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Scale-Up of Agitation Fluidized Bed Granulation. II. Effects of Scale, Air Flow Velocity and Agitator Rotational Speed on Granule Size, Size Distribution, Density and Shape

Satoru WATANO,*[,a] Yoshinobu SATO,[a] Kei MIYANAMI,[a] Takayuki MURAKAMI,[b]
Nobumasa NAGAMI,[b] Yoshihiro ITO,[c] Tetsuro KAMATA,[c] and Nobuhito ODA[c]

Department of Chemical Engineering, University of Osaka Prefecture,[a] 1-1 Gakuen-cho, Sakai, Osaka 593, Japan, Taiho Pharmaceutical Co., Ltd.,[b] 224-2 Ebisuno, Hiraishi, Kawauchi-cho, Tokushima 771-07, Japan, and Fuji Paudal Co., Ltd.,[c] 10-18 Kitamachi 3-chome, Nerima-ku, Tokyo 179, Japan.

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Scale-up characteristics of agitation fluidized bed granulation using a pharmaceutical standard formulation was described. The effects of scale, air flow velocity and agitator rotational speed on granule properties such as granule mass median size, size distribution, apparent density and shape factor were investigated experimentally. Based on the results obtained, the effects of these parameters on granule growth and the mechanism of granule formation in different sized equipment were discussed.

Key words scale-up; granulation; agitation fluidized bed; scale factor; operating variable; granule property

Scale-up is the most important operation among manufacturing processes in all industries.[1)] It is conducted to determine the operating conditions applicable to large scale batches for production, in order to produce products of the same quality which has been optimized in laboratory scale experiments. Especially, the scale-up of powder handling processes is difficult, and most of the scale-up is experimentally investigated because the dynamic behavior of powder and the effects of operational variables on powder properties are difficult to estimate.

Agitation fluidized bed granulation,[2)] the application of which is increasing remarkably in the chemical and pharmaceutical industries, is the most difficult to scale-up among the granulation processes, because the granulation mechanism is very complicated and the process variables related to granule growth are large in number. Although some studies related to agitation fluidized bed granulation such as granule growth during moisture control,[3)] process control using a bed height control system[4,5)] and monitoring of granule growth by an image processing system[6)] have already been reported, there have been no systematic investigations into the granule growth mechanism. Therefore, to scale-up the granulation process, the granule growth mechanism and the effects of process variables on granule properties must be elucidated first.

In the previous paper,[1)] we optimized operational variables such as spray condition, moisture measurement method, powder feed weight and drying efficiency, which were required for the scale-up of agitation fluidized bed granulation.

This paper describes the scale-up characteristics of agitation fluidized bed granulation. The effects of scale and process variables on granule properties were investigated experimentally. Based on the results obtained, the mechanism of granule growth in different scales was also discussed here.

Experimental

Equipment For wet granulation, an agitation fluidized bed[2—6)] in three sizes (NQ-125, 230, 500, Fuji Paudal Co., Ltd.) were used. Their vessel diameters were 125, 230 and 500 mm, respectively. Details of the equipment and each dimension were described[1)] previously.

Powder Samples The starting materials for granulation was the pharmaceutical standard formulation defined by the working group for the preparation of standard formulations,[7)] and it 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 as a binder solution through a binary nozzle located at the top of the vessel (top spray method).

Operating Conditions Operating conditions for scale-up experiments are summarized in Table 1. Operating conditions such as spray conditions, method for moisture measurement and control, powder feed weight and drying efficiency were preliminarily optimized.[1)]

Here, the scale-up experiments were conducted as follows:

Table 1. Operating Conditions

	NQ-125	NQ-230	NQ-500
Vessel diameter (mm)	125	230	500
Powder feed weight (kg)	0.36	2.23	22.9
Agitator rotational speed (s^{-1})	2.5—15.0	2.5—10.0	0.83—5.0
Air flow velocity (m/s)	0.4, 0.6, 0.8	0.4, 0.6, 0.8	0.4, 0.6, 0.8
Air temperature (°C)	80	80	80
Moisture content	$W=18\%$ constant for 15 min		
Spray nozzle	655 type	3B type	2B type
Insert diameter (i.d., mm)	1.0	1.0	2.0
Air pressure (Pa)	1.5×10^5	1.5×10^5	3.0×10^5
Nozzle height (mm)	100	200	500

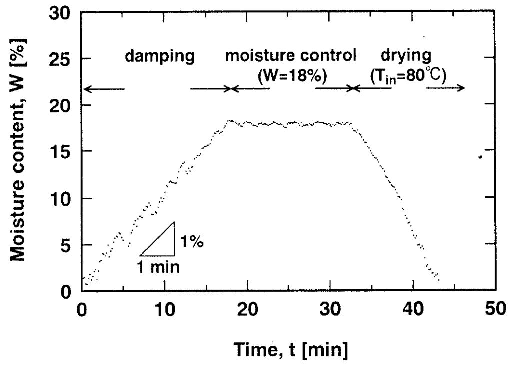

Fig. 1. Example of Moisture Control Method

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* To whom correspondence should be addressed.

(i) Premixed powder samples were fed into the vessels and agitated with fluidization air for 300 s.

(ii) Granulation experiments were started with spraying water as a binder solution. As shown in Fig. 1, the moisture content was programmed to reach 18% with initial 18 min. After reaching 18%, the water level was maintained at 18% for 15 min by a moisture fixed command control. This moisture control was intended to maintain a constant adhesion force by a liquid bridge, in addition to prevent external disturbance.

(iii) Granulated products were dried with fluidization air in the vessel. The fluidization air was kept constant at 80 °C regardless of vessel size.

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

The apparent density of granules was measured using a measuring cylinder, and the granule shape factor was measured by means of an image processing system (Image Eye, Fuji Paudal Co., Ltd.).[6]

Results and Discussion

Effect of Agitator Rotational Speed and Vessel Scale on Granule Diameter Figure 2 illustrates the effects of agitator rotational speed and vessel scale on granule mass median diameter. As seen in Fig. 2, the granule mass median diameter decreased with an increase in agitator rotational speed and vessel scale. As the air flow rate increased (compare (A), (B) and (C)), the diameter also tended to increase. Essentially, granule diameter is determined by its internal adhesion force by a liquid bridge and its external separation force. In this study, since the moisture content was kept constant in every run, it was presumed that the internal adhesion force by liquid bridge was kept constant. Therefore, it could be said that the external separation force largely influenced granule size.

In considering the phenomena that granule size decreased with increased agitator rotational speed and decreased air flow rate, the main external separation force in an agitation fluidized bed was judged to originate from agitator rotation; intensive centrifugal force or shear stress due to agitator rotation should pull apart the granule particle or prevent granule adhesion. By contrast, the fluidization air should have a buffering action; an increase in fluidization air should diminish the effect of agitator rotation. Therefore, an increase in agitator rotational speed, *i.e.*, an increase in the separation force, should make the granule smaller, while an increase in fluidization air flow velocity should diminish the effect of agitator rotation and make the granule larger.

Comparing the data obtained by different sized equipment, the larger the vessel size, the smaller the granule diameter became. If the vessel size was large, granules were blown higher by fluidization air, then suffered a larger impact upon falling. Also, although the mean stresses were the same, granules received stronger local stress in the large scale equipment because the inhomogeneity of granule behavior increased with vessel size. This additional

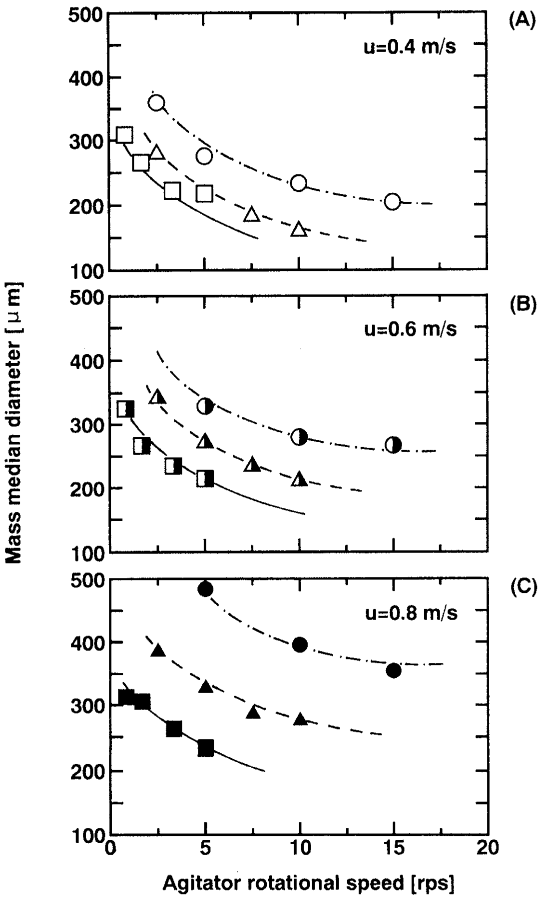

Fig. 4. Effect of Agitator Rotational Speed and Vessel Scale on Granule Apparent Density

(A), air flow velocity $u=0.4$ m/s; ○, NQ-125; △, NQ-230; □, NQ-500. (B), air flow velocity $u=0.6$ m/s; ◑, NQ-125; ▲, NQ-230; ◨, NQ-500. (C), air flow velocity $u=0.8$ m/s; ●, NQ-125; ▲, NQ-230; ■, NQ-500.

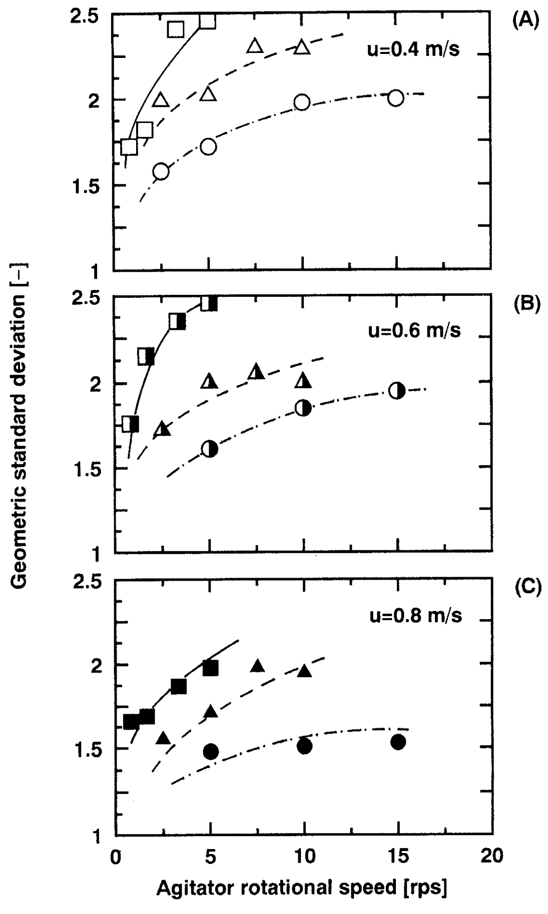

Fig. 3. Effect of Agitator Rotational Speed and Vessel Scale on Geometric Standard Deviation (Particle Size Distribution)

(A), air flow velocity $u=0.4$ m/s; ○, NQ-125; △, NQ-230; □, NQ-500. (B), air flow velocity $u=0.6$ m/s; ◑, NQ-125; ▲, NQ-230; ◨, NQ-500. (C), air flow velocity $u=0.8$ m/s; ●, NQ-125; ▲, NQ-230; ■, NQ-500.

external force should serve as a separation force or granule compaction force. Granules were thus smaller with an increase in vessel size.

Effect of Agitator Rotational Speed and Vessel Scale on Granule Size Distribution Figure 3 indicates the effects of agitator rotational speed and vessel scale on granule size distribution (geometric standard deviation). Geometric standard deviation increased with an increase in agitator rotational speed and vessel scale. Also, an increase in air flow rate resulted in a decrease in geometric standard deviation (compare (A), (B) and (C)). In terms of the granule growth mechanism, agitation fluidized bed granulation was situated between fluidized bed granulation and agitation granulation, and it has been reported that the granulated products produced by fluidized bed have a rough surface, small density and sharp particle size distribution, while the products of agitation granulation are spherical and well compacted, with wide particle size distribution. These differences in granule growth mechanism and granule properties originated from the correlation between the adhesion force and the external force. For example, when the external force is considerably large, properties of granulated products should be similar to those produced by agitation granulation. By contrast, when the adhesion force is large, the resulting granulated products resemble granules produced by fluidized bed granulation. Therefore, an increase in agitator rotational speed or a decrease in air velocity resulted in an increase of external force, which caused a wide particle size distribution. In addition, we can confirm the phenomena that the external force increases with vessel scale, because geometric standard deviation increased with an increase in vessel scale regardless of air flow rate.

Effect of Agitator Rotational Speed and Vessel Scale on Apparent Density of Granules Figure 4 shows the effects of agitator rotational speed and vessel scale on apparent density of granules. As seen in Fig. 4, apparent density of granules increased with an increase in agitator rotational speed and vessel scale. As the air flow rate increased (compare (A), (B) and (C)), the density tended to decrease.

As discussed earlier, the external force increased with an increase in agitator rotational speed and a decrease in air flow velocity. If the external force increased, the granules were more compressed by the force and the density also increased. Thus, the granules exhibited large apparent density when the external force was large (large agitator rotational speed and small air velocity). In addition, since the force increased with vessel size, the granules were more compressed and showed large apparent density when granulation was conducted in large scale equipment.

Effect of Agitator Rotational Speed and Vessel Scale on Granule Shape Factor Figure 5 indicates the effects of agitator rotational speed and vessel scale on the granule

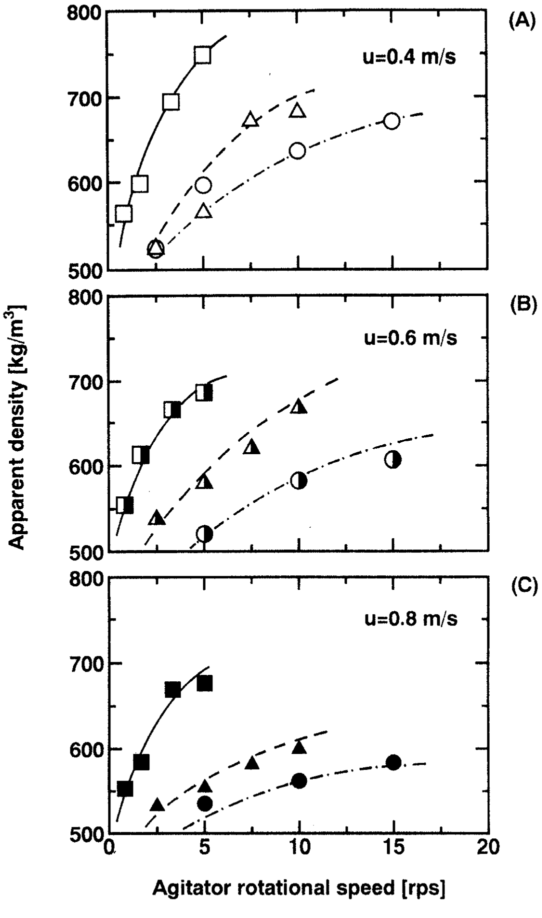

Fig. 4. Effect of Agitator Rotational Speed and Vessel Scale on Apparent Granule Density

(A), air flow velocity $u=0.4$ m/s; ○, NQ-125; △, NQ-230; □, NQ-500. (B), air flow velocity $u=0.6$ m/s; ◑, NQ-125; ▲, NQ-230; ◨, NQ-500. (C), air flow velocity $u=0.8$ m/s; ●, NQ-125; ▲, NQ-230; ■, NQ-500.

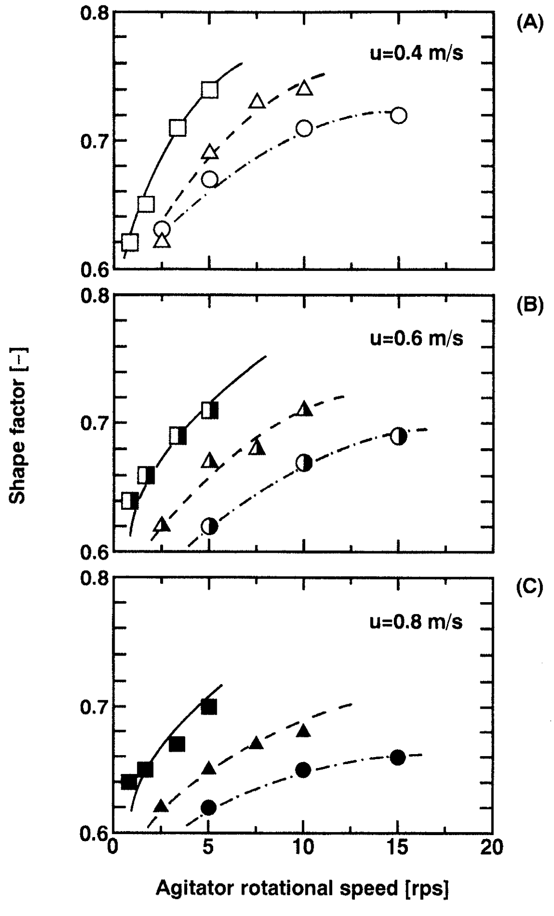

Fig. 5. Effect of Agitator Rotational Speed and Vessel Scale on Granule Shape Factor

(A), air flow velocity $u=0.4$ m/s; ○, NQ-125; △, NQ-230; □, NQ-500. (B), air flow velocity $u=0.6$ m/s; ◑, NQ-125; ▲, NQ-230; ◨, NQ-500. (C), air flow velocity $u=0.8$ m/s; ●, NQ-125; ▲, NQ-230; ■, NQ-500.

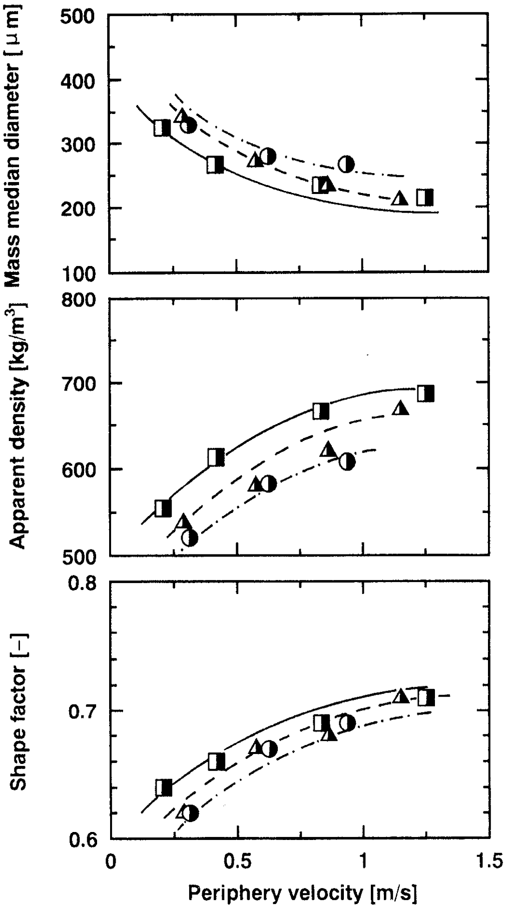

Fig. 6. Effect of Periphery Velocity on Granule Properties

Air flow velocity $u=0.6$ m/s. ◑, NQ-125; ▲, NQ-230; ◨, NQ-500.

shape factor. Here, as a granule shape factor, the following sphericity was used:

$$\phi=\frac{4\pi\Sigma S}{L^2} \quad (1)$$

where S and L indicate projected granule area and perimeter, respectively.

As seen in Fig. 5, the granule shape factor increased with an increase in agitator rotational speed and vessel scale. The granule shape factor decreased as the air flow rate increased (compare (A), (B) and (C)). Also, the granule shape factor showed almost the same tendency as apparent density of granules. In this case, when the external force increased, the granules became more spherical and the shape factor increased. Thus the granules exhibited a large shape factor when the external force was large (large agitator rotational speed and small air velocity). In addition, since the force increased with vessel size, the granules were made more spherical and showed a large shape factor in large scale equipment.

Scale-up Characteristics of Agitation Fluidized Bed Granulation To investigate the scale-up characteristics of agitation fluidized bed granulation, granule properties were plotted against periphery velocity in Fig. 6. Almost the same shaped curves were obtained when the periphery velocity was the same. This implied that the periphery velocity was one of the most important factors in the scale-up of granulation. However, the mass median diameter decreased while the apparent density and shape factor increased slightly with the vessel scales. This was because the external force increased with the vessel scale. Therefore, we must consider the additional separation force when the vessel scale increases. In the next paper, the effects of agitator blade angle and powder feed weight on granule properties will be investigated. The scale-up theory based on kinetic energy similarity, in which adhesion force and external force are taken into consideration will be also described.

Conclusion

The scale-up of granulation by an agitation fluidized bed of three sizes (vessel diameter 125, 230, 500 mm) was conducted using a pharmaceutical standard formulation. The effects of scale, air flow velocity and agitator rotational speed on granule properties such as granule size, size distribution, density and shape factor were investigated experimentally and the following conclusions were obtained:

1) The granule mass median diameter decreased with decreased air flow rate and increased agitator rotational speed and vessel scale. Since the adhesion force was kept constant by a moisture fixed command control, these results originated from the facts that the external separation force increased with agitator rotational speed and vessel scale. A decrease in air flow rate accelerated the effect of agitator rotation, thus the granule size decreased with air flow rate.

2) Granules showed wide particle size distribution when the agitator rotation was high, air flow rate was small and vessel scale was large. It was found that a large external force resulted in wide particle size distribution.

3) Apparent granule density and the shape factor both increased with decreased air flow rate and increased agitator rotational speed and vessel size. This implied that granules were compressed to a spherical shape with an increase in external force. Also, the apparent granule density change showed almost the same tendency as the granule shape factor.

4) Granule properties showed almost the same tendencies when the periphery velocity was the same. However, mass median diameter decreased, while apparent density and shape factor increased with vessel scales. This was because the external force increased with vessel scale. We must consider the additional separation force when vessel scale increases.

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