

## Scale-Up of Wet Kneading in a Novel Vertical High Shear Kneader

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**A novel multi-functional vertical high shear kneader has been developed and its performance in wet kneading has previously been reported [Watano *et al.*, *Chem. Pharm. Bull.*, 50(3), 341–345 (2002)]. In this study, scale-up of wet kneading in the novel vertical high shear kneader was conducted. Pharmaceutical excipients composed of lactose, cornstarch and micro-crystalline cellulose were used as powder samples. Kneading operations were conducted under various operating conditions and three different vessel scales. The dried pellets were then prepared by extruding the wet kneaded masses through a dome-type extruder and their drying by a fluidized bed. The physical properties such as strength and disintegration time of the dried pellets were evaluated. It was found that the properties of the dried pellets and their scale-up characteristics were well expressed by an agitation power per unit vessel volume and dimensionless Froude number.**

**Key words** scale-up; wet kneading; vertical high shear kneader; agitation power; Froude number

Kneading is an operation to mix and disperse binder liquid into powder material in micro scale, which is well used in the pharmaceutical, agriculture, food, chemical, forage and fertilizer industries. Most of the cases, kneading operations are conducted to prepare wet mass for extrusion, and the performance of the kneading seriously affects the quality of the final product or process efficiency. Therefore, it is important to quantitatively understand the kneading process. Previously, we have developed a novel multifunctional vertical high shear kneader, which has several advantageous points such as easy to disassemble with easy cleaning, and its performance in wet kneading of pharmaceutical powders has been reported.<sup>1)</sup> We have shown that the newly developed kneader was very effective to uniformly disperse water in wet kneading with minimizing the adhesion onto vessel wall<sup>1)</sup> and the wet kneading conditions seriously determined the physical properties of dry pellets prepared by extruding the wet kneaded mass and fluidized bed drying.<sup>2–5)</sup> However, mechanism of kneading and its scale-up characteristics have not been studied yet.

In this study, wet kneading was conducted in the novel vertical high shear kneader under various operating conditions and vessel scales and the dried pellets were prepared by ex-

trusion granulation of the wet kneaded masses and the fluidized bed drying. Physical properties of the pellets such as strength and disintegration time were evaluated and the effects of the operating parameters and vessel scales on the physical properties were investigated experimentally. By using the several dimensionless factors, the scale-up characteristics were analyzed.

### Experimental

**Apparatus** Figure 1 shows a schematic diagram of a novel multifunctional vertical high shear kneader.<sup>1)</sup> Three different sized kneaders, all of which obeyed geometric similarity, were used for the scale-up experiments. Their dimensions and vessel scales are listed in Table 1. The bottom of the kneader's vessel is equipped with a kneading blade that rotates horizontally. The kneading blade is composed of scraper, main blade, dispersion blade, and 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 with high shear stress to the mass (typically, main agitator blade of high shear type 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 direction. 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

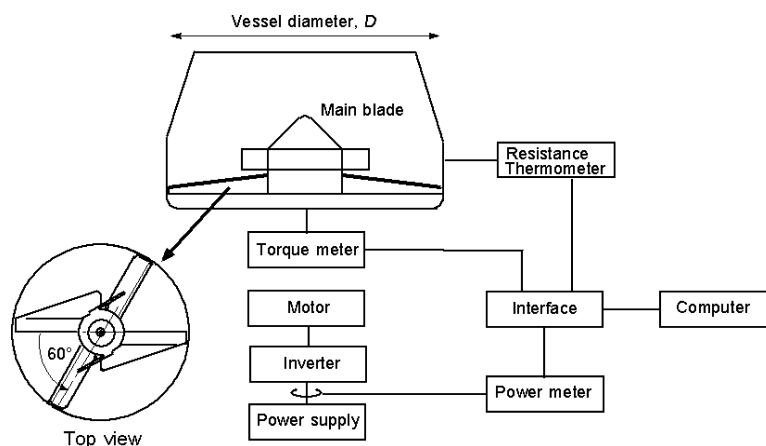


Fig. 1. Schematic Diagram of Multifunctional Vertical High Shear Kneader

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Table 1. Dimensions of Each Scale

	SPG-10	SPG-25	SPG-200
Vessel volume [l]	9.8	25.8	206
Vessel diameter, $D$ [mm]	290	400	800
Scale ratio [—]	1.00	2.63	21.0
Total charge mass [kg]	1.50	4.07	32.45

Table 2. Powder Samples

Samples	Company and grade	Charge mass ratio [%]
Lactose	DMV (Pharmatose 200M)	67.2
Cornstarch	Nihon Shokuhin Kako Co., Ltd. (Cornstarch W)	28.8
Microcrystalline cellulose	Asahi Kasei Co. (Avisel PH101)	4.00
Total	—	100

repeatedly folding effect. These effects effectively function to promote wet kneading. Beneath the kneading blade, a torque meter is equipped at the main drive shaft. Several operating parameters such as torque of main drive shaft, power consumption of motor drive and temperature of kneaded mass can be continuously measured and monitored *via* a personal computer.

For extrusion granulation after the kneading, a dome-type extruder<sup>2-4)</sup> (DG-L1, Fuji Paudal Co. Ltd.) was used. 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. Drying of the wet extruded pellets was conducted by using a fluidized bed (NQ-125).<sup>5)</sup>

**Powder Samples** Table 2 lists powder samples used. Pharmaceutical excipients composed of lactose, cornstarch and micro-crystalline cellulose were used as powder samples. Hydroxypropylcellulose (HPC-L) was used as a binder, which was added as a form of dry powder into the powder samples before mixing. The charge mass of the binder was set at 3 wt% based on the dry powder mass. Purified water was used as a binder liquid. Its addition ratio was determined to be 30 wt% based on the total powder charge mass.

**Experimental Method** Experiments were conducted as follows; powder samples were fed into the kneader and mixed for 120 s. Binder liquid (water) was fed into the kneader instantaneously from the top lid through a stainless funnel. The kneading was conducted under the same kneading duration (10 min). The kneaded mass was then extruded through a dome type extrusion granulator. 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 Co. Ltd.)<sup>5)</sup> under the fluidization air temperature was 353 K.

**Evaluation Method** In the previous report,<sup>1)</sup> we have already reported that strength and disintegration time of dried extruded pellets were determined by the wet kneading conditions. In this study, we also tried to evaluate strength and disintegration time of the dried extruded pellets. By using these properties, scale-up characteristics were investigated. Here, strength of pellet was directly measured by a strength tester (Grano, Okada Seiko).<sup>7)</sup> Disintegration time was measured by using JP dissolution test vessel and paddle (agitation speed was 150 rpm).<sup>8)</sup> These experimental procedures were the same as previously reported.<sup>1)</sup>

## Results and Discussion

Mechanism of wet kneading is quite complicated, and its scaling up is also very difficult. In order to predict the kneading characteristics in the larger scale such as commercial size based on the data obtained by the smaller scale, the scale up characteristics of the wet kneading should be analyzed systematically.

So far, some methods have been proposed to scale up the agitation vessel. Tip speed of the blade is sometimes used when the shear stress near at the blade tip mainly determines the agitation behaviors.<sup>9)</sup>

Let us define the agitation rotational speed is  $n$  [ $s^{-1}$ ], diameter of the agitation blade is  $d$  [m]. The angular velocity of the agitator blade,  $\omega$ , is then described as

$$\omega = 2\pi n \quad (1)$$

Thus the tip speed of the blade  $v$  is expressed as

$$v = \left(\frac{d}{2}\right) \cdot \omega = \pi d n \quad (2)$$

Reynolds number is a well-known dimensionless number, which indicates flow dynamics or behaviors of fluid. In general, similarity of fluid dynamics is obtained by keeping the Reynolds number constant. The Reynolds number,  $Re$ , which is defined as a ratio of force of inertia to that of viscosity, is written as

$$Re = \frac{nd^2\rho}{\mu} \quad (3)$$

where  $\rho$  and  $\mu$  indicate the density and viscosity of the fluid.

Agitation power is also a well-known factor that can scale-up the agitation vessel<sup>10)</sup> based on the concept that the same agitation effect can be obtained if agitation power per unit volume is the same.

Agitation power,  $P$  [ $N \cdot m/s$ ], is calculated as

$$P = \omega T \quad (4)$$

where  $T$  indicates agitation torque [ $N \cdot m$ ], which is deducted the torque of idling from the one actually measured during the experiments.

Then the agitation power per unit vessel volume is written as

$$P_v = \frac{P}{V} \quad (5)$$

where  $V$  shows volume of vessel.

In addition to these dimensionless factors, Froude number,  $Fr$ , which is defined as a ratio of force of inertia to that of gravity, is also used for the scale-up of agitation vessel. The Froude number basically indicates the effect of gravity, and is used to study the shape of fluid surface and kinetic similarity of an object floating on a fluid with vortex. If the Froude number is the same, average fluid behavior becomes the same, leading to have the same vortex at agitated liquid surface.

$$Fr = \frac{n^2 d}{g} \quad (6)$$

Depending on the application, the optimum scale-up method differs; one can determine the optimum method by means of scale-up experiments. However, Reynolds number cannot be used for the scale-up of the kneading experiments, since density and viscosity of the kneaded mass is changed depending on the operating conditions and vessel scales. In addition, it is difficult to directly measure or predict these parameters during the kneading experiments. Therefore, in this experiments, tip speed, agitation power per unit vessel volume and Froude number have been used to investigate the scale-up characteristics of the wet kneading process.

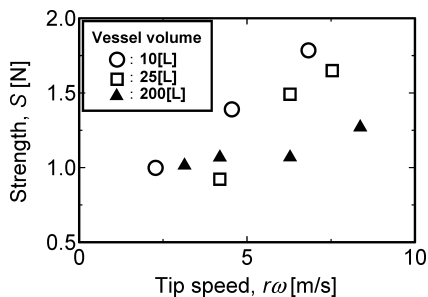


Fig. 2. Scale-Up Characteristics of Pellet's Strength by Means of Tip Speed

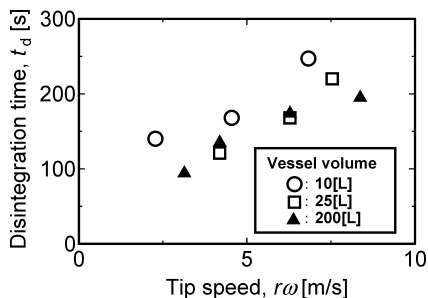


Fig. 3. Scale-Up Characteristics of Pellet's Disintegration Time by Means of Tip Speed

Figures 2 and 3 show the results of the scale-up by means of tip speed. Strength and disintegration time of pellets roughly became large when the tip speed was large. It was understood that the shearing stress at the blade tip was one of the main factors to affect the kneading conditions, however, the scale-up of the kneading was impossible by mean of the tip speed.

Figures 4 and 5 investigate the scale-up characteristics by means of agitation power per unit vessel volume. Strength and disintegration time of pellets increased linearly with the agitation power per unit vessel volume. This meant that the wet kneaded mass had more plasticity when it received larger energy from the agitation blade. Scale-up characteristics were also very clear; the physical properties of pellets (strength and disintegration time) prepared under various operating conditions and vessel scales indicated linear correlation with the agitation power per unit vessel volume, showing that the scale-up of the kneading and extrusion granulation processes are possible by the agitation power per unit vessel volume.

Figures 6 and 7 also indicate the scale-up characteristics by means of dimensionless Froude number. The scale-up characteristics were well expressed by the Froude number. Both properties also increased with Froude number. Considering the Eq. 6, the numerator of the fractional expression means the centrifugal force of the blade. Thus the kneading of wet mass progressed with receiving higher force from the blade. In addition, Froude number can predict the scale-up characteristics more precisely than the agitation power per unit vessel volume. It was because the agitation power required actual measurement of agitation torque during the kneading operation, which included scattering of data.

As a result, it was found that the scale-up of the wet kneading in the novel high shear kneader was accurately conducted by means of agitation power per unit vessel volume

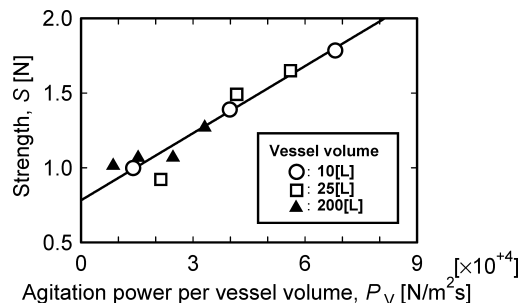


Fig. 4. Scale-Up Characteristics of Pellet's Strength by Means of Agitation Power per Unit Vessel Volume

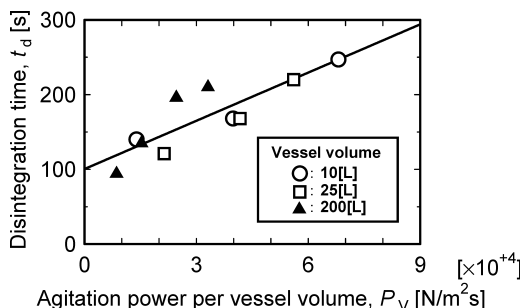


Fig. 5. Scale-Up Characteristics of Pellet's Disintegration Time by Means of Agitation Power per Unit Vessel Volume

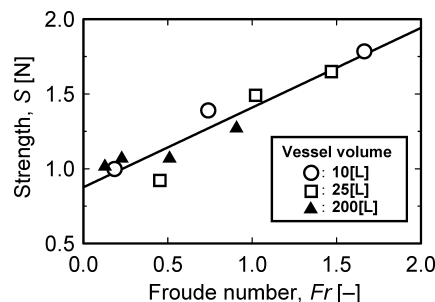


Fig. 6. Scale-Up Characteristics of Pellet's Strength by Means of Froude Number

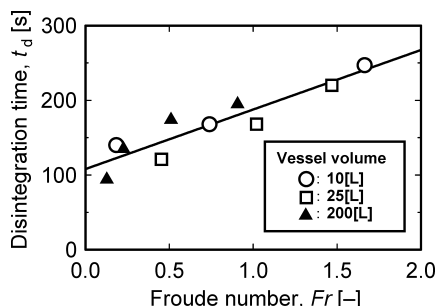


Fig. 7. Scale-Up Characteristics of Pellet's Disintegration Time by Means of Froude Number

and Froude number. However, Froude number is easier and more precisely predict the scale-up characteristics than the agitation power per unit vessel volume, since the agitation power requires the practical measurement of the agitation torque. Also, Froude number can predict the scale-up characteristics without conducting any practical experiments. However, it is noteworthy that this prediction method can be used

for the high shear kneader with the kneading blade. For the conventional high shear granulation, of which the flow pattern of powder mass is totally different from the present high shear kneader, the prediction method may be different. In the next paper, we will investigate the scale-up characteristics of vertical high shear granulator in detail.

### Conclusions

Wet kneading was conducted by a novel vertical high shear kneader and dry pellets were produced by extruding the wet mass by a dome type extruder and their fluidized bed drying. Physical properties (strength and disintegration time) of pellets prepared under various operating conditions and vessel scales were evaluated. The results indicated that the wet kneaded mass showed more plasticity when it received larger force/energy from the blade, leading to have larger strength and longer disintegration time. It was also found that scale-up of the wet kneading could be accurately conducted by means of the agitation power per unit vessel volume and

Froude number.

### References

- 1) Watano S., Okamoto T., Tsuchi M., Koizumi I., Osako Y., *Chem. Pharm. Bull.*, **50**, 341—345 (2002).
- 2) Watano S., Furukawa J., Miyamoto K., Osako Y., *J. Soc. Powder Technol. Jpn.*, **37**, 362—370 (2000).
- 3) Watano S., Furukawa J., Miyamoto K., Osako Y., *Chem. Pharm. Bull.*, **49**, 64—68 (2001).
- 4) Watano S., Yoshikawa T., Osako Y., Tsuchi M., *Chem. Pharm. Bull.*, **51**, 747—750 (2003).
- 5) Watano S., Yeh N., Miyamoto K., *J. Chem. Eng. Jpn.*, **31**, 908—913 (1998).
- 6) Watano S., Shimoda E., Osako Y., *Chem. Pharm. Bull.*, **50**, 26—30 (2002).
- 7) Okada K., *Pharm. Tech. Jpn.*, **10**, 31—36 (1994).
- 8) The Japanese Pharmacopoeia Fourteenth Edition, Society of Japanese Pharmacopoeia, Jihō Inc., 2001, pp. 101—104.
- 9) Takahashi K., Nakano T., He Y., Nomura T., Shimizu K., *J. Chem. Eng. Jpn.*, **27**, 598—601 (1994).
- 10) Perry H. R., Chilton C. H., "Chemical Engineer's Handbook," Fifth ed., McGraw-Hill, New York, 1973.