Development of a Novel Vertical High Shear Kneader and Its Performance in Wet Kneading of Pharmaceutical Powders

Satoru WATANO,*[,a] Takumi OKAMOTO,[a] Masamitsu TSUHARI,[b] Ichiro KOIZUMI,[b] and Yoshifumi OSAKO[b]

Osaka Prefecture University,[a] 1–1 Gakuen-cho, Sakai, Osaka 599–8531, Japan and Fuji Paudal Co., Ltd.,[b] Osaka 536–0005, Japan. Received October 5, 2001; accepted December 13, 2001

A novel multi-functional vertical high shear kneader has been developed. Wet kneading of pharmaceutical powders was conducted under various blade components and operating conditions. Compression properties of wet kneaded mass was analyzed and dispersion of binder liquid (water) among the mass was investigated by assaying tracer aqueous pigment. Pellets were produced through a dome type extrusion granulator with continuous extrusion pressure measurement device and a fluidized bed drier, and then the physical properties were measured. Quantitative relationship between the pellet's physical properties and the binder dispersion condition as well as the compression properties could be obtained. It was found that the newly developed kneader was very effective to uniformly disperse binder as well as impart high shear stress to the wet mass without generating obvious adhesion onto the vessel wall. It was also pointed out that the extrusion pressure could determine the physical strength of pellet. This method proposes a new methodology for continuous monitoring of kneading condition as well as predicting pellet's physical properties.

Key words wet kneading; vertical high shear kneader; extrusion pressure; pressure transmission; physical strength

Kneading of powder materials[1—3] has been well used in the pharmaceutical, agriculture, food, chemical, forage and fertilizer industries. Most of the cases, kneading operation is conducted just before the extrusion or molding processes, and the performance of kneading seriously affects quality of the final product or process efficiency. Therefore, it is important to quantitatively analyze and monitor the kneading process.

So far, a high shear mixer has been well used for wet granulation[4] as well as for wet kneading. In the case that the high shear mixer is used for wet kneading, several advantageous points such as easy to disassemble with easy cleaning can be pointed out. However, the problems such as enormous sticking on the vessel wall or larger physical strength of extruded pellets that may cause longer dissolution time have also been known on the contrary. It is required to improve the problems of high shear mixer while keeping the advantageous points when applied to wet kneading.

In this study, a multi-functional vertical high shear kneader has been newly developed and applied for wet kneading. Wet kneading of pharmaceutical powders composed of acetaminophen and excipients was conducted under various blade components and operating conditions. Dispersion of aqueous binder and compression properties of wet mass was investigated to quantitatively analyze the kneading condition. Dried pellets were then produced through a dome type extrusion granulator and a fluidized bed drier, and physical properties of the pellets were examined experimentally. Comparison between kneading performance of the novel kneader and of a conventional high shear mixer (granulator) was also conducted.

Experimental

Apparatus Figure 1 shows a schematic diagram of multi-functional vertical high shear kneader (SPG-10, Fuji Paudal Co., Ltd.) developed. The vessel is a laboratory size, which has an inner diameter of 290 mm and a capacity of 10 l. The bottom of the vessel is equipped with a kneading blade that rotates horizontally. Several operating parameters such as torque of main shaft, power consumption of motor drive and temperature of kneaded mass can be continuously measured and monitored *via* a personal computer. Chopper blade can also be installed onto the sidewall of the vessel, if necessary.

Figure 2 illustrates a newly developed kneading blade, and Fig. 3 shows appearance of various blades used. The kneading blade is composed of four parts; (a) scraper, (b) main blade, (c) dispersion blade, and (d) cap. The main blade has an edge having inclination of 20 degrees to the backward, opposite direction of the blade movement. This is designed so as to press down the wet kneaded mass, and to add high compaction force and high shear stress to the mass (typically, main agitator blade of high shear mixer (granulator) has an edge to the opposite direction of our kneading blade, thus powders are lifted up by the edge inclination). The dispersion blade equipped on the top of the main blade works to move away the wet mass to the vessel outside di-

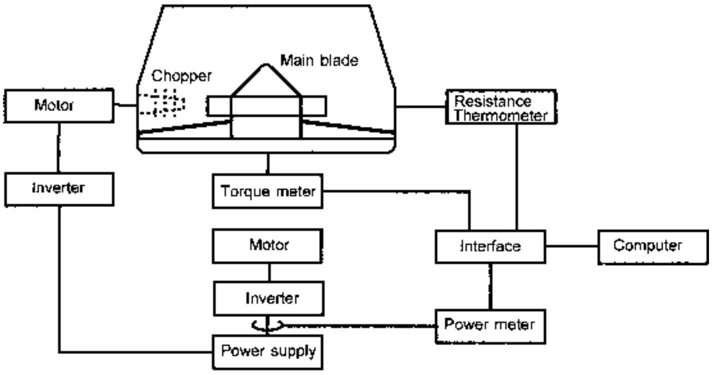

Fig. 1. Schematic Diagram of Multi-functional Vertical High Shear Kneader (SPG-10)

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

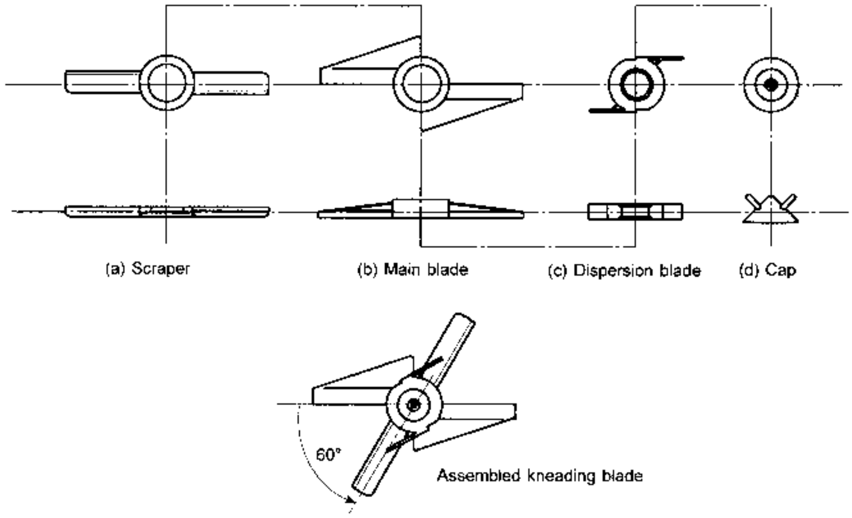

Fig. 2. Newly Developed Kneading Blades

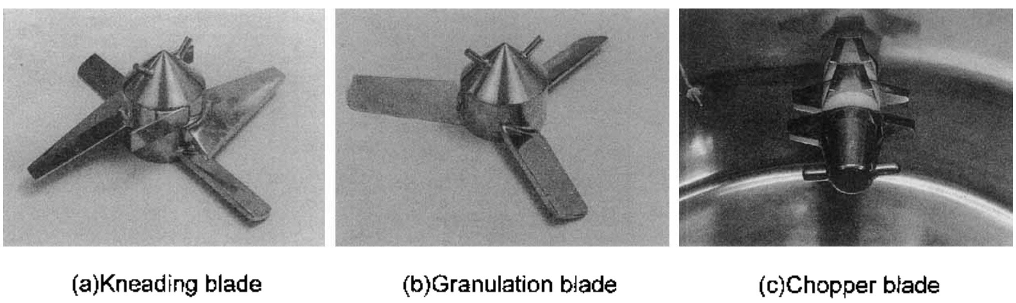

Fig. 3. Appearance of Various Blades

rection. This blade is also effective to prevent wet mass from staying at the upper part of the main blade. Under the main blade, a scraper is equipped so as to lift up the wet mass. Due to the both functions of upper main blade and lower scraper, the wet mass also receives repeatedly folding effect. These effects effectively function to promote wet kneading. Contrary to the kneading blade (Fig. 3a), an agitator blade (Fig. 3b) that is usually used for wet granulation has no effect to press down the powder bed. Also, due to the high centrifugal force and upward force from agitator blade, powder bed makes a vortex flow,[4,5] which causes heavy sticking on the wall of the vessel, especially in the wet kneading of high moisture content levels and of adhesive materials.

In the following, blade components are described using the abbreviations; kneading blade without chopper blade is shown as KB, the kneading and granulation blades with chopper blade are referred to as KBC and GBC, respectively.

Figure 4 draws a schematic diagram of dome type extrusion granulator[6] and a newly developed extrusion pressure measurement system. Extrusion granulation of the wet kneaded mass was conducted by using a dome-type extruder (DG-L1, Fuji Paudal Co., Ltd.). This extruder consists of a hemispherical dome type punching screen (diameter of the dome is 58 mm, diameter of each hole and width of the screen are both 0.8 mm, and the opening area ratio is 22.5%), single shaft, screws and extrusion blade at the extremity of the shaft. The kneaded mass moves forward by the screws then being extruded through the screen. Receiving compression force and tensile stress when it goes through the screen occurs the plastic deformation of the mass. Onto the hemispherical dome type screen, a hole (ϕ 5 mm) is made and a semiconductor pressure sensor is placed so as to measure pressure when the wet mass goes through the screen. The measured pressure is amplified and converted to a digital signal, which is processed by a personal computer.

Powder Samples Table 1 lists powder samples used. Acetaminophen as a model active ingredient and excipients composed of lactose, cornstarch and micro-crystalline cellulose were used as powder samples. The reasons that we used acetaminophen was as follows; i) analyze kneading perfor-

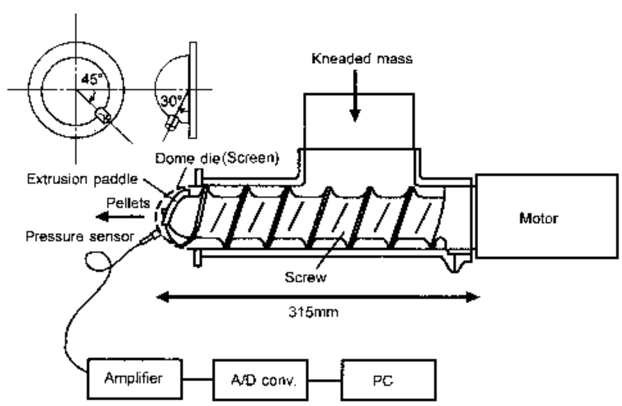

Fig. 4. Schematic Diagram of Dome Type Extrusion Granulator and Extrusion Pressure Measurement System

mance by using powder samples that were difficult to disperse binder liquid (water), ii) use powder samples that were difficult to knead in a conventional high shear type kneader, and iii) utilize model powder samples that were rather close to the actual dosage formulation.

Experimental Method Kneading experiment by a novel kneader was conducted as follows; powder samples were fed into the kneader and mixed for 120 s. Binder liquid (water) was fed into the kneader at once from the top lid through a stainless funnel. The kneading was conducted under the same operating conditions (the main and the chopper blades were set to run at 150 rpm and 3600 rpm, respectively). The kneaded mass was then extruded through a dome type extrusion granulator shown in Fig. 4. The mass feeding speed was 21.6 kg/min and the screw rotational speed was 60 rpm. The obtained pellets were then dried by a fluidized bed drier (NQ-125, Fuji Paudal

Table 1. Powder Samples

Material	Number median diameter	Charge mass (charge ratio)
Lactose[a)]	60 μm	0.705 kg (47.0%)
Cornstarch[b)]	15 μm	0.303 kg (20.2%)
Microcrystalline cellulose[c)]	40 μm	0.060 kg (4.0%)
Acetaminophen[d)]	11 μm	0.432 kg (28.8%)
(Total)		1.500 kg (100.0%)
Hydroxypropyl cellulose[e)]	21 μm	0.045 kg (3.0%)
Purified water		0.375 kg (25.0%)

a) DMV (Pharmatose 200 M); *b*) Nihon Shokuhin Kako Co., Ltd. (Cornstarch W); *c*) Asahi Chemical Industry Co., Ltd. (Avicel PH-101); *d*) Yamamoto Chemical Co., Ltd. *e*) Nippon Soda Co., Ltd. (HPC-L).

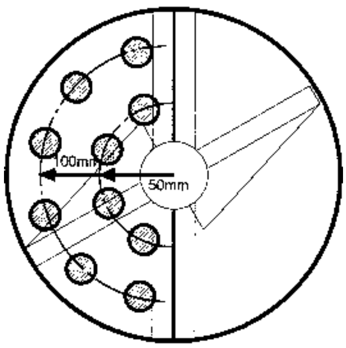

Fig. 5. Sampling Locations

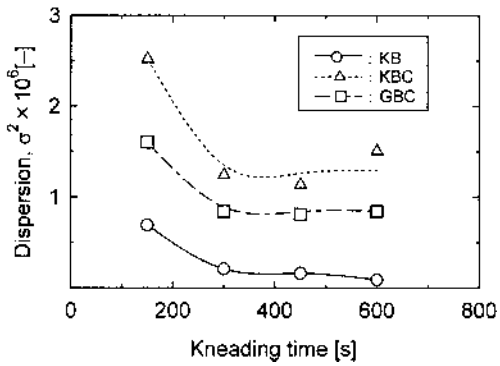

Fig. 6. Temporal Change in Water Dispersion

○: KB (kneading blade), △: KBC (kneading blade with chopper), □: GBC (granulation blade with chopper).

Co., Ltd.)[7)] under the fluidization air temperature was 353 K.

Evaluation Method Dispersion of water among the kneaded mass[8,9)] was measured by using an aqueous pigment (Food blue No. 1, Toushoku Pigment Co., Ltd.) as a tracer. 0.1 wt% of the pigment was dissolved into binder solution (water) before kneading, and the wet kneaded mass (5.0 g) during the kneading operation was periodically sampled out from 10 different sampling points by using a spear-type sampling device (Shionogi Qualicaps Co., Ltd.). Considering the symmetry, the sampling location was determined as shown in Fig. 5. The height of each sampling point was 30 mm from the bottom. After taking the sample, it was immediately dissolved into a purified water (900 cm^3, 300 K), and then absorbance of the pigment (wave length of 629 nm) was measured by using a UV-visible recording spectrophotometer (UV-160A, Shimadzu Co., Ltd.). By substituting the obtained absorbance into Eq. 1, dispersion of water, σ^2, can be calculated (we here assume that behavior of the pigment is the same as water, since the pigment is very much soluble to water).

$$\sigma^2 = \frac{1}{10}\sum_{i=1}^{10}(A_i - A_0)^2 \qquad (1)$$

where A_i and A_0 are absorbance of the pigment among the sample, and mean value of the A_i ($i=1$ to 10), respectively.

Compression test of kneaded mass was conducted by using a developed compression tester.[8,9)] As previously reported, the tester consisted of a hydraulic pump, displacement sensor, upper and lower punches, cylinder, and personal computer. A cylinder having outside diameter of 40 mm, inside 11.3 mm (cross sectional area was just 1.0 cm^2) and height of 110 mm was placed between the upper and lower punches and 3.0 g of wet kneaded mass was fed into the cylinder. The upper punch pressed the mass at the moving speed of 5.0 cm/min, then the pressure transmission, G, was calculated by using the following Eq. 2.

$$G = P_L / P_U \times 100 \qquad (2)$$

where P_L and P_U indicated pressure of the upper and lower punches, respectively.

Strength of extruded pellet was evaluated by a grinding degree.[10)] 100 g of the dried pellets were fed into a ball mill pot (ϕ100×106 mm) with grinding medias made of alumina (ϕ31 mm, 58 g×6). After being rotated in the ball mill pot (75 rpm) for 15 min, all the pellets and ground fine powders were corrected and then sieved by a vibrating sieve shaker for 5 min. Mass fraction on each sieve was measured and then size distribution was calculated based on a log-normal distribution. The grinding degree, D, was defined by using the ratio of mass of powders under the 500 μm (30 mesh) sieve to the powder total mass. This degree was proved to evaluate the physical strength of pellets by utilizing the volume grinding.[10)]

Strength of pellet was also directly measured by a strength tester (Grano, Okada Seiko).[11)] An extruded cylindrical pellet was placed on a flat adjustment stage and a pressing rod having a blade type extremity moved vertically at a speed of 100 μm/s and pressed the pellet from above. The direction of cut down 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 pellet, H.

Disintegration time was measured as follows; 0.1 g of dry pellets were put into a 900 ml of water (310 K) and agitated by a paddle at 75 rpm using JP dissolution test vessel and paddle.[12)] The time required for the pellets to completely dissolve into water was measured manually.

Results and Discussion

Kneading Performance Figure 6 indicates temporal changes in water dispersion under various blade components. Previous to the discussion, it can be noted that the kneading by the granulation blade only cannot be conducted by the following reasons; i) most of the kneaded mass formed "ball" like spherical agglomerate larger than 20 mm, and ii) adhesion onto the vessel wall was enormous.

In case of using kneading blade without installing chopper blade (KB), the dispersion of water decreased (water dispersed well) with elapsed time and also the value of dispersion was very small as compared to other two data. This implied that the water was uniformly dispersed among the kneaded mass. Contrary to the kneading blade only, the kneading and granulation blades with chopper blade (KBC, GBC) indicated larger dispersion values, which decreased at the initial stage, followed by almost the constant values after 300 s kneading. Also, the kneading blade with chopper blade (KBC) indicated worse dispersion condition than the granulation blade with chopper (GBC). Due to the difference in the mechanical force and dispersion process of each blade, the dispersion data obtained after being kneaded in a long time operation could not reach to the same value.

Figure 7 denotes the pressure transmission characteristics. In all cases, the pressure transmission increased almost linearly with kneading time. According to our previous study,[8,9)] this implied that water dispersion increased and elastic deformation of kneaded mass became easier with elapsed time. Also, there was no obvious difference between kneading and

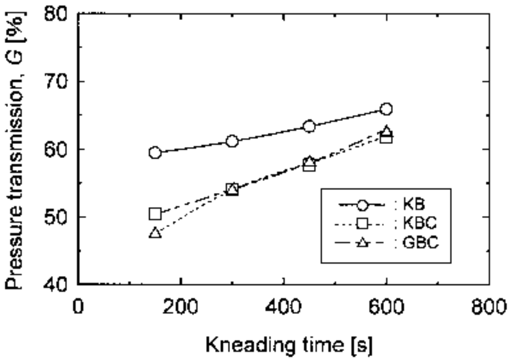

Fig. 7. Temporal Change in Pressure Transmission

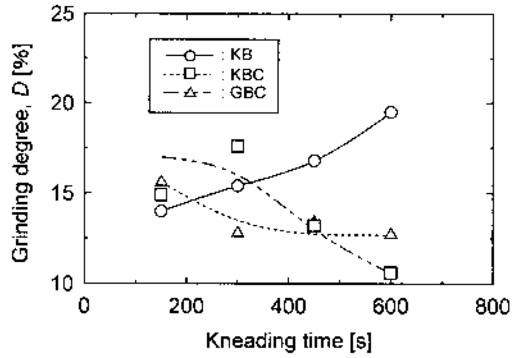

Fig. 9. Temporal Change in Grinding Degree

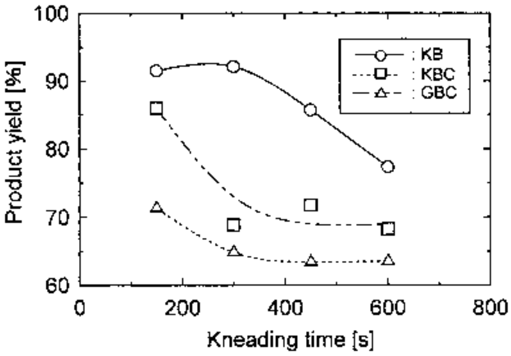

Fig. 8. Temporal Change in Product Yield

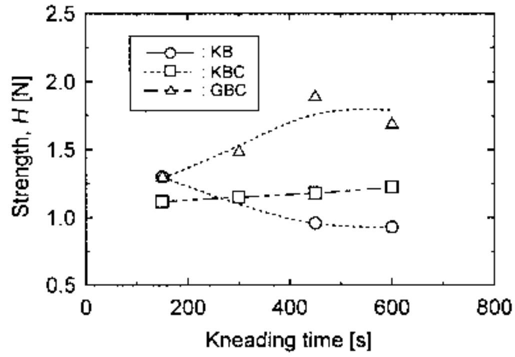

Fig. 10. Temporal Change in Granule Strength

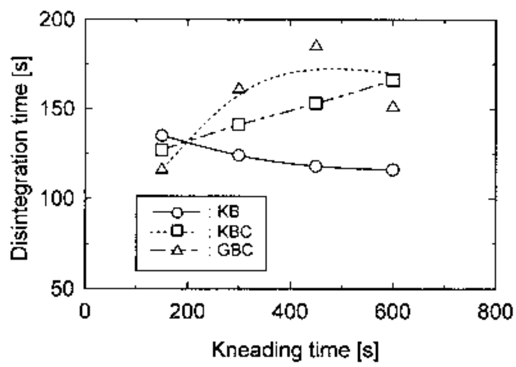

Fig. 11. Temporal Change in Disintegration Time

granulation blade with chopper, while the kneading blade without chopper indicated larger pressure transmission.

From the results obtained, the kneading process can be explained as follows. The big deference between with and without the chopper blade was a generation of "granulated particles" having diameter of about 5 mm. In case of installing chopper blade, granulated particles having rather hard strength could be obtained. Once this kind of "granulated particles" was produced, the water dispersion could not proceed anymore, while they were receiving high shear stress from the blade and their deformation characteristics changed. Therefore, water dispersion showed constant value, while pressure transmission increased with elapsed time.

Figure 8 describes product yield obtained by three blade components. Here, the product yield was defined as the amount of kneaded mass discharged automatically when the discharge door was opened. Seen from the figure, in all cases, the product yield decreased with kneading time, indicating adhesion onto the wall of vessel increased. However, in case of using the kneading blade only (KB), the decrease of product yield was small as compared to the other two cases. This proved the kneading blade designed not to make a vortex flow was effective to prevent powder adhesion. Also, self-cleaning function worked to decrease the powder adhesion.

Evaluation of Extruded Pellets Figures 9 and 10 indicate temporal changes in grinding degree and strength of dry pellets, respectively. The grinding degree increased and strength decreased with kneading time when the kneading blade (KB) was used. On the other hand, tendencies of these properties in case of using chopper blade for both kneading and granulation blades were completely contrary to the result obtained without chopper blade; grinding degree decreased and strength increased with kneading time. These results implied that the extruded pellets became strong (hard) when the chopper was installed while they became soft without the function of chopper blade.

Figure 11 shows temporal changes in disintegration time. The disintegration time of pellets prepared by using the kneading blade (KB) decreased due to the decrease in physical strength. On the other hand, the data obtained by using chopper blade (KBC, GBC) increased, because the pellets had large physical strength and contained small spherical "granulated particles" which were difficult to dissolve into water.

Measurement of Extrusion Pressure Figures 12 and 13 describe the relationships between extrusion pressure and granule grinding degree, and between extrusion pressure and granule strength, respectively. Figure 14 also describes rela-

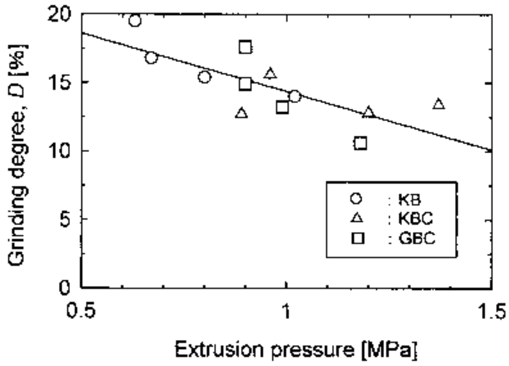

Fig. 12. Relationship between Grinding Degree and Extrusion Pressure
S.D.=0.746.

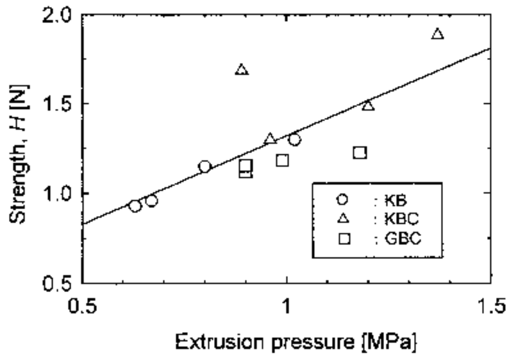

Fig. 13. Relationship between Granule Strength and Extrusion Pressure
S.D.=0.752.

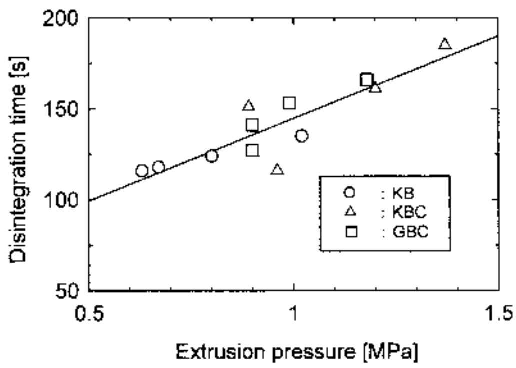

Fig. 14. Relationship between Disintegration Time and Extrusion Pressure
S.D.=0.871.

tionship between extrusion pressure and disintegration time. It is obvious that the granule properties can be linearly expressed by extrusion pressure, regardless of blade components. This implies that the extrusion pressure, *i.e.*, the resistance which the wet kneaded mass receives when passing through the pores of screen, determines the granule physical strength. Based on this concept, the granule properties prepared under different blade components can be explained as follows. In case of using the kneading blade (KB), water dispersion progressed and elastic deformation characteristics improved during the kneading operation because of the favorable movement of wet mass and of high shear stress and folding effect received by the blade. When the wet mass was extruded, the plastic deformation was easy, leading to receive small resistance force when the mass went through the pores on screen. Accordingly, shear stress required to deform the mass into pellet shape became small. This caused small extrusion pressure. Also, due to the small resistance and shear stress, the pellets became soft without compressed well. Therefore, the physical strength became small and disintegration time shortened when the kneading progressed. Contrary to this blade component, chopper rotation caused well-compressed small "granulated particles". Once the agglomerates were produced, water dispersion did not progress anymore, while surface of the agglomerate received high shear stress leading to improve the deformation properties. Although the complete deformation of small "granulated particles" required high shear stress during extrusion process, the resistance as well as extrusion pressure became large. This caused compaction of the pellets, leading to have large physical strength and prolongation of dissolution time. As a result of these findings, it can be concluded that the measurement of extrusion pressure is very effective to monitor kneading condition as well as to predict physical properties of extruded pellets.

Conclusions

A novel vertical high shear kneader has been developed and its performance in wet kneading was investigated. It was found that the newly developed kneader (kneading blade) was very effective to uniformly disperse water in wet kneading with minimizing the adhesion onto vessel wall. The used of chopper blade, however, generated well-compressed small agglomerates, leading to have large strength and prolongation of disintegration time of extruded pellets. This usage also caused large amount of adhesion onto the vessel wall. Therefore, in the wet kneading in high shear kneader, it is favorable to use our newly developed kneading blade without installing chopper blade. In addition to the kneading performance, the extrusion pressure during extrusion granulation was measured by a novel pressure measurement system. It was demonstrated that the extrusion pressure determined the physical strength of pellets. This measurement device was proved to be effective to monitor/predict physical properties of pellets.

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