Scale-Up of Agitation Fluidized Bed Granulation. IV.
Scale-Up Theory Based on the Kinetic Energy Similarity

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The scale-up theory based on kinetic energy similarity was proposed to elucidate the scale-up characteristics in agitation fluidized bed granulation. In this model, kinetic energy given to granules by agitator rotation and fluidizing air were taken into consideration. It was found that granule mass median diameter, apparent density and shape factor can be well expressed by the parameter \( \text{Ro}/u^2 \), which showed the ratio of kinetic energy by agitator rotation to that by fluidizing air. Based on the results obtained, effects of operational variables and scale factor on the granule properties could be explained theoretically and granule growth mechanism in agitation fluidized bed granulation was elucidated in detail.

Key words scale-up theory; agitation fluidized bed granulation; kinetic energy; scale factor; operational variable; granule property

Scale-up is the most important and sometimes the most difficult operation in the manufacturing processes of all industrial products. It is generally conducted to determine optimum operating conditions applied to large scale batches for marketing, in order to produce a product with the same qualities which was pre-examined in laboratory scale experiments. Scale-up is especially difficult in powder handling processes, because the dynamic behavior of powders and effects of operational variables on powder properties are not easily understood.

So far, we have focused on the agitation fluidized bed granulation process, and investigated the mechanism of granule growth1-2 and the effects of process variables on granule properties using laboratory scale equipment.3-5 However, despite good availability and infinite possibilities for broad application, the scale-up characteristics have not been well studied.

Kaji et al.6 investigated the effect of process variables on granule growth experimentally using two sizes of agitation fluidized bed. Ogawa et al.7 investigated scale-up characteristics using response surface methodology. We have also investigated the scale-up characteristics in agitation fluidized bed granulation experimentally.8-10 However, there have been few studies theoretically analyzing the scale-up of granulation, so that knowledge of the scale-up characteristics and establishment of a scale-up theory have been earnestly needed.

In this study, a scale-up theory in agitation fluidized bed granulation is described. This theory takes into consideration kinetic energy given to granules by agitator rotation and fluidizing air. The effects of the process variables and scale factor on granule properties such as granule size, density and shape were investigated theoretically. The validity of the theory was confirmed by comparing the results with those by experiment, and extremely good correlation was found between the two.

Experimental

Equipment Figure 1 illustrates the experimental set up. For wet granulation, agitation fluidized beds3-5 of three sizes (NQ-125, 230, 500, Fuji Paudal Co., Ltd.), of which the vessel diameter was 125, 230, and 500 mm, were used. As demonstrated in Fig. 1, this bed was equipped with an agitator blade to give tumbling and compaction forces to granules, thus making them spherical and well-compact. 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 5 mm apart to act as air distributors; heated air needed for particle fluidization 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.

Moisture content of the granules during granulation was measured by an infrared (IR) moisture sensor (Wet-eye, Fuji Paudal Co., Ltd.).3-4 Feedback control of the moisture content was exercised by regulating the rotational speed of a roller pump. The method of moisture measurement was described in detail in the previous paper.3,4-8-10 Fluidization air velocity was measured by a hot-wire anemometer, which was located at the center of an inlet air duct pipe to detect maximum air velocity. Inlet and outlet air temperature and humidity were measured by ceramic sensors.

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

Operating Conditions Operating conditions for scale-up experiments are summarized in Table 1. Powder feed weight, drying conditions and moisture measurement method were optimized previously.8,9 Three types of binary nozzles, differing shape, size and structure were used to spray water. To spray a water mist of 40 μm regardless of vessel scale, spray conditions of air pressure and diameter of nozzle insert were experimentally determined earlier.10 The spray nozzle height was also set so as to maintain a constant wet surface area.8,9

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 300s.
(ii) Granulation experiments started with spraying binder solution (water). As shown in Fig. 2, moisture content was programmed to increase 18% with 18 min.
(iii) Upon reaching 18%, moisture fixed command control maintained it there for 15 min. This moisture control was intended to keep constant adhesion force by a liquid bridge, in addition to prevent external disturbance.
(iv) After the granulation, granulated products were dried with fluidization air in the vessel. This was kept constant at 80°C regardless of vessel size.

Powder Samples Table 2 gives the powder samples used. A pharmaceutical standard formulation defined by the working group for preparation of standard formulation11 was used for granulation. In this formulation, lactose and cornstarch was mixed at 7:3 by weight, and hydroxypropylcellulose was added to the mixture at a level of 5% before granulation.

Purified water was sprayed by a binary nozzle located at the top of the vessel (top spray method).
**Experimental Set-up**

![Diagram of experimental set-up](image)

**Operating Conditions**

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

**Powder Samples Used**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Number median diameter (μm)</th>
<th>Mixing weight ratio (→)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>60</td>
<td>0.7</td>
</tr>
<tr>
<td>Cornstarch</td>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>21</td>
<td>0.05</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1.05</td>
</tr>
</tbody>
</table>

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

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

**Theory**

Although we applied the previously reported scale-up method using a centrifugal effect (=Froud number) and square root of vessel diameter, adequate correlation was not obtained.

When we looked back at the previous paper, which described effects of agitator rotational speed and fluidizing air velocity on granule properties, it was found that granule mass median diameter increased, but apparent density and shape factor decreased with an increase in fluidizing air velocity. Since granule adhesion force was kept constant by moisture fixed command control, these results originated from the decrease of external force due to the increased air velocity; the main external (separation) force in the agitation fluidized bed was experienced by agitator rotation, and the increase of air velocity acted to decrease the effect of agitator rotation. Therefore, we must estimate the effect of external force on granule properties in detail to determine scale-up characteristics theoretically. How-

**Evaluation of Operating Conditions**

Particle size distributions of granulated products were measured by sieve analysis with a row-lap 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.

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

![Graph showing change in moisture content](image)

**Change in Moisture Content while Controlling**

![Graph showing moisture content vs. time](image)
ever, although analysis of external force could be done by
kinetic equation, behavior of particles in the agitation
fluidized bed was so complicated that the theoretical
analysis by kinetic equation was also impossible.

We therefore focused on kinetic energy similarity, and
tried to use kinetic energy instead of external force; effect
of external force, which was determined by agitator rotation
speed, fluidizing air velocity and vessel diameter,
was evaluated by calculating the ratio of circumferential
kinetic energy given by agitator rotation to vertical kinetic
energy by fluidizing air, *i.e.*, calculation of the ratio is
expected to evaluate the effects of external force on granule
properties.

First, let us assume that there is an infinitely small area
on a rotating distributor as illustrated in Fig. 3, and kinetic
energy is given to the area uniformly. Here, we will consider
kinetic energy given to the infinitely small area based on
the following assumptions:

(i) Granules should move without having relative
velocity to agitator rotational speed or fluidizing air
velocity.

(ii) Horizontal velocity distribution is not considered.

(iii) Interaction between granules is disregarded.

Considering that total granule weight in the bed is
denoted as \( pL\pi R^2 \), where \( p \), \( L \) and \( R \) show granule
apparent density, bed height and radius of the vessel,
respectively, granule weight per unit area on the rotating
distributor is given by

\[
pL\pi R^2 / \pi R^2 = pL
\]  

(1)

Granule weight, \( m \) in the infinitely small area is thus
estimated as

\[
m = pL \times (rdr \cdot dr)
\]  

(2)

If we assume that angular velocity is \( \omega \) and radius of
the infinitely small area is \( r \), circumferential kinetic
energy given to the area by agitator rotation is denoted as

\[
\frac{1}{2} \cdot m(\omega r)^2
\]  

(3)

Total kinetic energy given to the granule by agitator
rotation is

\[
\frac{1}{2} \int_0^\pi \int_0^R m(r\omega)^2 \, dr \, d\theta
\]  

(4)

Similarly, the vertical kinetic energy given to granules in
the infinitely small area by fluidizing air can be described
as Eq. 5, if we assume that there is no vertical velocity
distribution.

\[
\frac{1}{2} \int_0^\pi \int_0^R \frac{1}{2} \cdot m \omega^2 \, dr \, d\theta = \frac{1}{2} \int_0^\pi \int_0^R pL \omega^2 r^2 \, dr \, d\theta
\]  

(5)

where \( u \) shows fluidizing air velocity.

Thus, the ratio of circumferential kinetic energy by
agitator rotation to vertical kinetic energy by fluidizing
air is

\[
\frac{1}{2} \cdot \int_0^\pi \int_0^R \frac{1}{2} \cdot pL \omega^2 R^2 = \frac{1}{2} \cdot \frac{1}{2} \cdot \int_0^\pi \int_0^R \frac{1}{2} \cdot pL \omega^2 R^2 \frac{1}{2} \cdot R^2 \omega^2 / 2u^2 = \frac{1}{2} \cdot (Ro/u)^2
\]  

(6)

Based on Eq. 6, the ratio of kinetic energy by agitator
rotation to vertical kinetic energy by fluidizing air can be
denoted by a simple expression of \( (Ro/u)^2 \). Using this
parameter, we tried to evaluate the effect of external force
on granule properties theoretically.

Results and Discussion

Figures 4, 5 and 6 indicate effect of parameter \((R_{o}/u)^2\) on granule mass median diameter \(D_{50}\), apparent density \(\rho_a\) and shape factor \(\phi\), respectively. In these figures, \(D_{50} (= 75 \mu m)\) and \(\rho_a (= 420 \text{ kg/m}^3)\) show mass median diameter and apparent density of powder samples before granulation. Thus all the vertical axis titles in these figures indicate dimensionless granule properties. In Fig. 6, the following sphericity was used as a granule shape factor:

\[
\phi = \frac{4\pi S}{L_p^2} 
\]

where \(S\) and \(L_p\) indicate granule projected area and perimeter, respectively.

Granule mass median diameter in this study varied from 150 to 450 \(\mu m\), which was within the range of sublized granule. The apparent density varied from 550 to 750 \(\text{kg/m}^3\) and shape factor changed from 0.62 to 0.75, which implied that granules were well compacted and made considerably spherical.

As seen in Figs. 4, 5 and 6, granule mass median diameter, apparent density and shape factor have linear correlation to parameter \((R_{o}/u)^2\), and all the plots are within the approximate line. In addition, granule mass median diameter had a tendency to decrease linearly but apparent density and shape factor increased linearly with \((R_{o}/u)^2\). Considering the effect of operating variables such as agitator rotational speed, fluidizing air velocity and vessel scale on granule properties, direction of the approximate line and its inclination angle were believed to indicate how the external forces contributed to these properties; if the ratio of rotational kinetic energy to vertical kinetic energy increased (increase of \((R_{o}/u)^2\)), external force necessarily increased, leading to the decrease of granule size and the increase of density and shape factor. With the same operating variables, increase of vessel diameter resulted in the increase of external force (increase of \((R_{o}/u)^2\)), hence the granule diameter decreased but density and shape factor increased.

Investigating the angle of inclination, it was found that granule apparent density and shape factor had also the same inclination angle. This implied that the effect of external force on these variables was almost the same.

Since the effects of agitator rotational speed, air velocity and vessel diameter on granule properties were examined theoretically, and could even be manipulated by the parameter of \((R_{o}/u)^2\), it may be possible to predict granule properties under random operating conditions in any scale granulator. This method will be significant in solving scale-up problems or designing manufacturing scale equipment in agitation fluidized bed granulation.

Conclusion

Granulation by agitation fluidized bed was scale-up theoretically. A simplified scale-up model considering kinetic energy given to granules by agitator rotation and fluidizing air was proposed. Plots of granule mass median diameter, apparent density and shape factor at various vessel scales, agitator rotational speeds and air velocities could be well expressed by the proposed model. The obtained results indicate that it is possible to predict granule properties with high accuracy under random operating conditions in any scale of agitation fluidized bed granulator.

References