).

Equipment and Procedure A planetary motion mixer that has two hook-shaped paddles (25AM-02-rr, DALTON Corporation) was used for kneading. The vessel is 320 mm in diameter and 310 mm deep. The paddles revolve at 1.2 rps and rotate at 2.76 rps. Four kilograms of powder mixture was kneaded with a predetermined amount of purified water for 5 min.

Two types of extrusion granulator (cylindrical and double-shafted) with punched screens (pore diameter: ϕ0.5 mm) were used. The cylindrical extruder (HG-200, HATA Iron Works) is a vertical type equipped with two upper blades to push the wet kneaded material forward and four bottom blades to extrude it through a cylindrical screen (Fig. 1). The two types of

Table 1. Quantitative Formulation of Samples

	Formulation I		Formulation II	
Lactose monohydrate	96.0%		67.2%	
Corn Starch	—		28.8%	
Microcrystalline cellulose	4.0%		4.0%	
(Total)	100.0%		100.0%	
Hydroxypropyl cellulose	a	b	a	b
	0.0%	3.0%	0.0%	3.0%
Purified water	15, 20, 25 or 30%			

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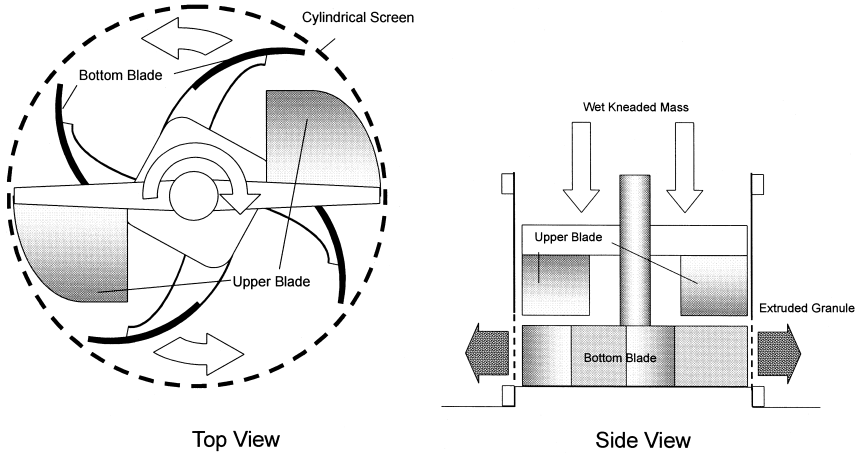

Fig. 1. Schematic Diagram of Cylindrical Extruder

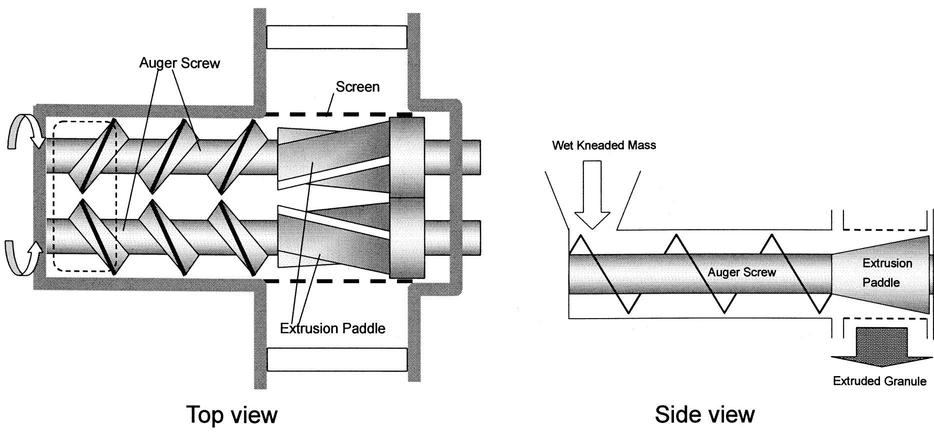

Fig. 2. Schematic Diagram of Double-Shafted Extruder

blades are attached to a coaxial shaft. The upper blades rotate in the reverse direction to the bottom ones. The double-shafted extruder (EXDR-60, Fuji Paudal Co., Ltd.) is a horizontal type equipped with two parallel shafts that have auger screws and extrusion paddles (Fig. 2). The kneaded material is extruded through the screen around the paddle. During the extrusion, the electrical currents, which indicate the load during extrusion, were monitored and analyzed by a personal computer.

The compression test of the kneaded mass was conducted using a compression tester[16] (AUTO GRAGH AG-50kNE, Shimadzu Corporation). The tester is composed of a cylinder and upper and lower punches, and the upper punch moves down at a speed of 10 mm/min and compresses the wet mass between an upper and lower fixed punch. An alloyed metal cylinder having an inside diameter of 11.3 mm was mainly used, and a transparent acrylic resin cylinder having an inside diameter of 19.9 mm was used to visually observe the wet mass during the compression. The compression force, its transmission force to the lower punch, and the moving distance of the upper punch were recorded and calculated as follows.

The sample height during the compression test, H_s, was calculated based on Eq. 1.

$$H_s = d_0 - d + s_e \qquad (1)$$

where d is a moving distance of the crosshead and d_0 is the distance at 10 N of compressing force without a sample. Also, s_e is the strain of the equipment under the pressure.

The loss of compression force, F_l, and pressure transmission, G, are shown in Eqs. 2 and 3, respectively

$$F_l = F - T \qquad (2)$$

$$G = T/F \qquad (3)$$

where F and T indicate the force of the upper punch and the one transmitted to the lower punch, respectively.

The loss of force is equivalent to the force supported by the inner wall of the cylinder. Here, the supporting force per unit area (support stress) was considered and defined; when the sample mass was compressed, the volume of sample and the contact area between the cylinder wall and the sample became small. The support stress on the inner wall of the cylinder, S_w, was calculated and expressed as

$$S_w = F_l/(\pi \times D \times H_s) \qquad (4)$$

$$S_w = \mu K P_u \qquad (5)$$

where D is the inner diameter of the cylinder, μ is the friction coefficient between the wet mass and cylinder, and P_u is the pressure of the upper punch $(=F/(\pi \times D^2/4))$. K is a Rankin factor, which can be taken as the radial pressure P_D subjected to P_u as

$$K = P_D/P_u \qquad (6)$$

The extruded granules were dried in an oven at 70 °C. The crushing energy of the sieved granule (500—710 μm) was then measured with a particle hardness tester (GRANO, Okada Seiko Co., Ltd.). The crushing energy of a granule was the integrated crushing force over 0—200 μm of crushing distance.

Results and Discussion

Figure 3A shows the electric currents of the cylindrical extruder for Formulation I with a water content of 15 and 20%. The difference in water content and the addition of a binder (HPC) hardly influenced the electric currents during the extrusion. Also, all the currents were slightly larger during the extrusion than for idling.

Figure 3B shows the electric currents of the double-

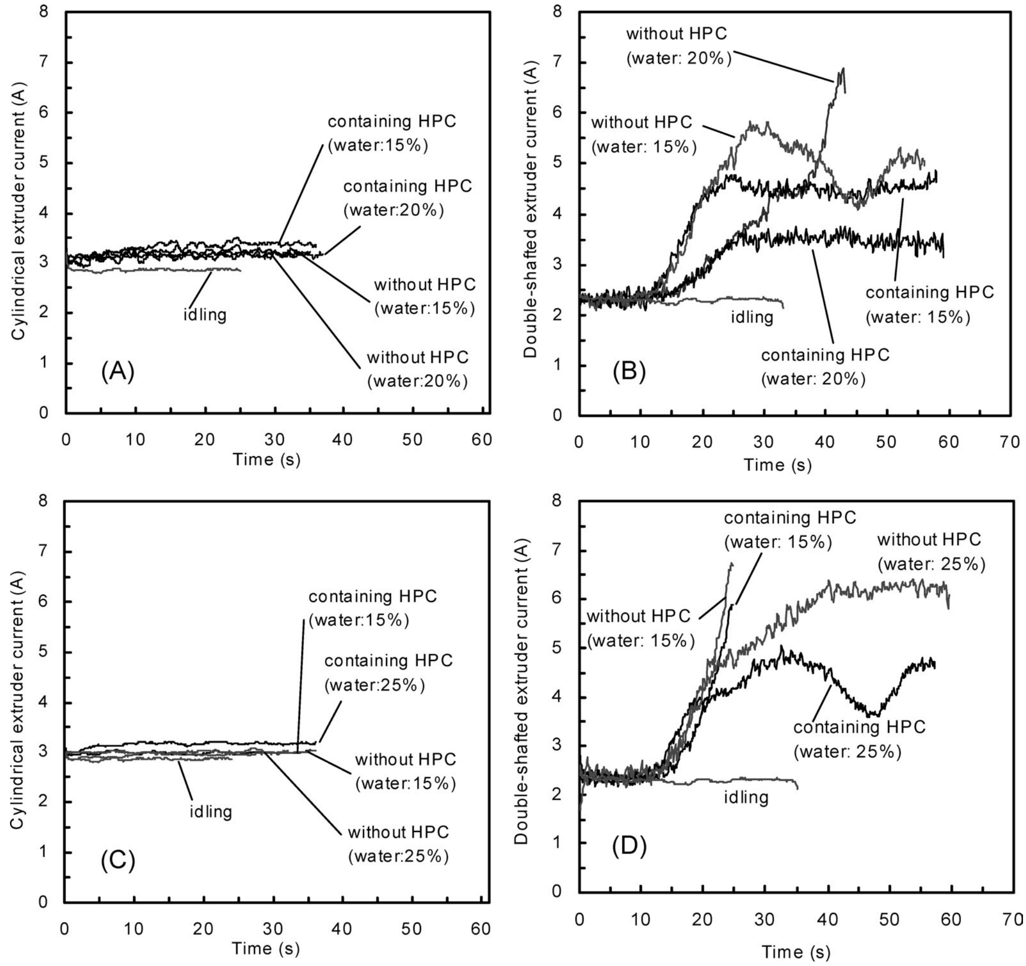

Fig. 3. The Electric Current of the Extruders

(A) Formulation I, cylindrical extruder, (B) formulation I, double-shafted extruder, (C) formulation II, cylindrical extruder, (D) formulation II, double-shafted extruder.

shafted extruder for Formulation I. At the initial stage of the extrusion, the electric current had the same value as for idling. The auger screws conveyed the wet mass and the gap between the extrusion paddles and screen was progressively filled, leading to an increase in the load of extrusion. The water content was 15 and 20% during the extrusion, and the difference in the formulation (with or without the binder (HPC-L)) caused the different load during the extrusion. At a water content of 15% without the binder, the electric current of the extruder increased to 6 A and the current was unstable. At a water content of 20% without the binder, the electric current of the extruder went up to 7 A and the operation was stopped, for fear of a screen break. At a water content of 15 and 25% with the binder, the electric current increased to 4.5 and 3.5 A, respectively, and then reached a plateau. Addition of the binder and water effectively lowered the extrusion load of the double-shafted extruder.

Figures 3C and D indicate the electric currents of the two types of extruder for Formulation II. The behavior of the electric currents for Formulation II was almost the same as that for Formulation I, regardless of whether cornstarch was present. The influence of water and binder on the load of the cylindrical extruder was small. On the other hand, for the double-shafted extruder, water and the binder greatly affected the load. The difference was considered due to the mechanistic difference between the two extruders; in the double-shafted extruder, the wet kneaded mass was strongly compressed by the auger screws to the extrusion paddles and the screen. By contrast, in the cylindrical extruder, there were enough spaces among blades to leak the pressure. In other words, the main extrusion force of the cylindrical extruder was shearing, while that of the double-shafted extruder was compression. Accordingly, it was considered that the double-shafted extruder was closely related to the characteristics of the compression test.

Figure 4 expresses pressure transmission curves as a function of compressing pressure with and without the binder (HPC-L). Addition of the binder greatly enhanced the transmission; the transmission gradually increased without the binder, while in the presence of the binder, there was an inflection point at which the transmission sharply increased. The transmission behaved similarly to the electric current of the double-shafted extruder.

Figures 5A and B indicate the support stress curves of the inner wall of the cylinder as a function of compression pressure for Formulation I. In the case of Formulation I-a (without the binder), the support stress was proportional to the compression pressure, regardless of the water content. In the case of Formulation I-b, the support stress was proportional to the compression pressure at a low compression pressure (stage A) as seen in Fig. 5A. However, at higher pressure (stage B), an inflection point appeared and the support stress

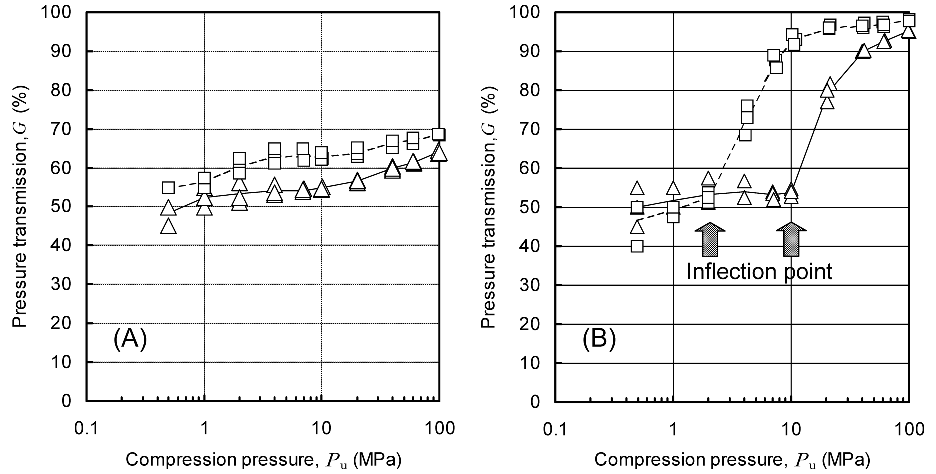

Fig. 4. Pressure Transmission Curves

(A) Formulation I-a (without HPC), (B) formulation I-b (containing HPC), water contents; △ 15%, □ 20%.

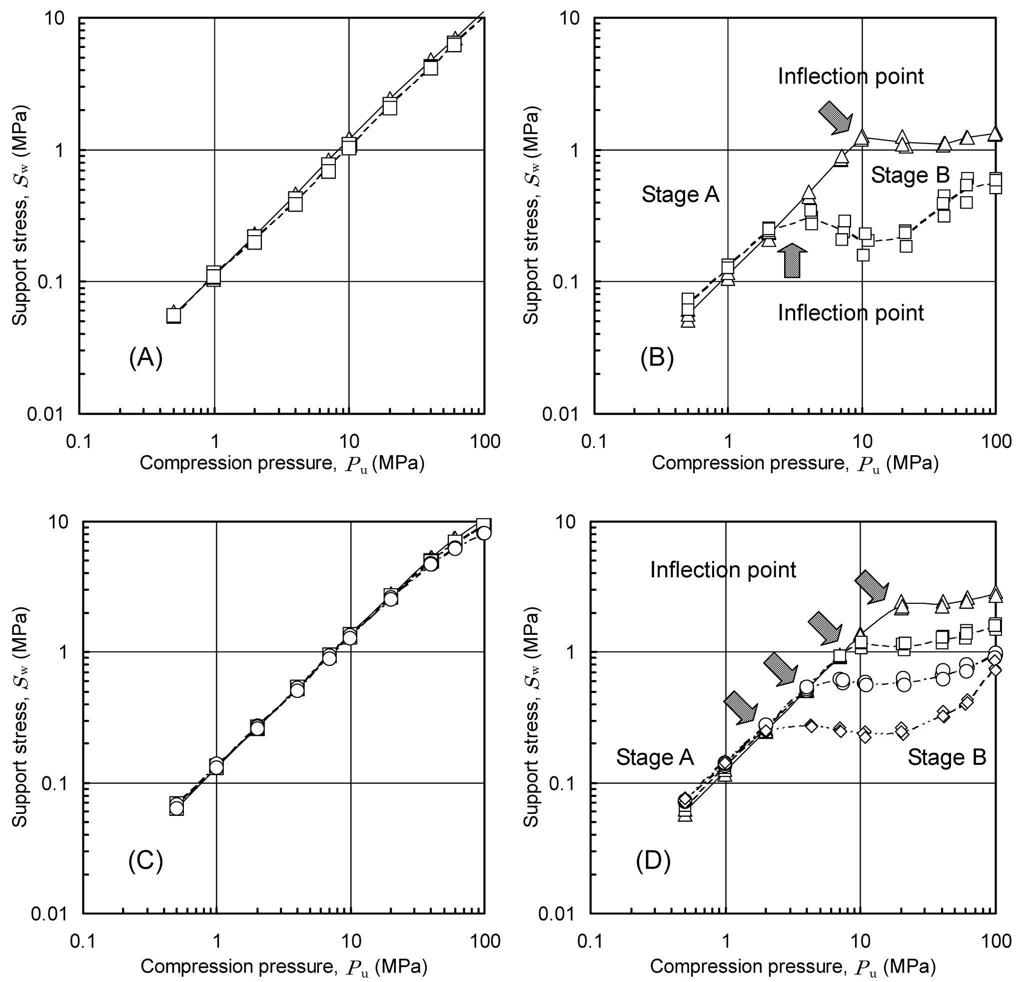

Fig. 5. Support Stress Curves

(A) Formulation I-a (without HPC) , (B) formulation I-b (containing HPC), (C) formulation II-a (without HPC) , (D) formulation II-b (containing HPC), water contents; △ 15%, □ 20%, ○ 25%, ◇ 30%.

was no longer proportional to the compression pressure; at the beginning of the stage B, the support stress decreased slightly with an increase in the compression pressure, and the support stress gradually increased again. As the water content increased, the behavior of the support stress curve did not change, but the inflection point was lowered.

Figures 5C and D illustrate the support stress curves of the inner wall of the cylinder as a function of the compression pressure for Formulation II. The behavior of the support stress of Formulation II was the same as that of Formulation I. In the presence of the binder, the state of the compressed wet mass changed drastically between the stage A and B (inflection point). Also, water greatly affected the state of the compressed wet mass because the pressures at the inflection point decreased in response to the water content. On the other hand, the proportional slopes at the stage A were about the same irrespective of the water and binder contents. Here, the proportional slope corresponded to the apparent friction coefficient, μK, in Eq. 5, and μK was considered to be constant during the stage A.

As is well known that cornstarch in Formulation II is insoluble and absorbs water, leading to an increase in the absorption capacity of the powder mixture. However, the effects of cornstarch on extrusion are not clear. Generally, the addition of cornstarch might influence the physical properties of a wet kneaded mass. By contrast, the above-mentioned phenomenon appeared regardless of the cornstarch presence. In other words, the addition of cornstarch hardly influenced the load of the extruder and result of the compression test. In the case of a dry mass, the mass properties are influenced by the characteristics of the particles (shape, adhesion, plasticity, elasticity *etc.*). However, in the case of a wet mass, the liquid among particles greatly contributes to the mass properties; the liquid binds or lubricates the particles, and it was considered that the viscosity of the liquid mainly contributed to the liquid characteristics. Thus the addition of insoluble materials like cornstarch scarcely changed the liquid viscosity, and the presence of cornstarch hardly influenced the mass properties.

Figure 6 indicates the support stress curves for Formulation I in an acrylic resin cylinder and Fig. 7, during the compression test. For Formulation I-b with a water content of 20%, the inflection point appeared at about 3 MPa of compression pressure. At this point, the voids of the wet mass disappeared completely. When the water content was 15% (Formulation I-b), the inflection point did not appear below 10 MPa, and a complete disappearance of the voids was not observed. This disappearance was attributed to the filling of the voids among the wet mass with liquid. It could be safe to say that the voids were filled with liquid at the inflection point, and the inflection point was "the critical point" of in compression of the wet mass. Therefore, when the water content was large enough, the critical pressure (the pressure at the inflection point) was low, since the voids were filled with

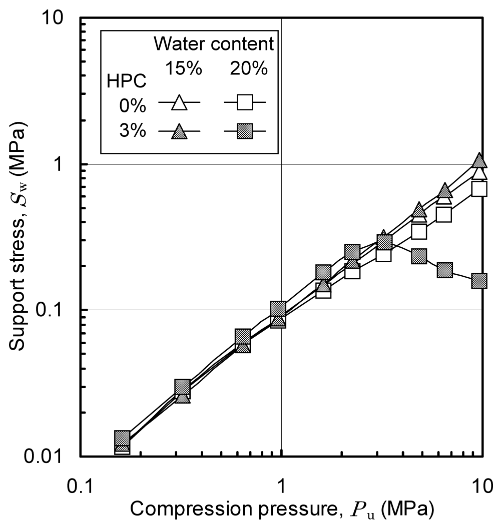

Fig. 6. Support Stress Curves (Formulation I, Acrylic Resin Cylinder)

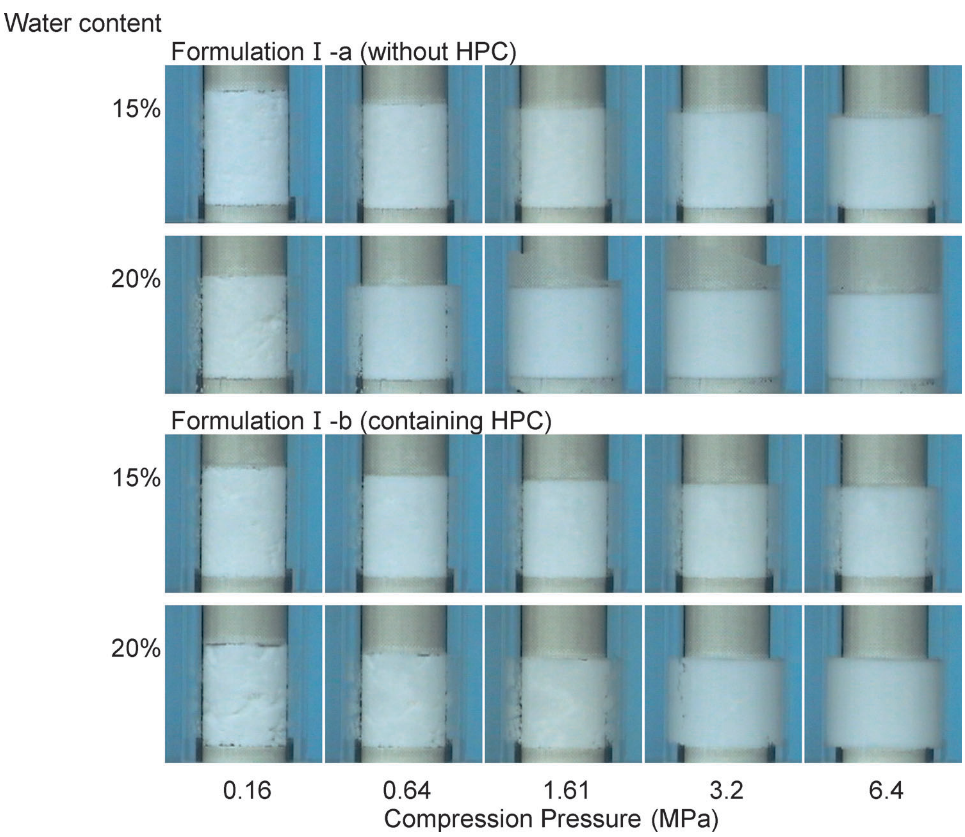

Fig. 7. Side Views of Compression Test (Formulation I)

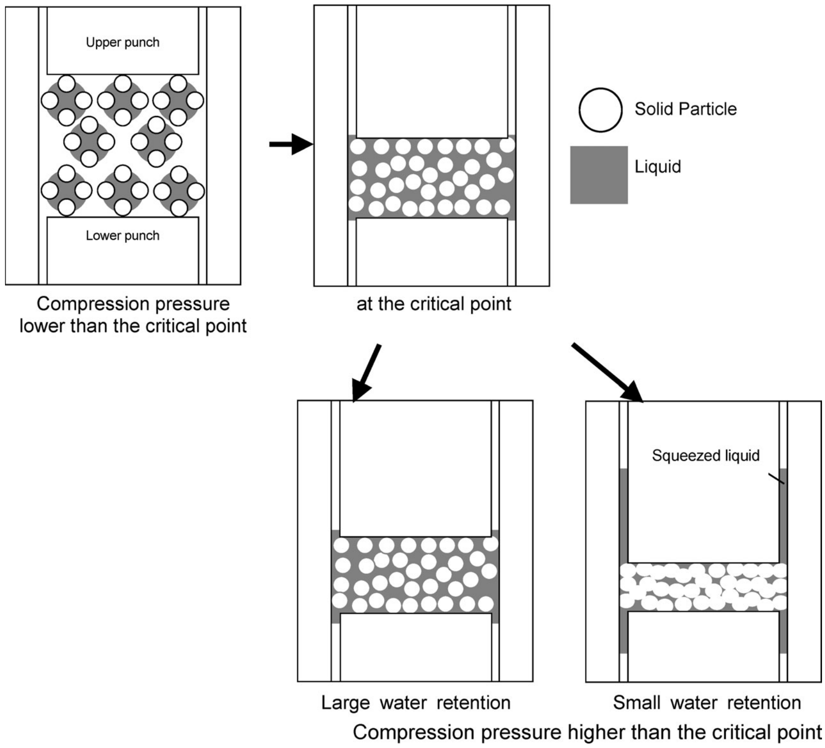

Fig. 8. The Models for Compression Behaviors

liquid at low pressure. Formulation I-a with a water content of 20%, the support stresses remained proportional to the compression pressure (obvious inflection points were not observed), which was the same as in Fig. 5A. However, a complete disappearance of the voids was observed and liquid was squeezed out from the wet mass. This squeezing was related to the fact that an inflection point did not appear on the support stress curve, since the squeezing of liquid was not observed in the presence of the binder.

Figure 8 explains a model of the compression behavior. At a compression pressure lower than the critical point (stage A), voids still existed among particles and the pressure of the upper punch transmitted through the medium of discontinuous wet mass powder. At the critical point, the voids of wet mass were completely filled with liquid. For the formulations having large retention such as those containing enough binder, the liquid was maintained among the solid particles without squeezing under high pressure, and the medium of the pressure transmission turned to continuous liquid from discontinuous particles and liquid (K was closer to "1" and μ became extremely small). Then the apparent support stress became small at a compression pressure higher than the critical point. However, if the water retention of the formulation was poor, *i.e.* no or a small amount of binder, excess liquid was squeezed from the wet mass regardless of the water content. The particles then directly contacted with each other, leading to friction between them and the medium of pressure transmission could not change from solid particles to liquid. In addition, μK didn't change markedly after voids were filled with liquid, and the support stress was consequently kept proportional to the compression pressure. In general, HPC and other soluble celluloses are used as a binder. However, the soluble celluloses act as a lubricant in the wet mass. Thus this is more significant function for the extrusion granulation.

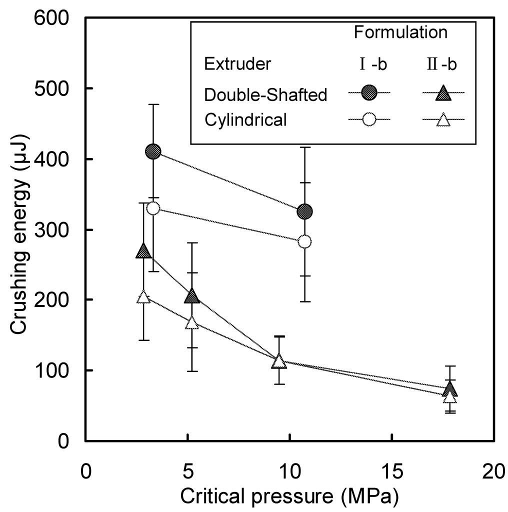

Fig. 9. The Relationship between Crushing Energy of Granule and Critical Pressure of Wet Kneaded Mass (Containing HPC)

Error bar: Standard deviation ($n=20$).

Figure 9 expresses the relationship between the crushing energy of a granule and the critical pressure of the wet kneaded mass. The crushing energy increased with a decrease in critical pressure, and a large difference in crushing energy between Formulation I and II was observed, regardless of extruder type. However, for both formulations, the increase in crushing energy with a decrease in critical pressure was larger for the double-shafted extruder than cylindrical extruder. In other words, the granule strength was more sensitive to the critical pressure of the wet mass in the double-shafted than cylindrical extruder. On the other hand, the electric currents of the double-shafted extruder decreased with the water content as seen in Figs. 3B and D, and the critical pressure decreased with the water content. The load of the double-shafted extruder was also found to be sensitive to the critical pressure. It was confirmed that critical pressure was a significant factor for a high-compressing extruder; the difference in the formulation mainly influenced the strength of the granule, and type of extruder also significantly changed the property of granules.

The appearance of the inflection point on the support stress curve avoided overload of the double-shafted extruder. Also, the lower critical pressure resulted in a smaller load of extrusion. For the formulation having an obvious inflection point in the compression test, the friction of kneaded mass was small and the current during high-compressing extrusion was also small. For the formulation without any obvious inflection point (liquid is squeezed and the support stress is not lower), when the wet kneaded mass is compressed in a high-compressing extruder, the friction of the compressed kneaded mass during extrusion and the load of extrusion rapidly increased. In other words, for high-compressing extrusion (as with a double-shafted extruder), it is favorable that the formulation has an inflection point in the compression test. In addition, the fact that the formulation has an obvious inflection point means that it has enough water retention.

Conclusion

The characteristics of a wet kneaded mass were analyzed by the compression test using several formulations. The electric current during extrusion was also measured continuously. For the compression test of the wet mass, an inflection point was appeared during the compression. At the inflection point, the voids of the wet mass were filled with liquid. Below the critical pressure, the support stress of the wall was proportional to the compression pressure and the apparent friction coefficient was fixed. Above the critical pressure, the water retention was significant for the friction of the compressed wet mass. In the case of large water retention, the apparent friction coefficient above the critical pressure became much smaller than that below, since the medium of pressure transmission was changed from a powder to liquid. On the other hand, in the case of small water retention, the liquid in the wet mass was squeezed out and the change in the apparent friction coefficient was small. It was considered that a high-compressing type extruder required a kneaded mass that had a large water retention and low critical pressure in the compression test. It could thus be estimated whether the formulation was suitable for a high-compressing type extruder. It was also suggested that the friction of the wet kneaded mass and the aptitude of the formulation for extrusion were understood by using the compression test. The compression test is therefore a very useful procedure at the first stage of a formulation study.

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