Scale-Up of Agitation Fluidized Bed Granulation. I. Preliminary Experimental Approach for Optimization of Process Variables

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Granulation scale-up with an agitation fluidized bed of three sizes (vessel diameter 125, 230, 500 mm) was preliminary investigated. In order to evaluate accurately the scale-up factor on granule properties, process variables such as spray conditions, method for moisture measurement and control, powder feed weight and drying efficiency were optimized.

Key words scale-up; granulation; agitation fluidized bed; optimization; operational variable

Scale-up is an operation to produce a product of the same quality as is obtained using smaller equipment. It is an important and even necessary operation in all industrial manufacturing processes. In powder handling processes, the scale-up is especially difficult because (i) the behavior of powder is unpredictable, (ii) properties of powder are hard to control, and (iii) dynamic characteristics are difficult to understand. Most of the scale-up of powder handling processes has been conducted by experienced expert operators, and there have been only a few studies[1] posing a theoretical approach to scale-up problems.

In pharmaceutical industry, scale-up has become recently a significant subject, because GMP (good manufacturing practices) strongly demand accurate product reproducibility in scale-up. Although various unit operations have moved to a greater scale in manufacturing oral dosage forms, granulation is the most difficult operation to scale- up. Therefore, theoretical approach to the scale-up of the granulation process is imperative.

In this paper, a preliminary experimental investigation into the scale-up of agitation fluidized bed granulation was described. Operating conditions such as spray conditions, method for moisture measurement and control, powder feed weight and drying efficiency were optimized.

Experimental

Equipment A schematic diagram of the experimental apparatus is illustrated in Fig. 1, and the dimensions and scale-up ratio of each granulator are shown in Table 1. For wet granulation, an agitation fluidized bed[2,3] of three sizes (NQ-125, 230, 500, Fuji Paudal Co., Ltd.) was used. The vessel diameters were 125, 230 and 500 mm, respectively. In this fluidized bed, the agitator blade was equipped to provide tumbling and compacting effects on the granules, which make the granules spherical and well-compacted. Under the blade, three circular plates of different diameter for NQ-125, five plates for NQ-230 and seven plates for NQ-500 were superimposed 3 mm apart to function as air distributors; particles were fluidized by heated air, which was blown from the slit between each

Table 1. Dimension and Scale-Up Ratio

	NQ-125	NQ-230	NQ-500
Vessel diameter (mm)	125	230	500
Scale-up ratio based on			
diameter	1	1.84	4
cross sectional area	1	3.39	16
volume	1	6.23	64

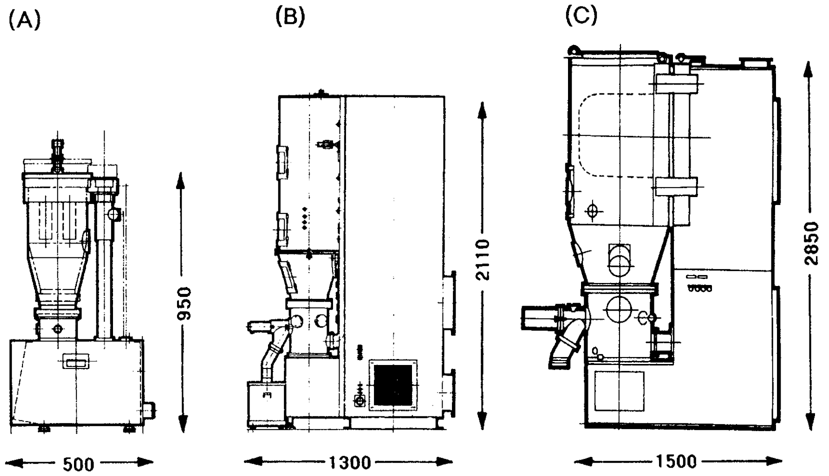

Fig. 1. Schematic Diagram of Experimental Apparatus Employed
(A), NQ-125; (B), NQ-230; (C), NQ-500.

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circular plate to create a circulating flow. Fine powders lifted up by the fluidization air were entrapped by bag filters and brushed down by pulsating jet of air.

The moisture content of granules during granulation was measured by an infrared (IR) moisture sensor (Wet-eye, Fuji Paudal Co., Ltd.).[4,5] Feedback control of moisture content was conducted by regulating the rotational speed of the roller pump.

Fluidization air velocity was measured by a hot-wire anemometer, which was located at the center of the inlet air duct pipe to detect maximum air velocity. Inlet and outlet air temperature and humidity were measured by ceramic sensor.

The main operational variables such as inlet air temperature, air velocity, and agitator rotational speed were feedback controlled to maintain a stable operation. All the operational variables were on-line monitored by a personal computer, then stored on hard disk.

Evaluation of Operating Conditions Spray mist size was measured by the He–Ne laser scattering method (LDSA-1300A, Meiwashoji Co., Ltd.).

Particle size distributions of 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 the granulated products were computed by log-normal distribution using a personal computer.

The number median diameter of each powder sample was measured using an image processing system (Image Eye, Fuji Paudal Co., Ltd.).[6]

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

Powder Samples Table 2 gives the powder samples used. Pharmaceutical standard formulation, defined by the working group for the preparation of standard formulations[7] was used for granulation. Lactose and cornstarch were mixed at a ratio of 7:3 by weight, and hydroxypropylcellulose was adopted as a binder at a level of 5%, which was mixed into the above mixture as a dry powder before granulation.

Purified water as a binder solution was sprayed through a binary nozzle located at the top of the vessel (top spray method).

Results and Discussion

Optimization of Spray Mist Size and Spray Area Key parameters for controlling the granule properties in fluidized bed granulation are spray mist size,[8] spray nozzle height[8] and moisture content[9] (Fig. 2). These parameters were thus optimized first.

Table 2. Powder Samples

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

Figure 3 shows the mass median spray mist size against the binder liquid flow rate at various insert diameters, air pressures and nozzle types.

In the case of 655 and 3B nozzles, the spray mist size increased slightly with an increase in binder liquid flow rate, while in the case of the 2B nozzle, the spray mist size was kept almost constant regardless of liquid flow rate. The same tendency was also observed when the diameter of nozzle insert and spray air pressure varied. By selecting an appropriate diameter of nozzle insert and air pressure, the spray mist size was kept almost constant around 40 μm, regardless of spray nozzle type.

In order to optimize other spray condition, spray nozzle height was optimized.

Figure 4 demonstrates the effect of spray nozzle height on mass median diameter and geometric standard deviation of granules produced by NQ-125 at a moisture content of 18%. Increasing the nozzle height resulted in a decrease in geometric standard deviation, in accordance with the results of Davis and Gloor[10] and Schæfer and Wørts,[8] and this observation could be explained by the more uniform wetting obtained by the simultaneous increase in wetted surface area.[8] Granule mass median diameter showed a large value when the nozzle height was 50 mm, while other data decreased slightly with an increase in nozzle height. At a nozzle height of 50 mm, local wetting was presumed to occur, which resulted in a wide granule size distribution and large mass median size.

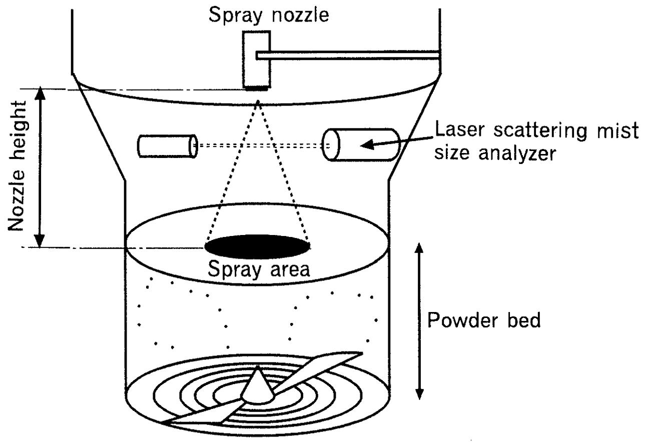

Fig. 2. Schematic Diagram of Optimization for Spray Condition

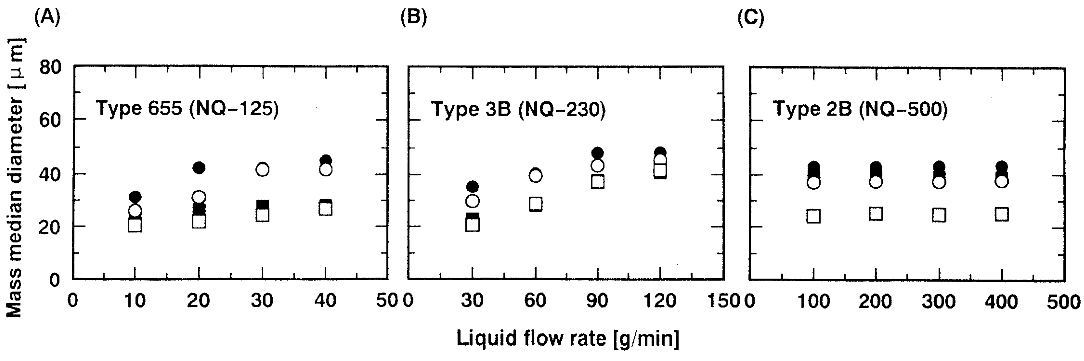

Fig. 3. Plots of Mass Median Diameter of Spray Mist against Liquid Flow Rate

(A) Type 655 (NQ-125); ○, i.d. = 0.7 mm, $P = 1.5 \times 10^5$ Pa; □, i.d. = 0.7 mm, $P = 2.0 \times 10^5$ Pa; ●, i.d. = 1.0 mm, $P = 1.5 \times 10^5$ Pa; ■, i.d. = 1.0 mm, $P = 2.0 \times 10^5$ Pa; (B) Type 3B (NQ-230); ○, i.d. = 1.0 mm, $P = 1.5 \times 10^5$ Pa; □, i.d. = 1.0 mm, $P = 2.0 \times 10^5$ Pa; ●, i.d. = 1.3 mm, $P = 1.5 \times 10^5$ Pa; ■, i.d. = 1.3 mm, $P = 2.0 \times 10^5$ Pa; (C) Type 2B (NQ-500); ○, i.d. = 1.5 mm, $P = 2.0 \times 10^5$ Pa; □, i.d. = 1.5mm, $P = 3.0 \times 10^5$ Pa; ●, i.d. = 2.0 mm, $P = 2.0 \times 10^5$ Pa; ■, i.d. = 2.0mm, $P = 3.0 \times 10^5$ Pa.

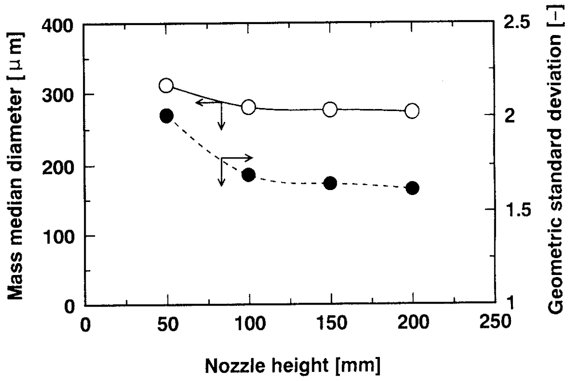

Fig. 4. Effect of Spray Nozzle Height on Mass Median Diameter and Geometric Standard Deviation of Granulated Products

NQ-125, moisture content = 18%, agitator rotational speed = 600 rpm. ○, mass median diameter; ●, geometric standard deviation.

These results implied that the nozzle height largely affected granule properties, and nozzle height, *i.e.*, surface wetting area, must be kept constant to evaluate the scale-up characteristics correctly. We therefore determined an appropriate spray nozzle height based on the assumption that the effect of nozzle height, *i.e.*, surface wetting area, could be neglected if the ratio of spray area to vessel cross sectional area was kept constant regardless of vessel size. For the NQ-125, we selected 100 mm as an optimum height, because granule diameter and geometric standard deviation changed slightly with nozzle height; in addition, too much nozzle height caused powder adhesion on the vessel wall. Table 3 summarizes these conditions. By setting the spray nozzle height at 100 mm for NQ-125, 200 mm for NQ-230 and 500 mm for NQ-500, almost the same spray area ratio (about 30% of the vessel cross sectional area) could be maintained.

Moisture Measurement Figure 5 indicates the relationship between moisture content and IR sensor output. The granules, sampled out during granulation, were dried using a shelf drier, and wet basis moisture content was measured by the decreased water weight.

As seen in Fig. 5, the plots were within the approximate line, even if the vessel size varied. Originally, the relation between moisture content and IR sensor output should have been different with each sensor. In addition, these relations should be different if particle flow pattern, particle concentration, measuring length and sensor location varied. However, careful treatment of these parameters enabled us to obtain adequate correlation, as shown in Fig. 5.

In any case, since adequate agreement was obtained, we used an approximate function (Eq. 1) by means of the least square method in measuring moisture content:

$$W = -3.647X^2 + 17.45X + 1.039 \quad (1)$$

where W was moisture content and X was IR sensor output.

Powder Feed Weight and Drying Efficiency Drying efficiency is proportional to the feed rate of the heated air in a fluidized bed. Basically, the drying efficiency decreases with an increase in vessel size, because the drying efficiency is proportional to diameter^2, while the volume is proportional to the diameter[3]. Therefore, the initial powder feed weight must be determined taking into account the drying efficiency.

Table 3. Spray Condition

Nozzle type	655	3B	2B
Granulator	NQ-125	NQ-230	NQ-500
Nozzle insert (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
Spray angle (deg.)	38.5	31.6	24.8
Spray area/vessel cross sectional area (%)	31.36	31.95	30.25

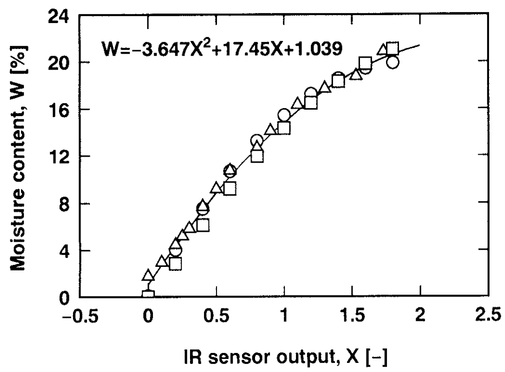

Fig. 5. Relationship between Moisture Content and IR Sensor Output

○, NQ-125; □, NQ-230; △, NQ-500.

Table 4. Powder Feed Weight

Granulator	Powder feed weight (kg)	L/D (—)	Scale-up ratio (—)
NQ-125	0.36	0.5	1
NQ-230	2.23	0.5	6.23
NQ-500	22.9	0.5	64

L/D = ratio of powder bed height to vessel diameter.

Conventionally, practice of maintaining a constant bed height regardless of vessel size has been often used in the scale-up of fluidized bed granulation. Although this method can maintain constant drying efficiency, this cannot be applied to a large scale-up because particle flow pattern and external force stressed on granule particles differed greatly. In addition, thinking about manufacturing efficiency, a larger powder feed is preferable. The effect of the scale-up ratio on granule properties can also be accurately evaluated only when the powder is fed in proportion to the scale-up ratio. Therefore, we decided to feed initial powder samples in proportion to diameter[3], and to control drying efficiency using the following method. Here, the initial powder feed weight was based on the feed weight in NQ-125; according to the preliminary experimental result, a particle flow pattern was good when the initial powder bed height was 62.5 mm ($L/D = 0.5$). In this case, the powder feed weight had become 0.36 kg, and the feed weight of the larger scales should be as listed in Table 4.

To control drying efficiency of air, regulation of the fluidization air temperature is one method. The heat transfer coefficient h between gas and granules in fluidized bed granulation can be estimated theoretically as

$$h = Nu_p \cdot \lambda / D_p \quad (2)$$

where λ is thermal air conductivity and D_p is granule diameter. As we have already reported,[11] heat transfer coefficient h between gas and granules in fluidized bed granulation can be estimated theoretically as

$$Nu_p = 2 + 0.6 Re_p^{1/2} \cdot Pr^{1/3} \quad (3)$$

where Nu_p is a granule Nusselt number, Pr is a Prandtl number and Re_p is a granule Reynolds number.

Once the heat transfer coefficient has been estimated, heat transfer from gas to granules can be calculated. By means of this method, a decrease in drying efficiency due to the increase of scale could be compensated for increasing the inlet air temperature.

For example, assuming that the air temperature of NQ-125 is 31 °C, the air temperature of NQ-230 and NQ-500 must be 48 and 80 °C to maintain constant drying efficiency. However, this method cannot be applied to a large scale-up ratio or to the powder samples which are very sensitive to temperature.

Another method for controlling drying efficiency is to use the moisture control method.

Figure 6 illustrates moisture control in the scale-up experiments. By setting the desired moisture content and damping speed, drying efficiency can be maintained at a constant level during damping and granulation processes. However, drying time increased with an increase in vessel size, because this method could not keep a constant drying time since it could not be applied to the drying process. According to the literature,[9] the longer the drying time, the larger the granule attrition; thus, we measured the granule median diameter change during the drying process

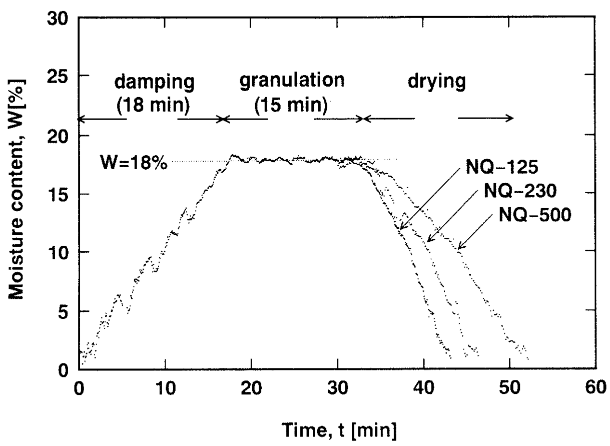

Fig. 6. Example of Moisture Control Experiment

of each scale granulator to investigate the effect of attrition. Here, moisture content during granulation was set at $W = 18\%$ to make a large granule with a spherical shape and high density. In practice, the granule shape factor and apparent density were around 0.69 and 650 kg/m^3, of which the superiority was easily confirmed by considering that the values of a typical fluidized bed were 0.54 and 490 kg/m^3.

Table 5 gives the effect of drying time on granule attrition. Here, we selected operating conditions so that the granule mass median diameter of each apparatus was almost the same (around 270 μm).

This table showed a tendency for granule attrition to increase slightly with vessel size, *i.e.*, an increase in drying time. However, considering the difference between the granule attrition of NQ-125 and NQ-500 was only 12 μm, which was within 5% of granule median diameter, the effect of drying time on granule attrition was supposed to be very small. This was because the granules were well-compacted and spherical, so that attrition during the drying process would not likely to occur. In addition, since the agitation fluidized bed had good gas–solid contact efficiency and the powder samples also had good drying characteristics, the drying time was very short and the effect of attrition was very small.

As a result, we could control the damping and granulation process by moisture control, while the granules were dried by maintaining a constant air temperature ($T_{in} = 80$ °C) without considering drying time.

In this paper, we have optimized the operational conditions for the scale-up of granulation by agitation fluidized bed. In the next paper, we will investigate the effect of scale-up factor on granule properties such as granule median diameter, apparent density and shape factor.

Conclusions

A preliminary experimental approach for the scale-up of granulation by an agitation fluidized bed of three sizes (i.d. 125, 230, 500 mm) was described. To accurately investigate the effect of scale factor on granule properties, several operating conditions were optimized and the following conclusions were obtained;

1) By regulating the liquid flow rate and air feed pressure, a constant spray mist size around 40 μm could be maintained regardless of vessel size.

2) The spray nozzle height was set at 100 mm for NQ-125, 200 mm for NQ-230 and 500 mm for NQ-500 to maintain a constant ratio of spray area to vessel cross sectional area.

3) The relationship between moisture content and IR sensor output was investigated using a granulator of three sizes. By optimizing the particle flow pattern, particle

Table 5. Effect of Drying Time on Granule Attrition

Granulator	Moisture content (%)	Air velocity (m/s)	Agitator rotational speed (rpm)	Mass median diameter (μm)	Drying time (min)	Granule diameter decrease by attrition (μm)
NQ-125	18	0.6	900	267	10	20
NQ-230	18	0.6	300	271	13	28
NQ-500	18	0.6	100	267	20	32

concentration, measuring length and sensor location, almost the same correlation was obtained regardless of vessel scale.

4) By means of moisture control, drying efficiency during the damping and granulation processes could be maintained constant. By controlling the drying process (constant air temperature), the effect of drying time increase, originated from an increase in granulator size, on granule attrition was very small. Taking into account these drying characteristics, we have decided to feed initial powder samples in proportion to diameter[3]; the initial powder feed weight was 0.36 kg for NQ-125, 2.23 kg for NQ-230 and 22.3 kg for NQ-500. By using this method, accurate evaluation of the effect of a scale-up factor on granule properties can be expected.

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