Scale-Up of Agitation Fluidized Bed Granulation. III. Effects of Powder Feed Weight and Blade Angle on Granule Size, Density and Shape

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This paper presents the experimental results of a study on the scale-up characteristics of granule compaction and sphericity in an agitation fluidized bed granulation. A pharmaceutical standard formulation was granulated using agitation fluidized bed of three sizes (vessel diameter: 125, 230, 500 mm). The effects of powder feed weight and agitator blade angle on the granule properties of size, density and shape were studied. It was found that granules were compressed and made spherical with an increase in agitator blade angle and vessel scale, while they were not influenced by the powder feed ratio.

Key words scale-up; granulation; agitation fluidized bed; powder feed weight; agitator blade angle; granule property

The scale-up problem in the powder handling process is serious, because the dynamic characteristics of powder are difficult to understand. Scale-up is especially difficult in the granulation process since the granule growth mechanism and effects of operational variables on granule properties are not clearly known. Therefore, there are few studies which have addressed the granulation scale-up systematically and theoretically.

For granulation scale-up in an agitation fluidized bed, we earlier determined optimal process variables needed for scale-up experiments[1)] and learned the effects of vessel size, air flow rate and agitator rotational speed on the granule properties of size, density and shape.[2)]

In this paper, effects of powder feed weight and agitator blade angle on these same properties in granulation scale-up by an agitation fluidized bed of three sizes (vessel diameter: 125, 230, 500 mm) were investigated experimentally using a pharmaceutical standard formulation. The mechanism of granule growth in different size equipment and scale-up characteristics in this typed granulation are discussed from the results obtained.

Experimental

Equipment For wet granulation, three sizes of agitation fluidized beds (NQ-125, 230, 500, Fuji Paudal Co., Ltd.) with respective diameters of 125, 230 and 500 mm were used. Details of the equipment and the dimensions were previously reported.[1,2)]

Powder Samples Table 1 gives properties of powder samples used. Starting materials for granulation were the pharmaceutical standard formulation defined by the working group for the preparation of standard formulations,[3)] which consisted of lactose and cornstarch (mixed at 7 : 3 by weight). Hydroxypropylcellulose was adopted as a binder at a level of 5%, and was mixed into the above mixture as a dry powder before granulation. Purified water was sprayed by a binary nozzle located at the top of the vessel (top spray method).

Operating Conditions Operating conditions for scale-up experiments are listed in Table 2. Optimal spray conditions, drying conditions and method for moisture control were reported earlier.[1)] In Table 1, powder feed ratio is defined as the ratio of powder feed weight (M) to standard powder feed weight (M_S; 0.36 kg for NQ-125, 2.23 kg for NQ-230 and 22.9 kg for NQ-500). The standard powder feed weight, which was defined previously,[1)] was proportional to the diameter^3 (volume similarity) to estimate the effect of powder feed ratio correctly regardless of vessel scale.

To evaluate the effect of agitator blade angle (Fig. 1), blade shape and the projected area were geometrically similar regardless of variation in vessel size.

In this study, scale-up experiments were conducted as follows:

(i) Premixed powder samples of prescribed weight were fed to the vessel and agitated with fluidization air for 300 s.

(ii) Granulation experiments started with spraying binder solution (water). As shown in the previous study,[2)] moisture content was programmed to increase 18% with 18 min. After reaching 18 %, moisture content was fixed to maintain it at 18 % for 15 min. This moisture control was intended to keep a constant adhesion force by a liquid bridge, in addition to prevent external disturbance.

(iii) After granulation was over, granulated products were dried by the fluidization air in the vessel. The fluidization air temperature was kept constant at 80 °C regardless of vessel size.

Evaluation of Granulated Products Particle size distributions of the granulated products were measured by sieve analysis with a row-tap shaker. Based on the weight of granules on each sieve, mass median diameter and geometric standard deviation of granulated products were computed by log-normal distribution using a personal computer.

Particle size distribution of powder samples listed in Table 1 was

Table 1. Properties of Powder Samples Used

Sample	Number median diameter (μm)	Mixing weight ratio (—)
Lactose[a)]	60	0.7
Cornstarch[b)]	15	0.3
Hydroxypropylcellulose[c)]	21	0.05
Total		1.05

a) Pharmatose 200M, DMV. *b)* Cornstarch W, Nippon Shokuhin Kakou Co., Ltd. *c)* HPC-EFP, Shin-Etsu Chemical Co., Ltd.

Table 2. Operating Conditions

	NQ-125	NQ-230	NQ-500
Vessel diameter (mm)	125	230	500
Initial powder feed weight (M_S, kg)	0.36	2.23	22.9
Agitator rotational speed (rpm)	600	300	150
Inlet air velocity (m/s)	0.6	0.6	0.6
Powder feed ratio (M/M_S)		1.0, 1.5, 2.0	
Agitator blade angle		θ = 15.0, 22.5, 30.0 deg.	
Moisture content		W = 18% const.	

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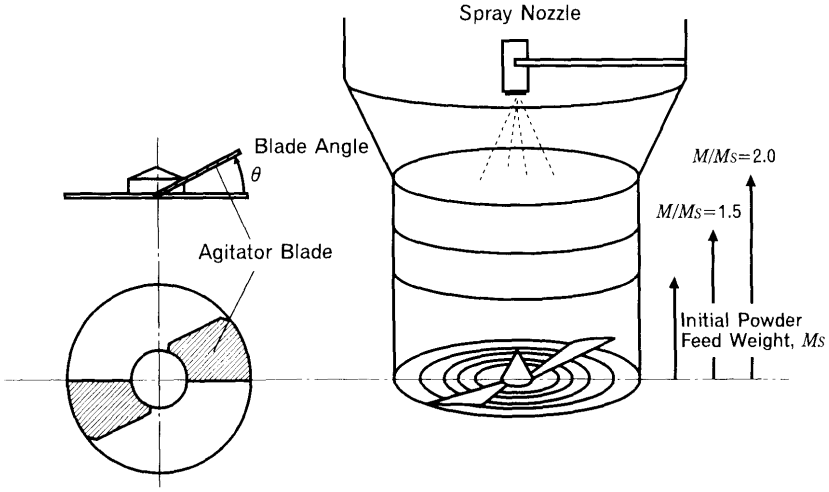

Fig. 1. Schematic Diagram of Experimental Apparatus

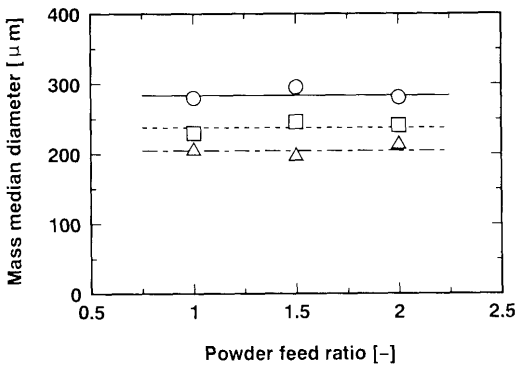

Fig. 2. Effect of Powder Feed Ratio on Granule Mass Median Diameter

○, NQ-125; □, NQ-230; △, NQ-500.

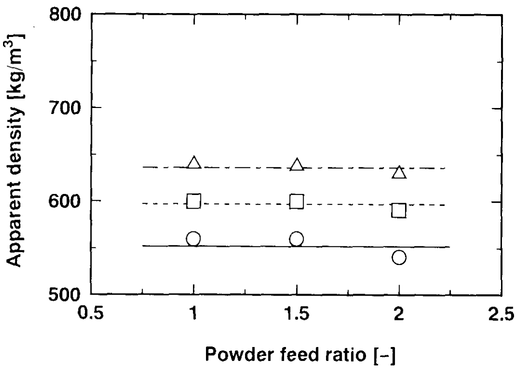

Fig. 3. Effect of Powder Feed Ratio on Granule Apparent Density

○, NQ-125; □, NQ-230; △, NQ-500.

measured using an image processing system (Image Eye, Fuji Paudal Co., Ltd.).[4)]

Apparent density of granules was determined using a measuring cylinder and granule shape factor was measured by an image processing system (Image Eye, Fuji Paudal Co., Ltd.).[4)]

Results and Discussion

Effect of Powder Feed Ratio on Granule Size, Density and Shape Figures 2, 3 and 4 illustrate the effect of powder feed weight on granule mass median diameter, apparent density and shape factor. As shown, all three features of each scale showed almost constant value despite the variation in the powder feed ratio.

As has been discussed with regard to the effects of operating variables on granule properties,[2)] properties of granule size, density and shape were determined by internal adhesion force by liquid bridge and external separation force. Since adhesion force by liquid bridge was kept constant by moisture fixed command control, granule properties were determined only by the external force. However, judging from the obtained results that these properties were the same, the external force was also constant regardless of powder feed weight. It thus appeared that there was no effect of powder feed weight on granule properties, and that the properties were determined by vessel scale, agitator rotational speed and air flow velocity if moisture content was kept constant.

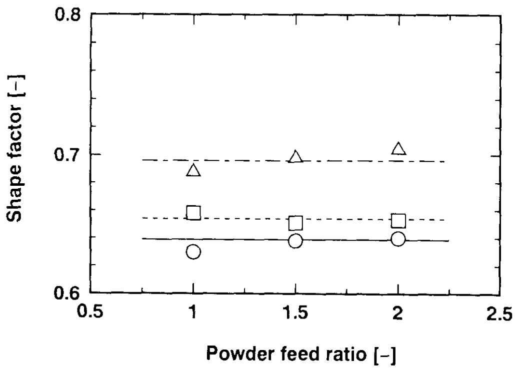

Fig. 4. Effect of Powder Feed Ratio on Granule Shape Factor

○, NQ-125; □, NQ-230; △, NQ-500.

In other granulation methods of agitation, tumbling and typical fluidized bed granulation, however, it is empirically understood that granule density increases with powder feed ratio owing to the effect of powder load. Considering the difference in granulation mechanism, granules in the agitation fluidized bed received no effect of powder load because they were fluidized. Moreover, due to the forced circulation by the agitator rotation, fluidized condition was assumed to be constant regardless of powder feed weight, while fluidized condition in the typical fluidized bed did influence powder feed weight. In other words, it is suggested that the agitation fluidized bed can maintain

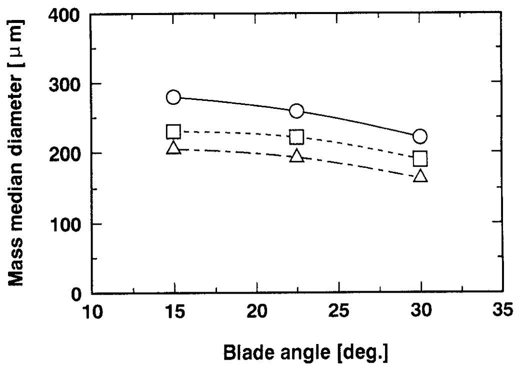

Fig. 5. Effect of Blade Angle on Granule Mass Median Diameter
○, NQ-125; □, NQ-230; △, NQ-500.

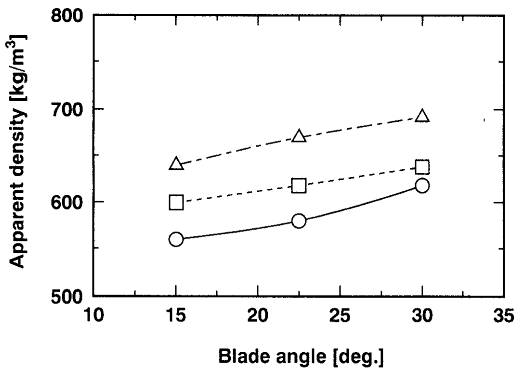

Fig. 6. Effect of Blade Angle on Granule Apparent Density
○, NQ-125; □, NQ-230; △, NQ-500.

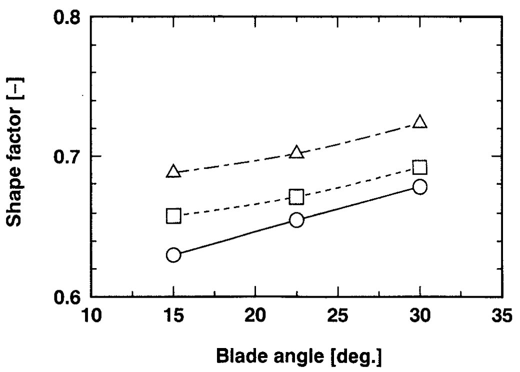

Fig. 7. Effect of Blade Powder Feed Ratio on Granule Shape Factor
○, NQ-125; □, NQ-230; △, NQ-500.

a fluidized condition regardless of powder feed weight.

Effect of Agitator Blade Angle on Granule Size, Density and Shape Figures 5, 6 and 7 illustrate the effects of agitator blade angle on granule mass median diameter, apparent density and shape factor. Here, powder feed ratio was kept constant at 1.0 (=the standard powder feed weight), regardless of vessel size.

As shown, granule mass median diameter decreased, and apparent density and shape factor increased markedly with an increase in blade angle. The same tendency was observed if the vessel scale varied. These results implied that an increase in agitator blade angle had great impact on the increase of external force. By expanding the blade angle, granules were compressed and made spherical because they were subjected to strong shear stress by the agitator rotation. Due to the strong stress, granule growth was also suppressed. This growth suppression by external force is easily confirmed since granule diameter decrease due to compaction was very small because the diameter was proportional to cubic root of volume. These granule growth mechanisms by adhesion force and external separation have been analyzed theoretically by computer simulation.[5]

Based on the results obtained, it was concluded that granule mass median diameter, apparent density and shape factor obtained by an agitation fluidized bed of three sizes were influenced considerably by agitator blade angle, while they were not altered by powder feed ratio. These results are very useful in the design or prediction of scale-up characteristics. In the next paper, we will propose a scale-up theory and report the effects of operating variables on granule growth theoretically.

Conclusions

The scale-up of granulation by three sizes of agitation fluidized beds (vessel diameter 125, 230, 500 mm) was conducted using a pharmaceutical standard formulation, and effects of powder feed weight and agitator blade angle on the granule properties of size, density and shape were investigated experimentally. No effect of powder feed weight on granule properties was found. However, the agitator blade angle had considerable influence on granule properties; granule mass median diameter decreased and apparent density and shape factor increased markedly with the increase in blade angle. This implied that granules were compressed and made spherical, and that granule growth was suppressed due to the strong shear stress by agitator rotation in case of large blade angle. These results provide useful information in the prediction of scale-up characteristics.

References

1) Watano S., Sato Y., Miyanami K., Murakami T., Ito Y., Kamata T., Oda N., *Chem. Pharm. Bull.*, **43**, 1212 (1995).
2) Watano S., Sato Y., Miyanami K., Murakami T., Nagami N., Ito Y., Kamata T., Oda N., *Chem. Pharm. Bull.*, **43**, 1217 (1995).
3) Sunada H., Kokubo H., Proceeding of the 6th International Symposium on Agglomeration, Nagoya, 1993, p. 873.
4) Watano S., Miyanami K., *Powder Technol.*, **83**, 55 (1995).
5) Watano S., Morikawa T., Miyanami K., *J. Chem. Eng. Jpn.*, **28**, 171 (1995).