Measurement of Physical Strength of Pharmaceutical Extruded Pellets

Satoru WATANO,*[,a] Eri SHIMODA,[a] and Yoshifumi OSAKO[b]

Department of Chemical Engineering, Osaka Prefecture University,[a] 1–1 Gakuen-cho, Sakai, Osaka 599–8531, Japan and Research and Development Department, Fuji Paudal Co., Ltd.,[b] 2–2–30 Chuoh, Joto, Osaka 536–0005, Japan.
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This paper describes a novel and simple method for measuring the physical strength of pharmaceutical pellets prepared by extrusion granulation. Pharmaceutical powders composed of lactose, cornstarch, and microcrystalline cellulose were kneaded with purified water and dry binder (hydroxypropylcellulose), then extruded through a dome-type extrusion granulator. The physical strength of the dried extruded pellets was measured with a novel system: pellets and grinding alumina media were both fed into a ball mill pot and then "grinding degree" was measured as defined by the ground fine powder fraction after being rotated in the pot. The grinding conditions such as grinding time and number of alumina balls were optimized. The measured physical strength and pellet strength measured with a typical strength tester was compared. Quantitative relationships between the strength and the physical properties of the pellets such as friability and disintegration time were also investigated. It was found that the newly developed system could easily and accurately evaluate the physical strength of extruded pellets and could also predict the various physical properties.

Key words strength; pellet; grinding degree; ball mill; extrusion granulation

Extrusion granulation is widely used in the pharmaceutical,[1] agricultural, food, ceramic, chemical, and other industries. Its advantages are simple construction and operation, easy, low-cost, mass production and uniform physical properties (size, density, main ingredient content, *etc.*).

Up to this time, many studies have been conducted on the extrusion process. For process monitoring, measurement of extrusion pressure has been used to understand the rheological properties[2,3] and the flow characteristics of kneaded mass.[4] It is also reported that it can be used to estimate extruder performance.[5] In addition, studies on the effect of the process parameters such as particle size,[6] mixing procedure,[7] and kneading conditions[3] on the extrusion process have been carried out.

However, evaluation methods, especially of the strength of extruded pellets have not been thoroughly studied. Although the Japanese Industrial Standards (JIS)[8] regulate the methods for measuring the strength and hardness of industrial and mineral materials, it does not cover medicines, agricultural chemicals, chemical fertilizers, silk yarn, and foodstuffs. In the pharmaceutical industries, the extruded pellets are widely used, and the strength of extruded pellets is a key factor in terms of handling, transportation, and storage. In addition, since strength affects physical properties such as dissolution and disintegration time, it is important to establish a method for measuring the strength of extruded pellets using a simple procedure.

In this paper, a simple method is proposed to measure the strength of extruded pellets. The grinding degree of pellets after being ground in a ball mill pot was used to estimate the strength. The validity of this method has been confirmed by comparison of the results with the strength data obtained from a typical strength tester. The relationship between the measured strength and the physical properties of pellets was also investigated quantitatively.

Experimental

Powder Samples Table 1 lists powder samples used.[1] The excipient consisted of lactose, cornstarch, and microcrystalline cellulose as starting materials. The total weight of the powder samples was 5.0 kg. Four levels of hydroxypropylcellulose (HPC-L) were adopted as a binder, which was mixed as a dry powder into the starting materials before kneading. The water content was 22% constant regardless of the binder content.

Equipment and Procedures For wet kneading, a batch-type kneader equipped with twin Z-shaped blades (KDHJ-20, Fuji Paudal) with effective volume of 12 l was used. Five killograms of the stating materials with several levels of binder were fed into the kneader and mixed for 300 s. Water was then instantaneously added to the mixture (the water required 30 s to be fully discharged into the mixture), and kneaded for 300 s. The kneaded mass was extruded through a dome-type extrusion granulator[9] (TDG-110, Fuji Paudal) with screw rotational speed of 80 rpm and powder feed speed of 2.2 kg/min. The pore size, pore opening area ratio, and thickness of the dome-shaped die were 0.8 mm, 22.8% and 0.8 mm, respectively. After kneading, the obtained pellets were dried in a fluidized bed dryer (MDD-400N, Fuji Paudal). The drying conditions were as follows: heated air temperature 363 K and exhaust air temperature at drying end-point 343 K. The dried pellets were manually sieved using a 250 μm opening wire sieve (60 mesh wire sieve) to remove fine powders arisen during the drying process.

Table 1. Powder Samples

Samples	Number median diameter (μm)	Charge mass ratio (%)	Charge mass (kg)
Lactose[a)]	60	67.2	3.36
Cornstarch[b)]	15	28.8	1.44
Microcrystalline cellulose[c)]	40	4.0	0.2
(Total)			(5.0)
Hydroxypropylcellulose[d)]	21	1.0—4.0[e)]	0.05—0.2
Purified water		22.0[e)]	1.10

a) DMV (Pharmatose 200 M). *b*) Nihon Shokuhin Kako Co., Ltd. (Cornstarch W). *c*) Asahi Chemical Industry Co., Ltd. (Avicel PH-101). *d*) Nippon Soda Co., Ltd. (HPC-L). *e*) Charge mass ratios of purified water and HPC-L are based on the powder total mass (5.0 kg).

* To whom correspondence should be addressed. e-mail: watano@chemeng.osakafu-u.ac.jp

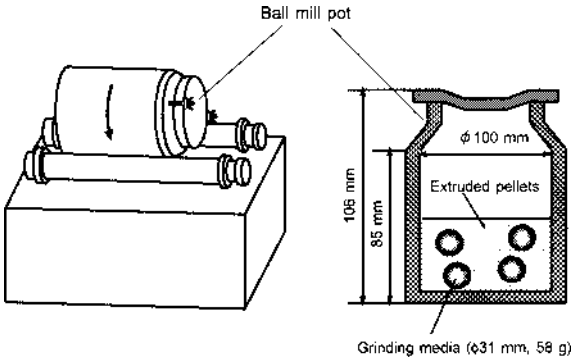

Fig. 1. Schematic Diagram of Grinding Degree Tester

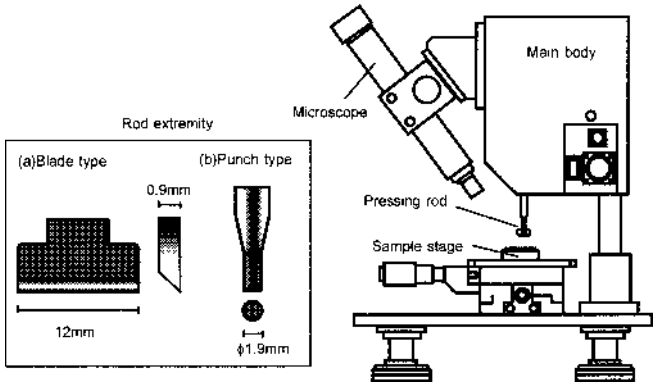

Fig. 2. Sketch of Strength Tester

Evaluation Methods The strength of extruded pellets was evaluated by the newly defined "grinding degree" described below. One hundred grams of the dried pellets were fed into a ball mill pot (Fig. 1) with several grinding media made of alumina (ϕ31 mm, 58 g×2, 4, 6, 8). The size of the grinding media was determined based on the results of a preliminary investigation (media that were too small could not grind hard pellets with high binder content, while media that were too large completely ground most of the pellets). The most effective pellet feed mass was selected and the pot rotating speed was determined based on the critical rotating speed.[10] After being rotated in the ball mill pot (75 rpm) for 3 processing times (5, 10, 15 min), all pellets and fine ground powders were collected and then sieved with a vibrating sieve shaker for 300 s. The mass fraction on each sieve was measured, and the size distribution was calculated based on a log-normal distribution. The grinding degree was defined by using the ratio of mass of powders under the optimum sieve (the optimization process will be shown in the next section) to the total powder mass.

Friability was measured by using a typical friability tester (Kayagaki Rika). 25 g of the dried pellets and 0.5 g of talc were fed into a friability tester with glass beads (ϕ7.3 mm, 0.52 g×50), and rotated at 25 rpm for 1200 s. The obtained powders were sieved through a wire sieve with 180 μm opening (83 mesh) and the friability was calculated based on the ratio of powder mass under this mesh to the total powder mass (25 g). It should be noted that the friability test evaluates the abrasion or surface grinding, while the grinding degree indicates the volume grinding (*i.e.*, the pellets are physically broken).

Strength of pellet was measured with a strength tester (Grano, Okada Seiko).[11] As shown in Fig. 2, an extruded cylindrical pellet was placed on a flat adjustment stage. A pressing rod with blade-type or punch-type extremities moved vertically at a speed of 100 μm/s and pressed the pellet from above. The direction of the downward cut was perpendicular to the major axis of the pellet. The moving displacement and pressed load (force) were measured continuously. The complete breaking load estimated the strength of the pellet.

Disintegration time was measured as follows: 0.1 g of dry pellets was placed in a 900 ml of water (310 K) and agitated with a paddle at 150 rpm using the JP dissolution test vessel and paddle.[12] The time required for the pellets to dissolve completely in water was measured manually.

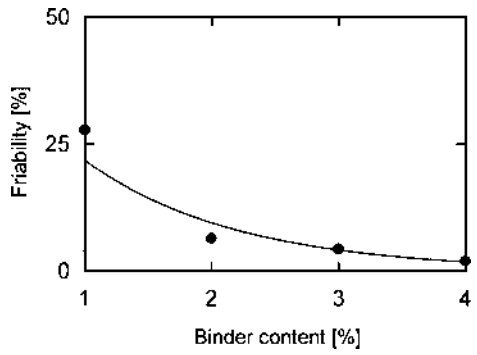

Fig. 3. Friability of Extruded Pellets as a Function of Binder Content

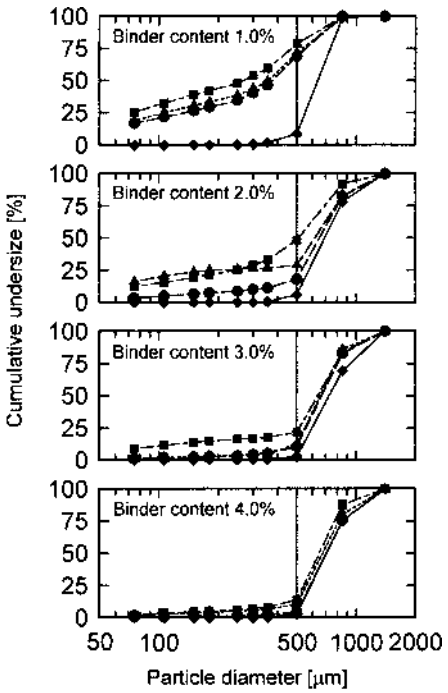

Fig. 4. Size Distribution Change at Various Grinding Times and Binder Contents

◆, 0 min; ●, 5 min; ▲, 10 min; ■, 15 min.

Specific surface area of pellets was measured with a BET adsorption method (Model 4200, Nikkiso).

Results and Discussion

Figure 3 shows the friability of extruded pellets as a function of binder content. The friability is almost constant when the binder content is greater than 2%. It is thus clear that the friability test cannot be used to estimate the strength of extruded pellets, especially in the range where the binding force is relatively large.

Figure 4 illustrates the size distribution change at various grinding times and binder contents in the ball mill pot. In the low binder content range (less than 2%), volume grinding where almost all of the pellets were broken was observed, while in the high binder content range (greater than 3%), surface grinding was observed. In the low binder content range, the increased grinding time resulted in a higher grinding effect, while in the high binder content range, the effect of grinding time on the size distribution change was small. It was also found that the mass fraction under 500 μm (30

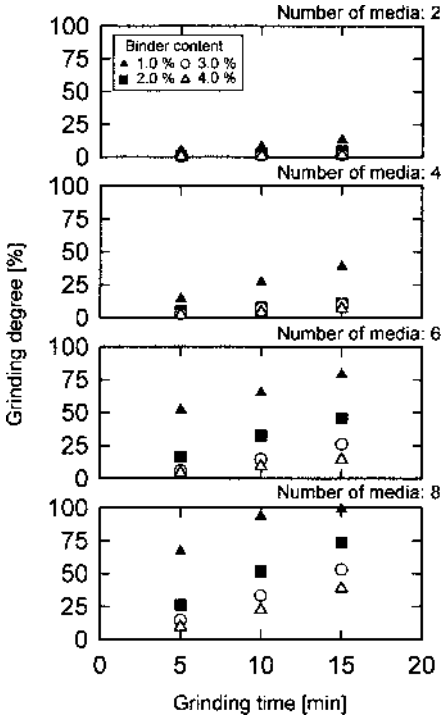

Fig. 5. Relationship between Grinding Degree and Grinding Time with Various Numbers of Grinding Media

mesh) sieve clearly showed a grinding effect. The grinding degree was thus defined by the following equation.

$$\text{grinding degree} = \frac{\begin{pmatrix}\text{mass fraction under}\\ 500\,\mu\text{m (30 mesh) sieve}\end{pmatrix}}{\text{total pellet mass (100g)}} \times 100\ [\%] \quad (1)$$

Figure 5 illustrates the relationship between grinding degree and grinding time with various numbers of grinding media. The grinding degree increased when the grinding time was long and the number of media was large. However, when there were 2 or 4 media, the grinding degree was small without showing clear difference despite the change in grinding times and binder contents. Also, in case that the number of media was 8, the grinding effect was so large that the grinding degree of soft pellets prepared with low binder content (less than 1%) was nearly 100%. Considering the binder content range and moisture content, it is safe to state that the pellets prepared under various conditions examined here cover most of the range of pharmaceutical pellet strength. Therefore, 6 media with grinding time of 15 min most clearly determined the difference in the strength of pellets prepared here, and we thus defined these operating conditions as optimal. The conditions were used to obtain the grinding degree, as described below.

Figure 6 shows the strength measurement results obtained using the strength tester. In this figure, the plots describe the average of 30 measurements and the vertical bars show data scattering.

Two types of the pressing rod extremity, the blade type and punch type, were used in this study. As seen from Fig. 6, both types tended to show greater strength at higher binder content. The punch type generally resulted in greater strength and wide data scattering, while the blade type resulted in less strength with small data scattering. Since both types yielded

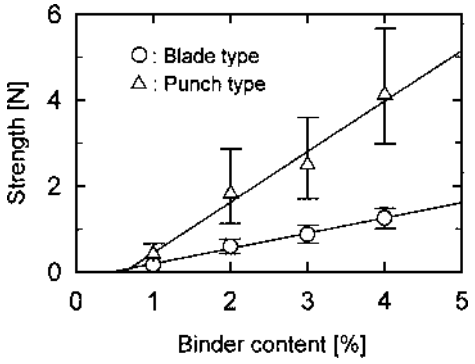

Fig. 6. Strength Measurement Results

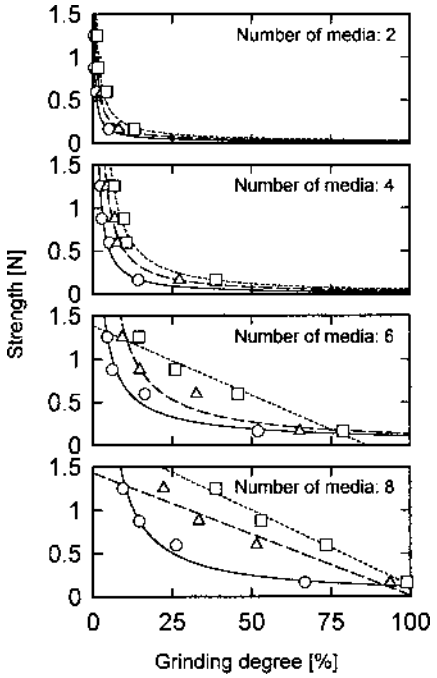

Fig. 7. Relationship between Strength and Grinding Degree of Pellets under Various Operating Conditions
○, 5 min; △, 10 min; □, 15 min.

almost the same degree of strength and data scattering when spherical granules were tested, these different strength characteristics were assumed to originate from the cylindrical pellet shape; when the pressing rod with the punch type extremity pressed a pellet, its supporting point was difficult to fix due to the distorted cylindrical shape, resulting in large data scattering. In addition, the greater strength obtained with the punch type extremity may originate from the absorption or distribution of pressure because of the distorted cylindrical shape. As a result of these findings, it was concluded that the strength measurement using a strength tester with the punch type extremity was not suitable for cylindrical pellets. Although the blade type extremity could be used for cylindrical extruded pellets, at least 30 experimental results must be obtained to avoid a data scattering.

Figure 7 illustrates the relationship between pellet strength and grinding degree under various operating conditions. Under the optimum conditions (6 media with grinding time of 15 min), the strength and grinding degree could be expressed by a straight line. In this case, the grinding degree

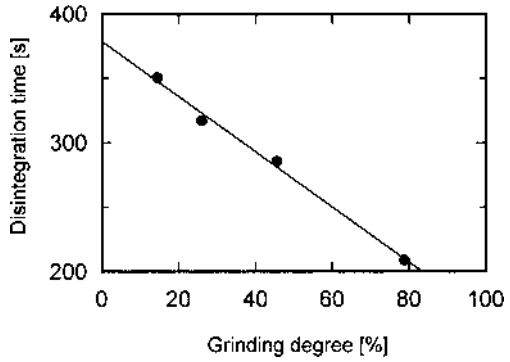

Fig. 8. Relationship between Disintegration Time and Grinding Degree of Pellets

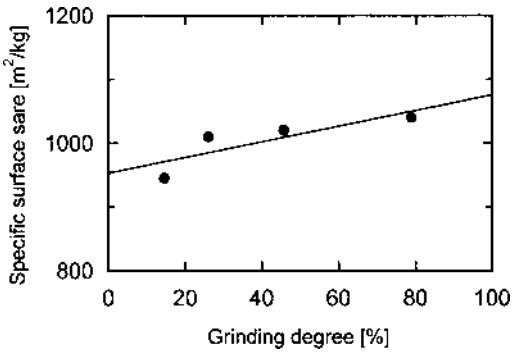

Fig. 9. Relationship between Specific Surface Area and Grinding Degree of Pellets

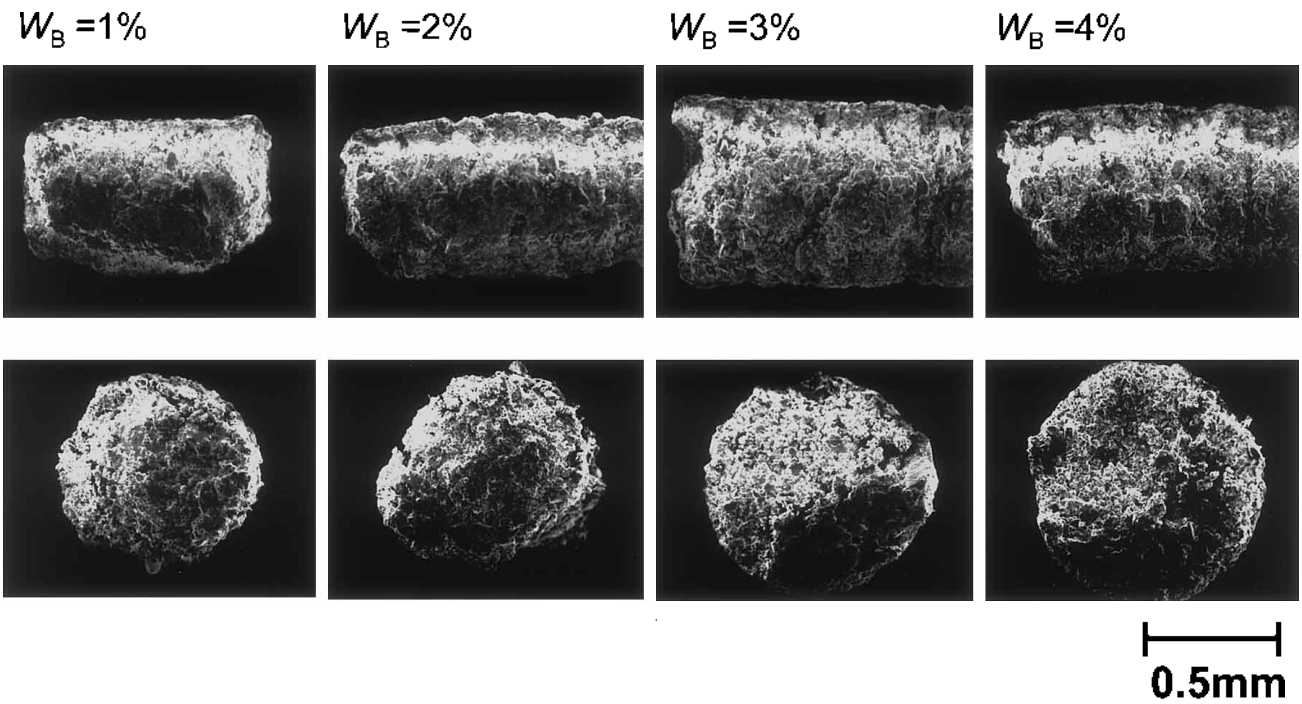

Fig. 10. SEM of Extruded Pellet Prepared with Various Binder Contents (W_B)

was considered to evaluate the physical strength of pellets accurately. In the following, strength measurements based on grinding degree were conducted under these optimum conditions.

Figure 8 shows the relationship between disintegration time and grinding degree. All the plots are on the regression line, implying that the disintegration time of pellets can be predicted by the grinding degree. Figure 9 also shows the relationship between the specific surface area and grinding degree. Although the difference is small, the specific surface area of pellets tended to increase with the increase in grinding degree (*i.e.*, strength decreased). The scanning electron micrographs (SEM) shown in Fig. 10 also confirm that the difference in the surface roughness and inside condensation (void) are small when the binder content varies from 1 to 4%. This may be due to the fact that the deformation property is mainly determined by the amount of water, *i.e.*, the solid–liquid occupied ratio. Although the surface roughness originating from wet-mass deformation characteristics are the same, the disintegration property when the pellets are dissolved in water or the physical strength when they are subjected to pressure or external forces may change significantly because the binding force of each powder differs based on the amount of binder. Although the difference in the specific surface areas is small, the specific surface area of each pellet is expressed by a straight line, indicating that this property can also be predicted by the grinding degree.

Conclusions

The simple "grinding degree" method is proposed to measure the strength of extruded pellets. This method measures a fraction of fine powders that occur after grinding the extruded pellets in a ball mill pot. An adequate correlation can be estimated between the physical strength of pellets as expressed by the grinding degree and the strength of pellets as measured using a strength tester. Evaluation of the physical properties of pellets also suggests that the physical properties such as disintegration time and specific surface area can be linearly expressed by the grinding degree. From these findings, it is concluded that the newly developed method can

easily and accurately evaluate the physical strength of extruded pellets as well as predict various their physical properties.

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