

Prediction of Granule Physical Property by a Novel Compression Energy of Wet Powder

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Wet granulation is a very important process and a reliable evaluation method for formulation study; thus it requires appropriate process control. In this study, a novel and effective method that involves a compression test of wet powder is proposed. Here, the compression energy, which could predict the capability of the wet powder for extrusion granulation as well as the physical properties of the final products, is used as a novel characteristic of wet powder. The compression energy was defined as the energy consumption derived from the compression speed and the transmission loss during the compression test. Lactose monohydrate was mixed with various additives such as hydroxypropylcellulose in the mass ratio of 0–10%. Various amounts of water were fed into the mixtures, which were kneaded in a planetary motion mixer to prepare the kneaded wet powders. The characteristics of these powders were evaluated by the compression energy. The kneaded wet powders were then extruded through an extrusion granulator, the electrical loads of the granulator during the operation were analyzed as the extrusion energy, and the physical properties of extruded granules were investigated. As a result, the granule strength and granule size distribution showed a good correlation with the compression energy. A good correlation was also observed between the compression energy of the kneaded wet powder and the extrusion energy regardless of the different additives and water contents. It was concluded that the compression energy of the wet powder could be used for the formulation study and the process control of wet granulation.

Key words compression test; wet granulation; formulation study; process control

Wet granulation is a significant process for handling powder materials. So far, many studies have been carried out to control the properties of granules.^{1–5} In wet granulation, extrusion granulation is regarded as an appropriate method to easily obtain uniform physical properties. Extrusion granulation consists of kneading and extrusion, and it is well known that the condition of the kneaded material significantly influences the properties of the final products⁶ as well as the condition of the extruder. However, the control of the kneading process has relied considerably on the operator's experience and ability to judge the condition of the wet powder by touching it. Therefore, a quantitative evaluation of the kneaded material is required for general process control.

A formulation study is very important for stable manufacturing and maintaining the desired quality. The study includes the design of the dosage form and manufacturing process. Various types and amounts of additives should be examined to achieve the desired aspects such as dissolution, stability and manufacturing suitability. However, a hurdle to process development is that active pharmaceutical ingredients (API) are usually very expensive and their quantity is tiny. It is thus difficult to sufficiently examine the effects of various parameters. If the properties can be evaluated by a smaller sample quantity, significant savings in the cost, time and labor can be made, leading to the achievement of the optimal formulation.

In our previous study, we have already reported that a compression test can easily evaluate the characteristics of a kneaded wet powder by using a small amount of sample.^{7–9} In this study, the compression energy of the wet powder, which could represent its granular physical properties and characteristics of wet powder quantitatively, was used as a novel characteristic.

Experimental

Powder Materials Table 1 lists the powder materials used and Table 2 provides a summary of the formulations. Lactose monohydrate (DMV) was used as a filler, and hydroxypropylcellulose (Nippon Soda), microcrystalline cellulose (Asahi Kasei), low-substituted hydroxypropylcellulose (Shin-Etsu Chemical) and carmellose calcium (Gotoku Chemical) were used as the additives. Two grades of HPC—SSL and L—were used; SSL is less viscous than L. Two grades of L-HPC—LH11 and LH20—were also used; LH11 and LH20 differ in their degrees of substitution. LH20 is more substituted. These materials were mixed and kneaded with purified water in a planetary motion mixer (25AM-02-rr, DALTON Corporation).

Table 1. Powder Samples

Material	Grade	Abbreviation
Lactose monohydrate	Pharmatose 200M	Lactose
Hydroxypropylcellulose	L	HPC-L
	SSL	HPC-SSL
Microcrystalline cellulose	PH-101	MMC
Low-substituted hydroxypropylcellulose	LH11	LH11
	LH20	LH20
Carmellose calcium	ECG-505	CMC Ca

Table 2. Formulation of Wet Powder

Filler	Additive type	Additive content (%)	Water content (%)
Lactose	—	—	8–14
	HPC-L	1, 3, 5	9–12
	HPC-SSL	0.5, 1, 3	10–12
	MCC	5, 10	10–25
	MCC (+HPC-L)	5 (1, 3)	10–25
	LH11	5, 10	10–30
	LH20	5, 10	10–30
	CMC Ca	5, 10	10–25

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Equipment and Procedure Figure 1 shows a schematic diagram of the experiment. A planetary motion mixer that has two hook-shaped paddles (25AM-02-rr, DALTON Corporation) was used for mixing and kneading. The vessel is 320 mm in diameter and 310 mm in depth. The paddles revolved at 1.2 rps and rotated at 2.76 rps. One kilogram of powder samples was fed and kneaded with a predetermined amount of purified water.

The compression test of the wet powder was conducted using a compression tester (AUTO GRAGH AG-50kNE, Shimadzu Corporation). The compression device comprised a cylinder with an internal diameter of 11.3 mm and upper and lower punches. The upper punch was pushed down by the crosshead of the compression tester at a speed of 10 mm/min and the kneaded wet powder was compressed between the upper punch and the lower fixed one. The compression force, its transmission force to the lower punch, and the position of the crosshead were recorded every 50 ms.

In this study, the compression energy E_C was defined to evaluate the properties of the wet powder. E_C is the integrated compression power consumption, which is the multiplication of the transmission loss and the compression speed, for the duration of the compression test (Eq. (1)):

$$E_C = \int_0^T (F_L \times v_C) dt \quad (1)$$

The transmission loss F_L is given by Eq. (2):

$$F_L = F_C - F_T \quad (2)$$

where F_C and F_T are the compression force of the upper punch and the transmission force to the lower punch, respectively.

The compression speed at a certain time v_C was calculated based on Eq. (3):

$$v_C = d(|y_0 - y| + \delta) / dt \quad (3)$$

where $(|y_0 - y| + \delta)$ represents the height of the wet powder being compressed; y , the position of the crosshead; and y_0 , its position at 10 N of compressing force without a sample. δ is the deflection of the equipment under the pressure.

The kneaded wet powder was also granulated using a dome-type extruder

(DG-01, Fuji Paudal). The dome-type extruder comprised a cylinder, auger screw and dome-shaped screen. The internal diameter of the cylinder is 56 mm and its length is 102 mm. A screen with a pore diameter of 0.8 mm was used. The kneaded wet powder was extruded through the screen. During the extrusion, the electrical currents, which indicate the load during extrusion, were continuously monitored and analyzed by a personal computer. Finally, the extrusion energy to extrude one gram of powder was calculated based on the integrated net electric power consumption divided by the amount of extruded powder mass.

The extruded granules were dried in an oven at 60 °C. The granule size distribution was measured by sieve analysis. The crushing energy of the sieved granule (710–1000 μm) was then measured using a particle hardness tester (GRANO, Okada Seiko Co., Ltd.). The crushing energy of a granule was calculated by the integration of the crushing force over 0–200 μm of crushing distance.

Results and Discussion

Figure 2 shows typical diagrams of the compression test. In the beginning, transmission loss F_L increased and compression speed v_C decreased slightly with an increase in compression force F_C . After that, F_L showed a peak at a certain point and v_C decreased sharply. This point is regarded as the critical point in the compression test of wet powder.⁹⁾ It indicates complete compression, where voids in the wet powder are eliminated. The obvious appearance of the critical point suggests that the wet powder has sufficient viscosity and water retention and hence it is suitable for extrusion. In the last stage of the compression test, F_L and v_C showed an almost constant value. Meanwhile, the compression power consumption, which is the multiplication of F_L and v_C , showed the same pattern as F_L . In addition, compression energy E_C showed an inflection at the critical point.

Figure 3 shows the compression energies for samples pre-

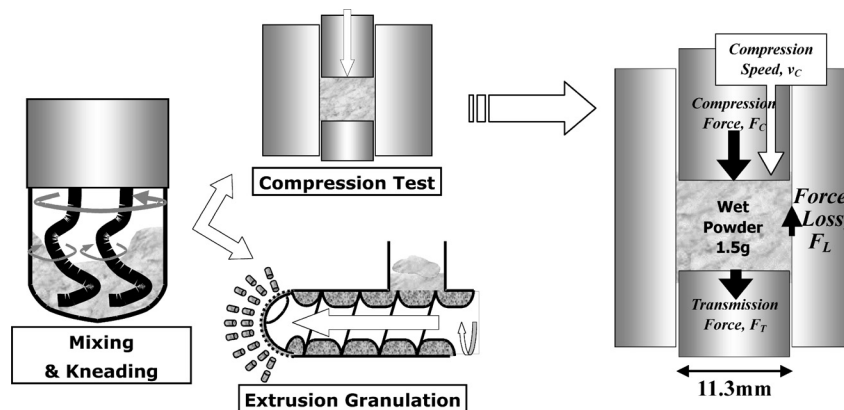


Fig. 1. Schematic Diagram of Experimental Set-up

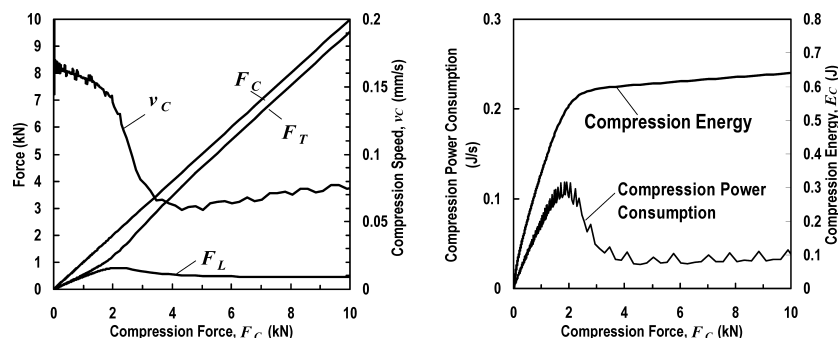


Fig. 2. Typical Diagram of Compression Test

Left: transmission force, loss of force, and compression speed. Right: compression power consumption and compression energy. Sample: extruded powder containing 5% HPC-L and 9% water.

pared at different kneading conditions with a formulation of lactose containing 5% HPC-L. The water contents were 9% and 10%. The kneading times were 3 and 10 min. The “extruded” wet powders were tested as the extensive kneaded condition. The difference in the kneading condition caused a difference in the compression energy; since the kneading time was longer and the water content was greater, the compression energy showed a smaller value. In other words, the progress of kneading resulted in a small compression energy. It was considered that the compression energy obviously represented the characteristics of the kneaded wet powder. Therefore, the compression energy was subsequently used for evaluation. Here, the compression energy under 1 kN—the compression energy calculated from 10 N through 1 kN of the compression force—was selected because it showed good correlations to various physical properties of granule.

Figure 4 shows the relationship between the size distribution of the dried granule and the compression energy of the kneaded wet powder. The samples used here were the same as those in Fig. 3. The fine fraction (710 μm pass) and coarse fraction (1000 μm on) of the granules were plotted against the compression energy under 1 kN. A good linearity was observed between the size distribution and the compression energy. The kneaded wet powder showed that a large compression energy resulted in a fine fraction, while a small com-

pression energy resulted in a coarse fraction.

Figure 5 shows the relationship between the crushing energy of the dried granule and the compression energy of the kneaded wet powder. The samples used here were also the same as those in Figs. 3 and 4. The drawn curve shows the tendency of the plots. A good correlation was also observed, *i.e.*, a low compression energy resulted in strong granules.

Based on Figs. 4 and 5, it was confirmed that the kneaded powder determined the properties of the extruded granule. It was considered that the plasticity of the wet powder mass increased and the extruded granule became heavier and stronger when the kneading was conducted properly. It is thus very important to understand the conditions of the kneaded powder quantitatively for process control. The characteristics of the granule could be predicted by using the compression energy of the wet powder.

Figure 6 shows the extrusion energy of various formulations against the compression energy. Many types of powder mixtures, water contents, and kneading conditions were examined. The data for all the samples are plotted in (A). The data for all the samples, except overloaded sample during the extrusion, are plotted in (B) and (C). Depending on the additives, the relationship between the extrusion energy and the

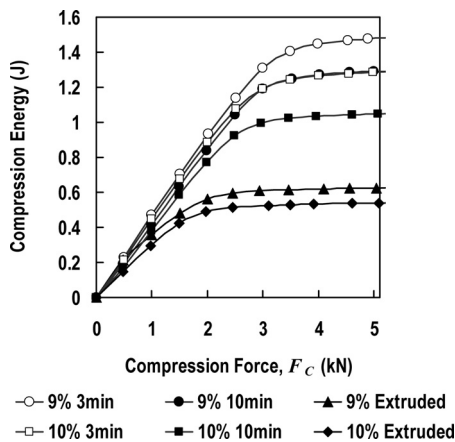


Fig. 3. Compression Energy Curves under Different Kneading Conditions
Sample: wet powder containing 5% HPC-L. %: water content, min: kneading time, extruded: extruded powder.

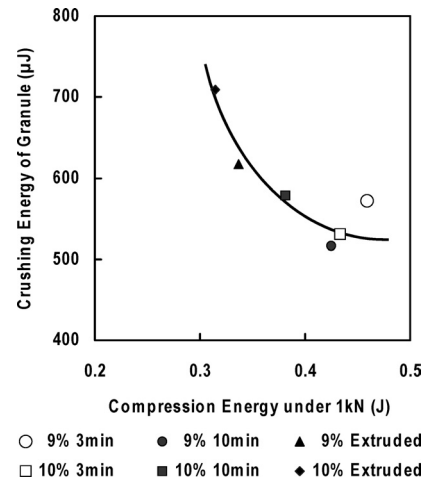


Fig. 5. Relationship between Crushing Energy of Granule and Compression Energy
Sample: wet powder containing 5% HPC-L. %: water content, min: kneading time, extruded: extruded powder.

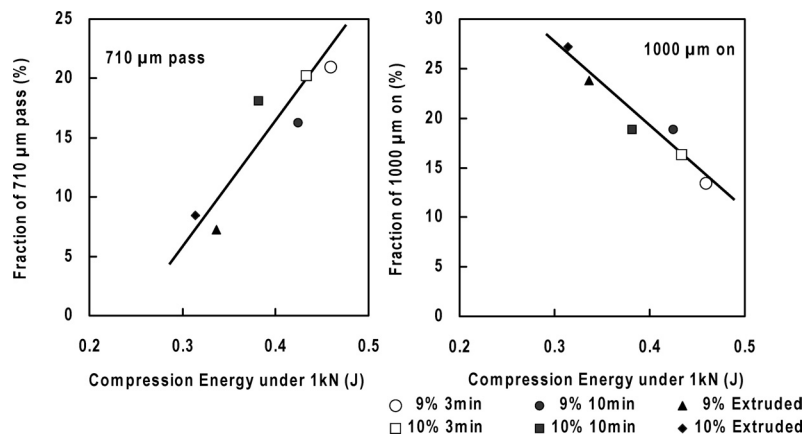


Fig. 4. Relationship between Granule Size and Compression Energy
Sample: wet powder containing 5% HPC-L. %: water content, min: kneading time, extruded: extruded powder.

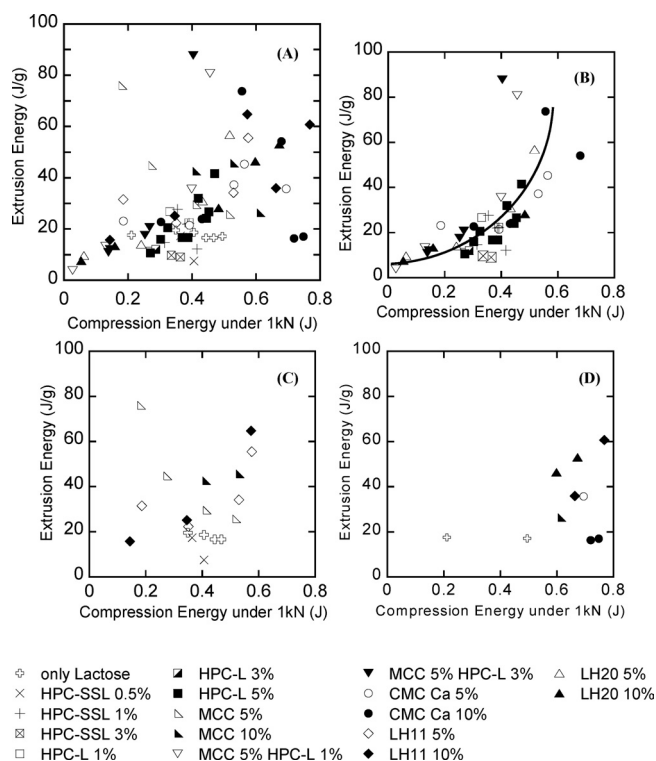


Fig. 6. Relationship between Extrusion Energy and Compression Energy for Various Wet Powders

(A): all examined samples, (B): group I, (C): group II, (D): overloaded sample during extrusion.

compression energy showed different behaviors. Group I (Fig. 6B) comprises the set of samples in which the critical point can be observed during the compression test. The samples show a good correlation, where a large compression energy required a large energy for extrusion regardless of the difference in the formulation. Group II (Fig. 6C) comprises the other samples that did not show an obvious critical point. A clear correlation could not be observed in this figure. The overloaded sample data was plotted in (D). In the case of poorly prepared powders, where there was a shortage of water, large friction, and low plasticity, the extruder stopped due to overload.

The formulation of Group I was generally used for extrusion granulation, and it had a sufficient viscosity and water retention for extrusion. It was considered that the extrusion energy of Group I could be roughly predicted by the compression energy.

In contrast, Group II formulations were unsuitable for extrusion. The viscosity and water retention of the kneaded mass were low, and an obvious critical point was not observed under the compression test. That is why, the compression behavior of Group II was different from that of Group I.

In most cases where the compression energy exceeded 0.6 J, the wet powder caused extruder overload. The main reason for the overload should be the shortage of water. In other words, the extruder overload and appropriate water content could be predicted by the compression test. In the sample with a compression energy below 0.6 J (only lactose), the reason for the overload appeared to be the low water retention.

Therefore, the compression test could estimate the extrusion load and the appropriate water content by using only small amounts of the powder sample without extrusion. In other words, wet powder that shows a large compression energy will lead to an overload during extrusion and additional examination of the formulation or condition will be required.

Conclusion

Compression tests of wet powder and extrusion granulation were carried out using various lactose-based formulations. The compression energy was used as a novel characteristic derived from the compression test. The granule size distribution and granule strength represented a good linear correlation with the compression energy. The compression energy also showed a good correlation with the energy consumption during extrusion, despite the difference in formulation. It was considered that the extrusion load could be roughly predicted by the compression energy without conducting actual extrusion experiments. This will lead to substantial savings in labor for formulation study and the examination of the manufacturing process.

It was thus suggested that the compression energy expressed the condition of the kneaded wet powder and provided valuable information for wet granulation. The compression energy of the wet powder should be a very useful parameter for formulation study and process control of wet granulation.

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