Scale-Up of High Shear Granulation Based on the Internal Stress Measurement

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Scale-up of wet granulation in a vertical high shear mixer was conducted. Pharmaceutical excipient powders composed of lactose, cornstarch and micro-crystallinecellulose, and hydroxypropylcellulose as a binder were mixed together and then granulated with purified water under various operating conditions and vessel scales. A novel internal stress measurement system was developed and stress of normal and tangential directions that granules received from the agitator blade during the granulation was continuously measured. The results indicated that granules received stress mainly from the tangential direction, which also showed the largest value near at the vessel wall. The effects of the agitator tip speed and the centrifugal acceleration on the measured stress was investigated. It was found that the tip speed of the agitator blade could be the main factor for the granule growth. The physical properties such as strength, size distribution and compressibility of granules prepared by changing the operating conditions and the vessel scales were evaluated and the scale-up characteristics of high shear granulation were investigated experimentally. The results showed that these physical properties had linear correlations with the tip speed. It was finally concluded that the scale-up of high shear granulation could be well conducted by means of the tip speed of the agitator blade.

Key words scale-up; granulation; high shear mixer; tip speed; physical property

Recent trend in wet granulation process is toward an improvement of process efficiency, stability of product quality as well as laborsaving on manufacturing. With such improvements and recent temporary increases in demand for granulation, use of a high shear mixer has become major interest lately especially in pharmaceutical, food, agriculture and chemical industries. One of the major reasons is that high shear granulation produces nearly spherical and well-compacted granules in relatively short time and the equipment itself is simple in construction.

Contrary to the remarkable advantages, high shear granulation in a high shear mixer is sensitive to even minor changes in moisture content, amount of binder and the operating conditions.[1)] Therefore, there is a great need for reliable system for process monitoring and control of granule growth. So far, a number of investigations have been made regarding different devices to monitor the process conditions and to terminate granulation operation at the optimal operating time (end point). Torque measurement of a main driving shaft using a strain gauge technique was described by Lindberg *et al.*[1,2)] Leuenberger[3,4)] measured power consumption of motor drive and tried to monitor process conditions. Bier *et al.*[5)] reported that records of power consumption and torque were in good agreement. Holm *et al.*[6)] investigated the relationship between granule growth and power consumption curves and also demonstrated the possibility of end-point determination by power consumption meters.[7)] Watano *et al.* measured the granule growth continuously by means of a novel image processing system[8)] and feedback controlled the granule growth by using a fuzzy logic.[9)]

Although many different studies regarding the measurement of high shear granulation have been conducted, all of them were used for understanding the mechanism of granule growth or detecting the operational end-point. Obviously, no study used the measurement data for the granulation scale-up, much less to propose the scale-up characteristics of high shear granulation.

The aim of the present study has been to analyze the scale-up characteristics of high shear granulation. A novel internal stress measurement system was developed and stress that granule received from the agitator blade was continuously measured during the high shear granulation. Relationship between the measured stress and several scale-up parameters was investigated. The analysis of the scale-up characteristics of the high shear granulation was conducted and a practical method for the scale-up was proposed.

Experimental

Apparatus Figure 1 shows a schematic diagram of the experimental apparatus. Vertical high shear mixers (SPG-10, 25, 200, 400 Fuji Paudal Co., Ltd.) with four different vessel scales were used for high shear granulation.[8,9)] Every granulator completely obeyed the geometric similarity. Dimensions of each scale are listed in Table 1. The bottom of the vessel was equipped with an agitator blade (main impeller) rotating horizontally, which promoted agglomeration and compaction. A chopper blade was also provided on the sidewall to break up wetted masses into small granules. Torque of the agitator shaft was continuously measured by a digital torque meter and then processed by a computer.

Stress that granules received from the agitator blade was measured by a novel stress measurement system. As shown in Fig. 1, the stress measurement system composed of a sensor and strain gauges. A sensor made of stainless straight bar having a width of 5 mm, thickness of 1 mm and length of 115 mm received stress from granule bed and strain gauges glued at the upper part of the bar detected strain of the bar, which was transmitted to an amplifier and then calculated *via* a computer. Since the bottom end of the sensor was just above the agitator blade, the stress that the sensor received was considered to be the average value of the stress distribution in the depth direction. In order to measure the stress of both tangential and normal directions of the stress, the facing directions of the sensor (stainless bar) can be changed by 90 degrees. In addition, the distance between the sensor and the vessel center can be changed. As shown in Fig. 2, stress of both tangential and normal directions was measured by changing the distance from the vessel center (35, 70, 105 mm from the center). The direction of positive value of the tangential stress was set at the same direction of the agitator rotation, while the positive direction of the normal stress was the direction from the center to the vessel wall.

Powder Samples Materials used are listed in Table 2. Starting material

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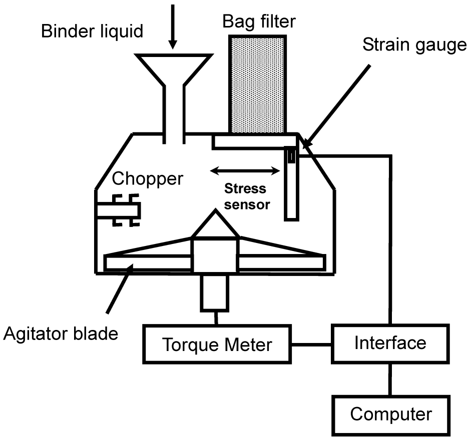

Fig. 1. Schematic Diagram of Experimental Set-Up

Table 1. Dimensions of Each Scale and Operating Conditions

	SPG-10	SPG-25	SPG-200	SPG-400
Vessel volume [l]	9.8	25.7	205.9	401.8
Vessel diameter [mm]	290	400	800	1000
Scale ratio[a)] [—]	1.00	2.63	21.0	41.0
Total charge mass [kg]	2.20	5.79	46.2	90.2
Binder (water) content [%]	22 (constant)			
Operating time [min]	10 (constant)			

a) Scale ratio was determined based on the 3rd power of the vessel diameter.

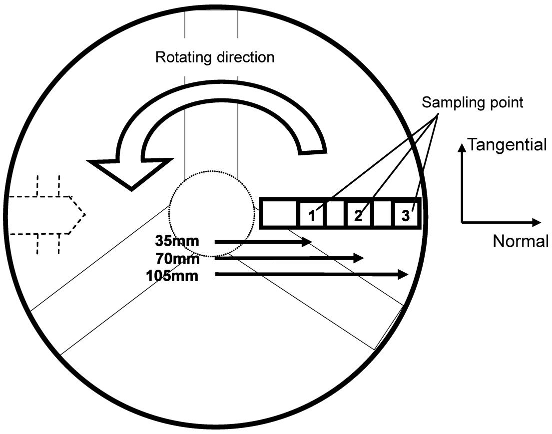

Fig. 2. Locations of Stress Sensor

Table 2. Powder Samples

Sample	Company and grade	Charge mass ratio [%]	
Lactose	DMV (Pharmatose 200M)	67.2	(100.0)
Cornstarch	Nihon Shokuhin Kako (Cornstarch W)	28.8	
Microcrystalline cellulose	Asahi Kasei Chemicals (Avicel PH101)	4.0	
Hydroxypropylcellulose	Tokuyama (HPC-L)	3.0	
(Total)		103.0	

(apparent density: 0.42 g/cm^3) was a mixture of lactose, cornstarch and micro-crystalline cellulose. Hydroxypropylcellulose (HPC-L) was adopted as a binder, which was mixed 3 wt% (dry basis) in the form of a dry powder into the starting material before granulation. Purified water was used as a binder solution.

Experimental Procedures Experiments were conducted as follows. The weighed powder samples and the dry binder (HPC-L) were fed into the granulator and mixed for 120 s. The agitator rotational speed was set to run at the prescribed rotational speed, while the chopper rotational speed was set at 50 rps (3000 rpm) constant regardless of the vessel scales. The binder solution (purified water) was added instantaneously from the top of the vessel (require just 1 min to discharge the liquid completely at every vessel scales). After the 10 min granulation, the granulated products were dried in a shelf drier at 50 °C for 24 h.

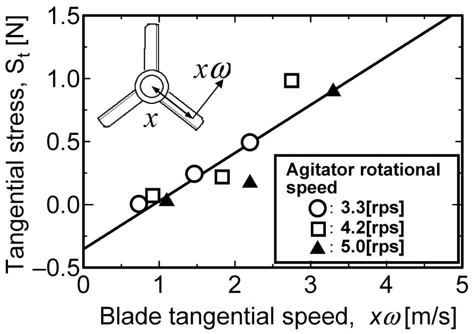

Fig. 3. Relationship between Blade Tangential Speed and Tangential Stress (SPG-10)

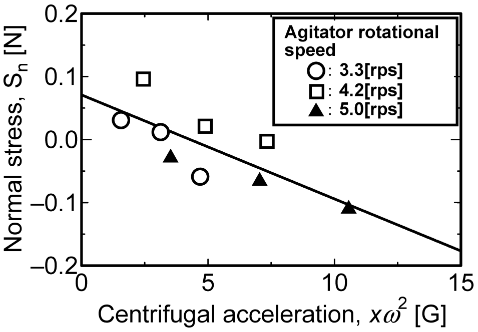

Fig. 4. Relationship between Centrifugal Acceleration and Normal Stress (SPG-10)

Evaluation of Granulated Products Size distribution of the granulated products was determined by a sieve analysis with a rotating sieve shaker. About 100 g of the products were shaken for 180 s. After measuring the weight of the products on each sieve, size distribution was calculated on the basis of a log-normal distribution with a personal computer. Strength of granule was directly measured by a strength tester (Grano, Okada Seiko).[10,11] A granulated particle (diameter range between 300 and 355 μm) was placed on a flat adjustment stage and a pressing rod moved vertically at a speed of 100 μm/s and pressed the granulated particle from above. The moving displacement and pressed load (force) were measured continuously. The complete breaking load estimated the strength of granulated particle. The strength of granulated particle accepted in this study was the average value of the 50 measurements. Compressibility was calculated by the bulk and the tapped densities of granules.

Results and Discussion

Measurement of Stress during Granulation Figures 3 and 4 indicate relationship between the blade tangential speed and the tangential stress, and relationship between the centrifugal acceleration and the normal stress, respectively. The centrifugal acceleration was normalized by using the gravity acceleration (9.8 m/s^2).

Here, the blade tangential speed, v, is expressed as (see Fig. 3):

$$v=x\cdot\omega \qquad (1)$$

where x and ω express distance from the center and angular velocity of the agitation blade, respectively. In the case that the $x=r$ (radius of the vessel), the blade tangential speed is equivalent to the blade tip speed.

Seen from the figures, it was obvious that the tangential stress has a linear correlation with the blade tangential speed, while the normal stress has a linear correlation with the centrifugal acceleration. The tangential force stress increased linearly with the blade tangential speed, while the normal stress decreased linearly with the centrifugal acceleration. In addition, the normal stress was quite small as compared to the tangential force. The reason why the normal stress indicated negative value when the centrifugal acceleration was larger than 5G was that the granules were bounced back against the vessel wall due to the vortex flow at the large centrifugal acceleration, leading to change the collision direction between granules and the stress measurement system.

Figures 5 and 6 investigate the effects of the sensor distance from the vessel center on the tangential and normal stresses, respectively. The tangential stresses at 35 mm were almost zero regardless of the rotational speed and the tangential stresses increased greatly with the distance and the agitator rotational speed. This implied that most of granules received stress of tangential direction at the extremity of the blade. By contrast, the normal stress decreased with the distance and the agitator rotational speed. This meant that near at the vessel wall, granules were bounced back and the stress of opposite direction increased corresponding to the increase in the distance and the rotational speed.

Figure 7 investigates the effect of the sensor distance on the ratio of stress, R_s, which is defined as a ratio of the tangential stress to the normal stress as:

$$R_s=\left|\frac{S_t}{S_n}\right| \qquad (2)$$

Seen from the figure, the R_s increased almost linearly with the distance, except one data taken at 3.3 rps of agitator rotational speed with 70 mm distance. In this case, the normal stress, the denominator of Eq. 2, was approximately zero, leading to have the large fraction. The Fig. 7's relationship proved that granules received much larger tangential stress than normal stress when the sensor location was closer to the vessel wall. This also implied that the tip speed could be the main factor of high shear granulation where granules formed vortex and spiral flow.

Based on the obtained results, it was found that the granules received stress mainly from the tangential direction and the stress from the normal direction was negligible small as compared to the tangential stress. Also, due to the vortex flow in the high shear mixer, the granules received the stress of tangential direction mainly near at the vessel wall. These findings implied that the tip speed, which was closely related to the tangential stress, would be the most important factor in the high shear granulation. In addition, granule growth took place by the "shear stress" from the agitator blade not by the "impaction force against wall", since the shear stress is a function of the first power of the rotational speed while the impaction force was a function of the second power of the rotational speed.

Scale-Up Characteristics of High Shear Granulation Figure 8 shows the effect of the agitator rotational speed on the granule strength under various vessel scales. The granule strength increased with the agitator rotational speed at every vessel scales, while the increase inclination was more rapid with the larger scales. For other properties such as granule mass median diameter, geometric standard deviation and compressibility, no systematic expression could not be ob-

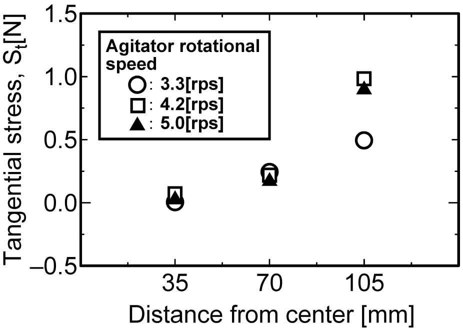

Fig. 5. Relationship between Distance from Vessel Center and Tangential Stress (SPG-10)

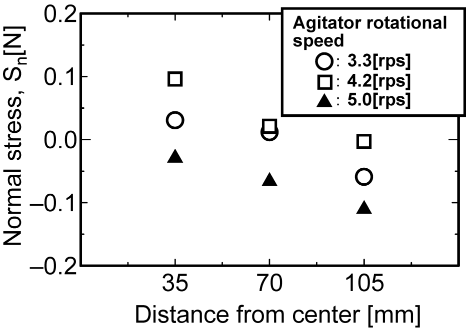

Fig. 6. Relationship between Distance from Vessel Center and Normal Stress (SPG-10)

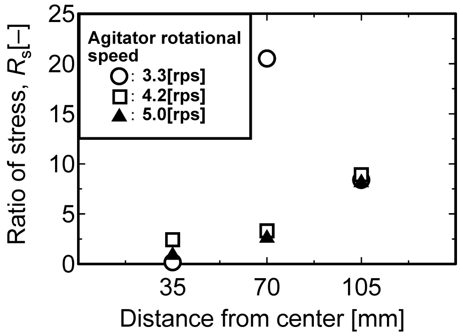

Fig. 7. Relationship between Sensor Distance and Ratio of Stress (SPG-10)

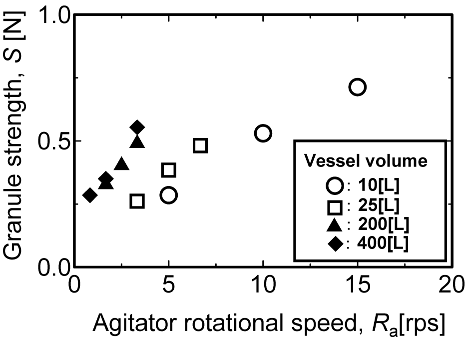

Fig. 8. Effect of Agitator Rotational Speed on Granule Strength

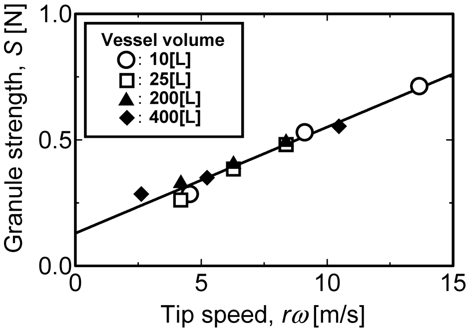

Fig. 9. Effect of Tip Speed on Granule Strength

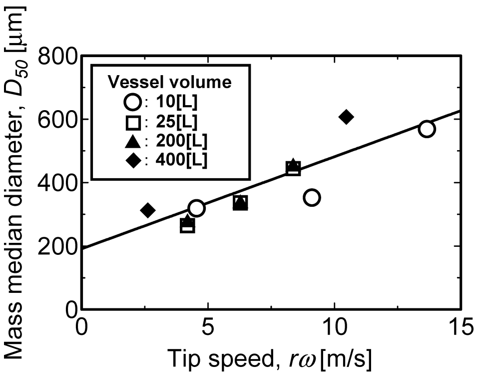

Fig. 10. Effect of Tip Speed on Granule Mass Median Diameter

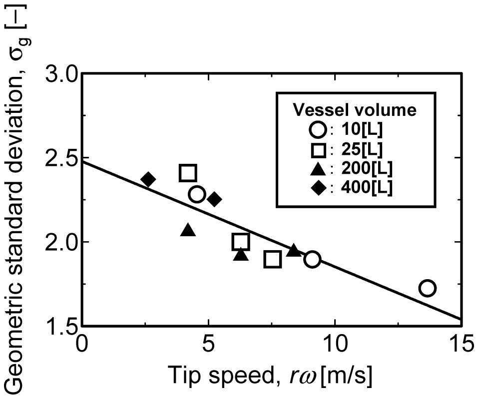

Fig. 11. Effect of Tip Speed on Granule Geometric Standard Deviation

tained by the agitator rotational speed.

Figure 9 investigates the effect of the tip speed on the granule strength. The granule strength was very well expressed by the tip speed regardless of the vessel scales. This confirmed that the shear stress (tangential stress) imposed on the granules from the blade gave tumbling and compaction effects on granules, leading to produce well-compacted granules.

Figures 10 and 11 indicate the effect of the tip speed on the granule mass median diameter and geometric standard deviation, respectively. The granule mass median diameter increased almost linearly with the tip speed, while geometric standard deviation decreased linearly with the tip speed.

With an increase in the tip speed, shear stress that was imposed on granules also increased. The higher shear stress promoted better dispersion of the binder liquid. The well-dispersed binder liquid should cause uniform and large number of adhesion between powders. Thus the size distribution became narrower (smaller geometric standard deviation) and the median size also became larger.

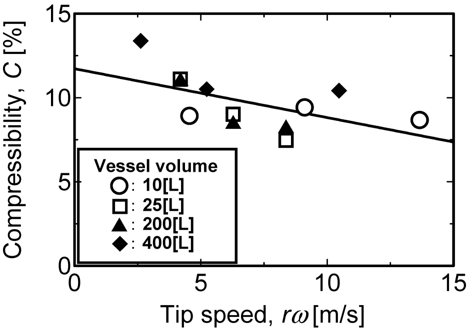

Fig. 12. Effect of Tip Speed on Granule Compressibility

The effect of the tip speed on granule compressibility is shown in Fig. 12. The granule density increased and the surface also became smoother (better flowability), leading to have the smaller compressibility of granules.

Conclusions

Wet granulation was conducted in a high shear mixer under various operating conditions and vessel scales. The stress that granules received from the agitator blade was continuously measured by a novel stress measurement system. The results indicated that the stress of tangential direction was mach larger than that of normal direction, and the stress of tangential direction had linear correlation with the agitator blade tip speed. This confirmed the main factor that determined the granule growth was the tip speed. Scale-up characteristic of high shear granulation was analyzed by means of the tip speed. It was found that granule physical properties such as strength, mass median diameter, geometric standard deviation (size distribution) and compressibility had linear correlations with the tip speed. This proposed that scale-up of wet granulation in a high shear mixer could be achieved by the tip speed. So far, tip speed has sometimes used empirically as the scale-up factor in high shear granulation; however, no theoretical reasons have been reported. The present work provides scientific justification that the scale-up of high shear granulation is well conducted by means of the agitator blade tip speed.

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