# Scale-Up of Agitation Fluidized Bed Granulation. V. Effect of Moisture Content on Scale-Up Characteristics

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**Characteristics of granulation scale-up with moisture variation were investigated using an agitation fluidized bed of four sizes (vessel diameter 125, 230, 500 and 750 mm). Agitation fluidized bed granulation was done under various levels of moisture content and the vessel sizes. Granule properties of mass median diameter, geometric standard deviation, apparent density, shape factor and friability were investigated to know the effect of moisture content on the scale-up characteristics. It was found that a linear relationship between granule mass median diameter and moisture content was observed regardless of the vessel size, however, the mass median diameter decreased as this size. The geometric standard deviation decreased with increase in moisture content, showing that granule size distribution was narrowed as granule growth progressed; the deviation increased, however, with increase in vessel size. The apparent density and shape factor tended to increase with moisture content and vessel size. It was concluded that these phenomena could be explained by the adhesion and separation force experienced by the granules during granulation. Also, the scale-up characteristics could be well explained by the moisture content.**

**Key words** scale-up; granulation; characteristic; agitation fluidized bed; moisture content

Scale-up has recently become a significant subject especially in the pharmaceutical industry, because GMP (good manufacturing practices) strongly demand accurate product reproducibility when scale-up occurs. Although various units operations are at work in the manufacturing processes of oral dosage forms, granulation is the most difficult operation to scale-up, because (i) the behavior of powder is unpredictable, (ii) the properties of powder are hard to control, and (iii) dynamic characteristics of granulation are difficult to understand. Therefore, adequately reliable tools and quantitative information are not yet available.

We have already reported the scale-up characteristics of agitation fluidized bed granulation under various fluidizing air velocities and agitator rotational speeds,[1,2] and elucidated the effects of these variables on granule properties. Also, using the kinetic energy similarity, the simple scale-up theory of agitation granulation was proposed.[3] However, we have not previously investigated the effect of moisture content on the scale-up characteristics of agitation fluidized bed granulation. The analysis of granulation scale-up by means of moisture content has been anticipated, because moisture measurement has become a convenient method to monitor granule growth; the granule properties in a large scale granulator can be easily estimated if the scale-up characteristics can be explained by the moisture content.

In this paper, scale-up characteristics of agitation fluidized bed granulation were investigated under various levels of moisture content using four scales of granulator (the diameters of the vessel were 125, 230, 500 and 750 mm). Granule properties of mass median diameter, geometric standard deviation, apparent density, shape factor and friability were investigated, and the effect of moisture content on the scale-up characteristics was evaluated in detail.

## Experimental

**Equipment** A schematic diagram of the experimental apparatus is illustrated in Fig. 1. For wet granulation, agitation fluidized beds[1-5] of four sizes (NQ-125, 230, 500 and 750, Fuji Paudal Co., Ltd.) were used. The vessel diameters were 125, 230, 500 and 750 mm, respectively. An agitator blade[2] (blade angle was 15°) was installed in this fluidized bed to provide tumbling and compacting effects on the granules, which made them spherical and well-compacted. Under the blade, three circular plates of different diameter for NQ-125, five plates for NQ-230, seven plates for NQ-500 and eleven plates for NQ-750 were superimposed 0.5 mm apart which functioned as air distributors; particles were fluidized by heated air which was blown from the slit between each circular plate to create a circulating flow. Fine powders lifted up by the fluidization air were entrapped by bag filters and brushed down by a pulsating jet of air. An air knocker was also installed to prevent powder from adhering to the inside walls of the granulator.

The moisture content of granules during granulation was measured by an infrared (IR) moisture sensor (Wet-eye, Fuji Paudal Co., Ltd.).[6,7] Feedback control method controlled the moisture content 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 temperatures and humidities were measured by ceramic sensors.

The main operational variables of 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 a hard disk.

Table 1 lists the dimensions of each granulator and other detailed information.

As previously reported,[4] to maintain geometric similarity, powder samples were fed in proportion to the volume of the vessel used. The spray conditions were optimized so that the spray mist particle had a diameter of around 40 $\mu$m, regardless of the vessel size. The height of each spray nozzle was set so as to keep the ratio of sprayed wet area to vessel cross sectional area constant at about 30—35%.

To avoid the effect of granulation time on granule growth, damping speed was controlled to dampen to a predetermined moisture content in 20 min, regardless of the predetermined moisture content. Although we used a moisture fixed command control to maintain constant moisture content for 20—30 min in our previous study,[1,4] the method was not used this time for the following reasons:

1) This control was used to prepare well compacted and spherical granules, and thus was not applicable to the low moisture content range of this study.

2) The effect of moisture control on granule growth changed greatly if the moisture content varied, and so was not useful for correct evaluation of the moisture content.

Fluidization air velocity was kept at constant 0.7 m/s, and the agitator rotational speed of each granulator was determined to keep the agitator

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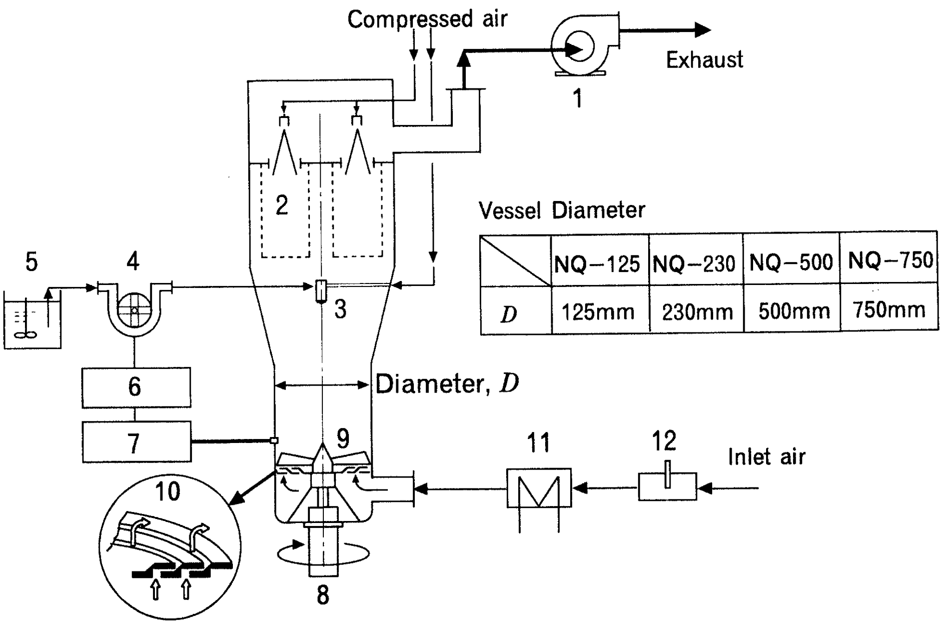

Fig. 1. Schematic Diagram of Experimental Apparatus Employed

1, blower; 2, bag filter; 3, spray nozzle; 4, pump; 5, purified water; 6, controller; 7, IR moisture sensor; 8, motor; 9, agitator blade; 10, slit plates (air distributor); 11, heater; 12, hot-wire anemometer.

Table 1. Dimensions and Operating Conditions

| | Equipment | NQ-125 | NQ-230 | NQ-500 | NQ-750 |
|---|---|---|---|---|---|
| Dimensions | Diameter of vessel (mm) | 125 | 230 | 500 | 750 |
| | Powder load weight (kg) | 0.36 | 2.23 | 22.9 | 77.3 |
| Spray nozzle | Type of nozzle | 655 | 3B | 2B | 2B × 2 |
| | Nozzle insert diameter (mm) | i.d. 1.0 | i.d. 1.0 | i.d. 2.0 | i.d. 2.0 |
| | Air pressure (Pa) | $1.5\times10^5$ | $1.5\times10^5$ | $3.0\times10^5$ | $3.0\times10^5$ |
| | Nozzle height (mm) | 100 | 200 | 500 | 800 |
| Granulation | Agitator rotational speed (rpm) | 600 | 300 | 150 | 100 |
| | Fluidization air velocity (m/s) | 0.7 | | | |
| | Moisture content (%) | 12—22 | | | |
| | Inlet air temperature (°C) | 80 | | | |
| | Damping time | Damping to pre-determined moisture content in 20 min | | | |
| Drying | Agitator rotational speed (rpm) | 300 | 150 | 75 | 75 |
| | Inlet air temperature (°C) | 80 | | | |
| | Fluidization air velocity (m/s) | 0.7 | | | |

periphery velocity constant at 1.25 m/s (for example, 600 rpm for NQ-125). The 600 rpm for NQ-125 was the most typical operating conditions for making subtilized granules using the agitation fluidized bed. These procedures to keep agitator periphery velocity constant were intended only to analyze the effects of moisture content and vessel scale on granule growth.

Drying conditions (air temperature and air velocity) were the same regardless of the vessel scale, and were intended to dry wet granules as soon as possible without violently fluidizing. The agitator rotational speed was maintained at almost minimum to avoid producing coarse granules in the drying process, thus eliminating the effect of granule attrition. After the drying, granules were exhausted and their physical properties were immediately measured and evaluated.

**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, mass median diameter and geometric standard deviation of the granulated products were computed by a log-normal distribution using a personal computer.

The apparent density of the granulated products was measured using a measuring cylinder.

The granule shape factor was measured by an image processing system called Image Eye system developed by Fuji Paudal Co., Ltd.[5] A circularity[5] was used to define the expression of granule shape factor.

Table 2. Powder Samples

| Sample | Median diameter ($\mu$m) | 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.

Friability of the granules was evaluated as follows: 25 g of the granulated products which had already been sieved to sizes ranging from 180 to 850 $\mu$m were fed into a friabilator with 25 g of glass beads (diameter of the beads was 7 mm), then rotated at 25 rpm for 20 min. After the rotation, the weight percent of the fraction that would go through 200 mesh (200 mesh under) was measured.

**Powder Samples** Table 2 gives the properties of powder samples used. Pharmaceutical standard formulation, defined by the Working Group for the Preparation of Standard Formulations,[7] was used for the granulation. Lactose and cornstarch were mixed at a ratio of 7 : 3 by

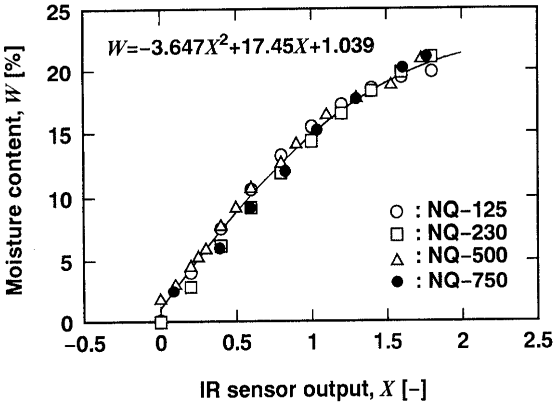

Fig. 2. Calibration Curve in Moisture Measurement by IR Moisture Sensor

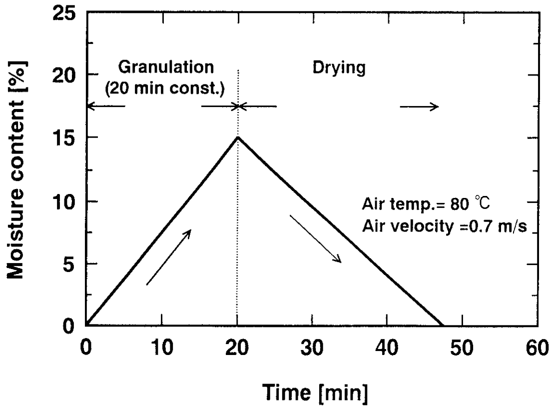

Fig. 3. Moisture Control Pattern

weight, and hydroxypropylcellulose was adopted as a binder at a level of 5 wt%, 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

**Moisture Measurement** Figure 2 indicates the relationship between moisture content and IR sensor output (calibration curve). Here, granules sampled out during granulation were dried using a shelf drier, and wet basis moisture content was measured by the decreased water weight.

As can be seen in Fig. 2, the plots were within an approximate line, even if the vessel size varied. According to our previous investigation,[7] the calibration curve was influenced only when the damping speed was relatively slow or high, because the water distribution among the particles changed markedly with this speed. Thus the influence of vessel size on the calibration curve could be neglected under a damping speed kept the same by moisture control. It was also found that the moisture measurement in larger scales could be easily done because the calibration curve in these scales could be estimated by the data obtained in smaller equipment.

In any case, since an adequate agreement was obtained in the calibration curves at various vessel sizes, we used an approximate function (Eq. 1) based on the least squares method in measuring moisture content:

$$W = -3.647X^2 + 17.45X + 1.039 \tag{1}$$

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

Figure 3 illustrates a moisture control pattern in this study. To avoid the effect of granulation time on granule growth, moisture content was programmed to increase to a predetermined value in 20 min, regardless of vessel scales. After reaching that predetermined value, the drying process started immediately; all the granules were dried under the same conditions.

**Effect of Moisture Content on Scale-Up Characteristics** Figure 4 illustrates the effects of moisture content and vessel size on granule mass median diameter. Here, to estimate only the two variables, experiments were conducted under the same fluidization air velocity and agitator peripheral velocity.[2,3]

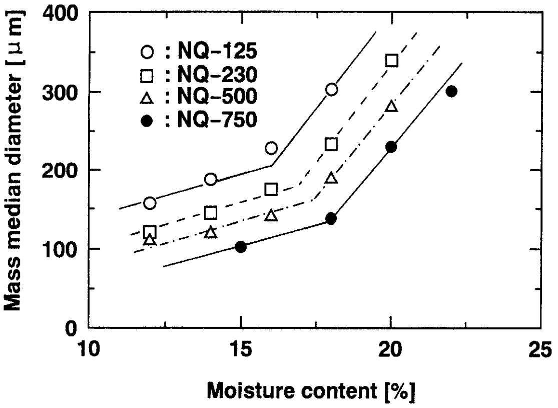

Fig. 4. Effects of Moisture Content and Vessel Size on Granule Mass Median Diameter

Agitator periphery velocity = 1.25 m/s constant.

As can be seen from the figure, granule mass median diameter had a linear relationship with moisture content regardless of the vessel size. Also, the linearity could be divided into two phases of low and high moisture content. In the low moisture content range, granule growth was slow because it was mainly determined by the layering of cornstarch particles onto lactose particles. In the high moisture content range, however, rapid granule growth was observed, because secondary agglomeration in which the agglomerated granules adhered to each other was believed to occur.

Looking at the figure carefully, the granule diameter decreased with an increase in the vessel size. To discuss these scale-up characteristics, the following model is proposed (Fig. 5).

As we have reported,[8,9] granule growth in agitation fluidized bed granulation is mainly determined by the adhesion force of a liquid bridge formed between two particles and a separation force applied to the pair. The separation force increased with decrease in fluidization air velocity and increase in agitator rotational speed and vessel size. This was because the separation force in agitation fluidized bed granulation was caused largely by the agitator rotation, and the increase in rotational speed and decrease in air velocity promoted the effect of agitator rotation.

With increased vessel size, the granules during granula-

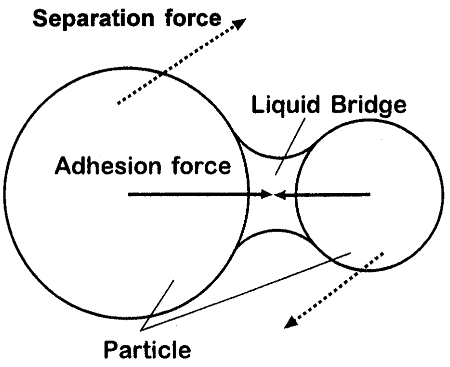

Fig. 5. Granule Growth Model

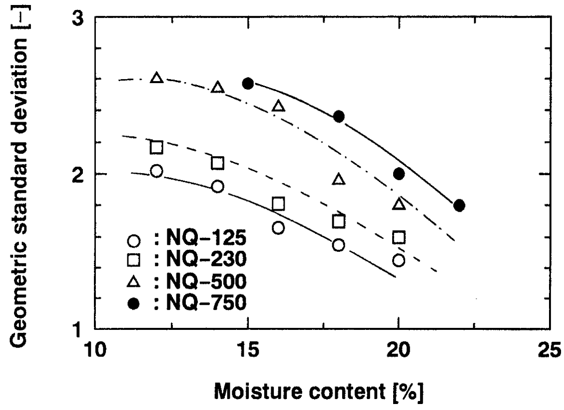

Fig. 6. Effects of Moisture Content and Vessel Size on Granule Geometric Standard Deviation

Agitator periphery velocity = 1.25 m/s constant.

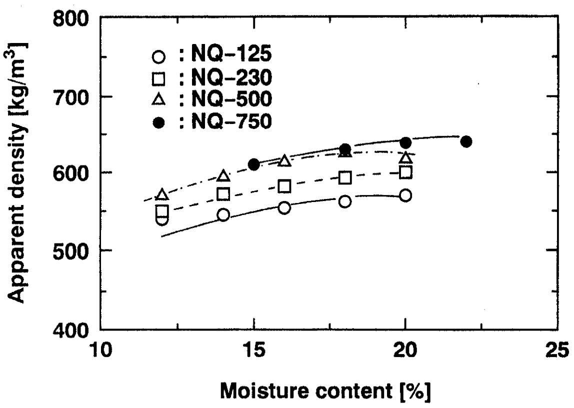

Fig. 7. Effects of Moisture Content and Vessel Size on Granule Apparent Density

Agitator periphery velocity = 1.25 m/s constant.

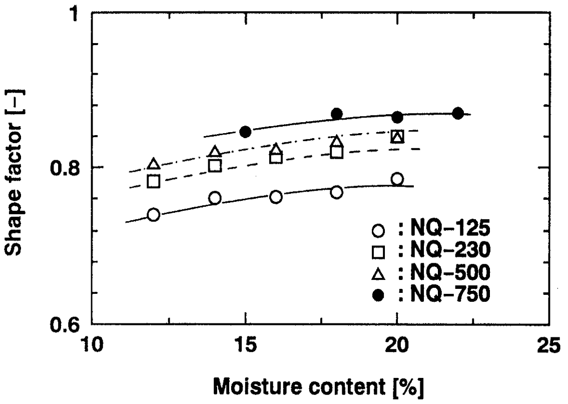

Fig. 8. Effects of Moisture Content and Vessel Size on Granule Shape Factor

Agitator periphery velocity = 1.25 m/s constant.

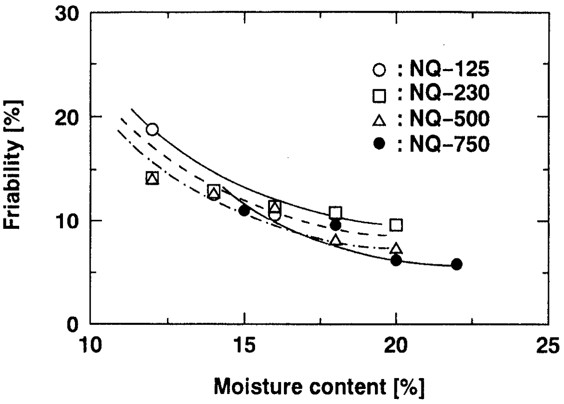

Fig. 9. Effects of Moisture Content and Vessel Size on Granule Friability

Agitator periphery velocity = 1.25 m/s constant.

tion received stronger local stress; they were tapped and compressed because the load of powder bed on them and the frequency of collision increased as vessel size grew. This additional external force served as a separation force and granule compaction force. Granules were thus made smaller with an increase in vessel size, although the moisture content was remained.

Figure 6 shows the effects of moisture content and vessel size on granule geometric standard deviation. The granule geometric standard deviation of all vessel sizes tended to decrease (particle size distribution narrowed) with increase in moisture content because granule growth progressed and the ungranulated fine powders were agglomerated. However, the granule geometric standard deviation increased with an increase in vessel size. As reported,[2] the geometric standard deviation increased with greater separation force. For example, granules produced by a typical fluidized bed granulator had a rough surface, small density and narrow (sharp) particle size distribution, while those obtained by high speed mixer or agitation granulator which underwent large external (separation) force were spherical and well compacted with wide particle size distribution. Therefore, an increase in vessel size resulted in an increase of external (separation) force, which caused broad particle size distribution.

Figures 7 and 8 show the effects of moisture content and vessel size on granule apparent density and shape factor, respectively. The density and shape factor showed the same tendency, and both data increased with moisture content and vessel size. The granules were compacted and made more spherical with increased moisture content because they were elastically deformed while receiving the external (separation) force in the high moisture content range. If the vessel size increased, granules were more compacted and made more spherical because they received the additional external force described in Fig. 5. Figure 9 shows the effects of moisture content and vessel size on granule friability. The friability of granules showed almost the same tendency as the apparent density and the shape factor: it decreased with moisture content and the vessel size. Granules were compressed and their strength or surface smoothness increased with greater moisture content and vessel size.

It was therefore concluded that the scale-up characteristics of agitation fluidized bed granulation could be well explained by the moisture content. The monitoring of moisture content in the scale-up experiment could be a reliable tool to analyze or predict the scale-up characteristics of the granulation process.

## Conclusions

The scale-up characteristics of wet granulation were investigated using an agitation fluidized bed of four sizes (vessel diameter 125, 230, 500 and 750 mm). Agitation fluidized bed granulation was done under various levels of moisture content and vessel sizes. Granule properties of mass median diameter, geometric standard deviation, apparent density, shape factor and friability were evaluated to know the effect of moisture content on the scale-up characteristics. The effects of moisture content and vessel size on these properties were then examined indetail, and a linear relationship was observed between granule mass median diameter and moisture content regardless of vessel size; the mass median diameter, however, decreased with increase in vessel size. The geometric standard deviation decreased with increased moisture content, showing that granule size distribution was narrowed as granule growth progressed; with increase in vessel size, however, the deviation increased. The apparent density and the shape factor tended to increase and the friability to decrease with moisture content and vessel size, indicating granules were compressed and made spherical with increase in these factors. It was elucidated that these phenomena could be explained by the adhesion and separation force applied to granules during granulation. It was also concluded that the moisture measurement should be a reliable tool to analyze and predict the granulation scale-up.

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