# Granulation of Core Particles Suitable for Film Coating by Agitation Fluidized Bed III. Effect of Scale, Agitator Rotational Speed and Blade Shape on Granule Properties and Development of a High Accuracy Scale-Up Theory

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**The preparation of core particles suitable for subsequent film coating was examined using different scales of agitation fluidized beds. Specifically, the effects of agitator rotational speed and agitator blade shape in different scales of granulators on granule properties such as mass median diameter, apparent density, friability and shape factor were studied. As the agitator rotational speed was increased or when the agitator blade height and angle were large, the mass median diameter and friability of the granules decreased, while the apparent density and shape factor increased, in a manner independent of the vessel size because the granules were subjected to greater compression, shearing and rolling effects. The same core particles could not be prepared using granulators with different vessel sizes by simply adopting a conventional scale-up theory[1,2] based on kinetic energy similarity. Here, a novel scale-up theory that takes into account agitator blade shape factors is proposed.[3] When the two scale-up theories were compared, our new theory was capable of predicting the granule properties more accurately than the conventional theory. By adopting this novel theory, the same core particles could be prepared under different operating conditions in any scale of granulator.**

**Key words** agitation fluidized bed granulation; scale-up theory; core particle

The preferred pharmaceutical dosage form differs according to country.[4] In Japan, powdered drugs are one of the most popular dosing forms. Powdered drugs have several advantages. Drug decomposition resulting from the compression of the drug into tablets is avoided, and elderly patients or patients who cannot swallow tablets can easily take powdered drugs. However, powdered drugs also have some disadvantages. First, powdered drugs are difficult to be handled. Moreover, powdered drugs often taste very bitter. Ibuprofen [(*RS*)-2-(4-isobutylphenyl)propanoic acid] is a widely used non-steroidal anti-inflammatory drug that is highly effective and safe for the treatment of moderate pain and fever. However, powdered ibuprofen has a strong, astringent and bitter taste that must be masked to make it easier to ingest. The masking of bitter tastes is very important for the production of powdered drugs. So far, we have already conducted several studies[1,3,5,6] on masking the bitter taste of powdered drugs. Coating the core drug particles is one suitable method for masking the strong bitter taste of drugs. A polymer film acts as a barrier and modifies the release rate of drugs in the mouth. Therefore, core drug particles that are coated with a film do not taste bitter. The core drug particles required for this method should have several properties: an appropriate granule size, a high apparent density, a low friability, and a spherical shape. Therefore, we have been focusing on the use of the agitation fluidized bed granulation process; since agitation fluidized bed granulation can impart compressive and shearing forces on the particles through the agitator, allowing core particles with suitable physical properties for the coating process to be produced. In this sense, the shape of the agitator blade is very important, and agitator blade shape have been investigated for solid–liquid mixing[7,8] in a mixer; in addition, the effects of the agitator blade shape on the granule properties produced using a high-shear mixer have been studied,[9] as have the effects of the agitator blade angle on the granule properties in agitation fluidized bed granulation.[10] However, few reports have examined the relation between the agitator blade shape and the granule properties in detail with regard to agitation fluidized bed granulation for the preparation of core particles suitable for use in the coating process. The optimum formulation of core particles, including ibuprofen, and the effects of the operating conditions on the granules' properties have been investigated using laboratory-scale equipment.[5] Although a scale-up theory for agitation fluidized bed granulation based on kinetic energy similarities has been proposed,[2] this theory does not take into account the agitator blade shape. Therefore, the scaled-up characteristics of core particles produced using agitation fluidized bed granulation have not been thoroughly studied.

So far, the scale-up of pharmaceutical wet granulation processes has been investigated.[11] Several scale-up methods for fluidized bed granulation, such as experimental design techniques,[12—14] computerized techniques for process control,[15,16] engineering techniques,[17] and empirical techniques,[18] have been studied. In these previous studies, the effects of the operating conditions of several scales of granulators on the physical properties of the granules, such as the granules' size, apparent density, friability, flowing ability, and compression ability, were investigated. However, few reports have indicated the effects of the operating conditions and the scale-up characteristics on the properties of the core particles for coating process in detail. The core particles' physical properties are very important because these properties determine the drug release from the coated particles.[6]

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Table 1. Operating Conditions of Agitation Fluidized Bed

| | Very small | Small | Middle | Large |
|---|---|---|---|---|
| Vessel diameter [m] | 0.16 | 0.25 | 0.40 | 0.70 |
| Vessel height [m] | 0.16 | 0.25 | 0.38 | 0.52 |
| Powder charge weight [kg] | 0.40 | 1.50 | 6.00 | 35.0 |
| Agitator rotational speed $N$ [rps] | 3.3—6.7 | 3.3—6.7 | 2.0—5.3 | 1.3—2.7 |
| Air flow velocity [m/s] | 2.5 | 2.5 | 2.5 | 2.5 |
| Air temperature [°C] | 60 | 60 | 60 | 60 |
| Spray nozzle insert [i.d., mm] | 1.0 | 1.0 | 2.2 | 2.2 |
| Spray air flow quantity [Nl/min] | 35 | 50 | 200 | 750 |
| Blade height [mm] | 7 | 10—20 | 15—30 | 20—40 |
| Blade angle [°] | 35 | 30—45 | 28—45 | 28—45 |

However, obtaining core particles with the same properties using different sizes of granulators is difficult using the conventional scale-up theory[2)] because the agitator blade shape differs granulators with different scales. The conventional scale up theory[2)] does not take agitator blade shape into account. Therefore, a highly accurate scale-up theory for obtaining granules with the same physical properties using any scale of granulator with any shape of agitator blade under different operating conditions is needed.

This paper describes the scale-up characteristics of agitation fluidized bed granulation for producing core particles suitable for subsequent coating. The effects of the scale-up and the operating conditions on the granules' properties were investigated experimentally. From these results, a novel scale-up theory that takes into account the agitator blade shape was proposed. A comparison of the two scale-up theories showed that our new, novel theory could predict granule properties more accurately than the conventional theory. By adopting this novel theory, the same core particles can be prepared using different operating conditions in any scale of granulator.

**Experimental**

**Powder Samples** The formulations for the core particles and the coating film are described in a previous paper.[5)] Core particle formulation No. 1, described in the previous paper,[5)] was adopted in this study.

**Equipment and Operating Conditions** Figure 1 illustrates a schematic diagram of the experimental set-up. For the wet granulation of the core particles, agitation fluidized beds (Very Small: MP-01, Small: MP-10, Middle: MP-25, and Large: MP-100; Powrex Co., Ltd.) were used. The moisture content of the granules during the granulation process was measured using a moisture sensor (RF-50, Kurabo Co., Ltd.; IR-MF100, CHINO Co., Ltd.). Granules sampled during the granulation were dried using a moisture meter (MX-50; A&D Co., Ltd.), and the wet basis moisture content was determined by measuring the reduction in weight. Based on these results, the moisture sensor outputs were used to calculate the moisture content. The binder was prepared using a 7% concentration solution and sprayed through a binary nozzle located at the top of the vessel. The powder samples mentioned above were granulated and dried under the conditions listed in Table 1. In this study, the moisture content was maintained at 18% by controlling the binder solution feed rate. The resulting granules were passed through a sieve, and particles under 850 $\mu$m in size were retained. The average yields of granules under 850 $\mu$m in size for each scale of granulator are shown in Fig. 2. As shown in Fig. 2, the yields were so high that it was possible to regard the retained granules as being representative of the entire sample. Thus, the retained granules were used to evaluate the granules' properties in this study.

**Size Distribution, Apparent Density, Shape Factor, Friability** The granules' physical properties were investigated using methods described in a previous paper.[5)]

**Scale-Up Theory** The scale-up theory, which was based on similarities in kinetic energy,[2)] made it difficult to obtain core particles with the same

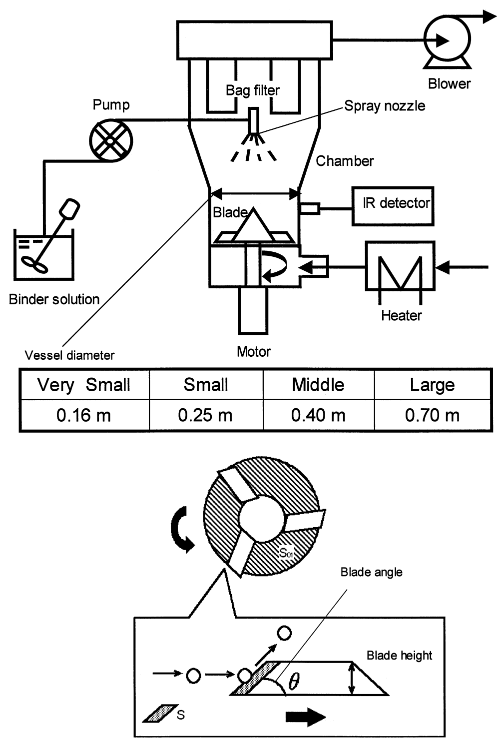


Fig. 1. Schematic Diagram of Experimental Set-Up

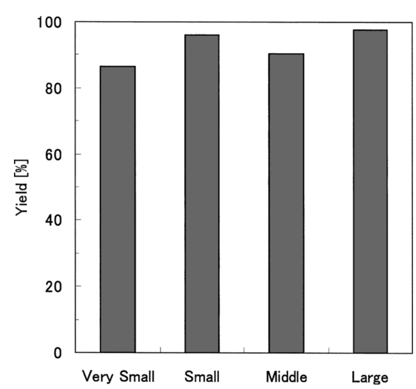


Fig. 2. Average Yields of Granules for Four Granulators

properties using different sizes of granulators, even if the ratio of $(R\omega/u)^2$ was maintained constant under the same moisture content. Here, $R$, $\omega$, and $u$ indicate the radius of the granulator vessel, the angular velocity of the agitator blade, and the airflow velocity of fluidization, respectively. The differences in the shapes of the agitator blades utilized by the different sizes of granulators are thought to be one of the reasons for this difficulty. Granules are tumbled and well-compacted by the agitator blade, and the kinetic energy of the agitator blade that acts on the granules is dependent on the blade angle, $\theta$, and the surface area, $S$, of the blade that comes in contact with the granules. The total kinetic energy of the agitator blade that acts on the granules, $F_{total}$, can be divided into the horizontal kinetic energy, $F_{hori}$, and the vertical kinetic energy, $F_{vert}$. When the agitator blade angle is $\theta$, $F_{hori}=F_{total}\times\cos\theta$ and $F_{vert}=F_{total}\times\sin\theta$, respectively. The ratio of $F_{vert}/F_{hori}$ becomes $\tan\theta$, which indicates the kinetic energy of the agitator blade that acts on the granules. When there is no agitator blade and only a rotor, the blade angle, $\theta_{01}$, is assumed to be 1°. To investigate the effect of the agitator blade angle, $\tan\theta/\tan\theta_{01}$ should be considered to represent the kinetic energy similarity. The agitator blade surface area, $S$, also affects the granule properties, since the granules come in contact with the agitator blade during granulation. To compare the differences in the vessel size, $S/S_{01}$ should be considered to represent the kinetic energy similarity, where $S_{01}$ indicates the rotor surface area of each granulator. As mentioned above, it is important to consider not only the parameter $(R\omega/u)^2$, but also the agitator blade shape parameters, $\theta$ and $S$. Therefore, an important parameter for a novel scale-up theory can be expressed by the following Eq. 1.

$$\left(\frac{R\omega}{u}\right)^2\times\frac{\tan\theta}{\tan\theta_{01}}\times\frac{S}{S_{01}} \quad (1)$$

## Results and Discussion

**Effect of Agitator Rotational Speed and Blade Shape on Granule Properties** Figures 3a—d show the effect of the agitator rotational speed in different scales of granulators on the granules' physical properties, such as mass median diameter, apparent density, friability and shape factor. As shown in Fig. 3a, the mass median diameter of the granules decreased as the agitator rotational speed increased. Granules were sheared and compacted well at high speeds of agitator rotation. Therefore, the granules' mass median diameter decreased considerably and the granules became relatively small. In addition, the granules' mass median diameter decreased as the vessel size increased. When a large vessel was used, the granules were subjected to stronger forces during the granulation process; the granules were strongly compressed because the powder bed load increased as the vessel size increased. Even though the moisture content remained the same, the granules' size decreased as the vessel size increased. As shown in Fig. 3b, the apparent density of the granules increased with an increasing agitator rotation speed. At a higher speed of agitator rotation, the granules were subjected to stronger forces from the agitator because the frequency of collision increased. As shown in Fig. 3c, the friability of the granules decreased with an increasing agitator rotational speed because the granules were toughened by the high compression energy produced by the high-speed rotation of the agitator. Similar to the effect on the mass median diameter of the granules, the increase in the powder bed load increased the granules' apparent density and decreased the friability when larger vessel sizes were used. As shown in Fig. 3d, the shape factor of the granules increased with an increase in agitator rotational speed. The agitator rolled the granules; therefore, the granules became spherical at high speeds of agitation. When larger vessel sizes were used, the granules were rolled more and became more spherical in shape because the area of contact between the agitator blade's surface and the granules was larger.

Figures 4a—d indicate the effects of the agitator blade height on the granule mass median diameter, apparent density, friability and shape factor. As shown in Fig. 4, the granules' mass median diameter and the friability of the granules decreased, while the apparent density and shape factor of the granules increased, as the agitator blade height increased.

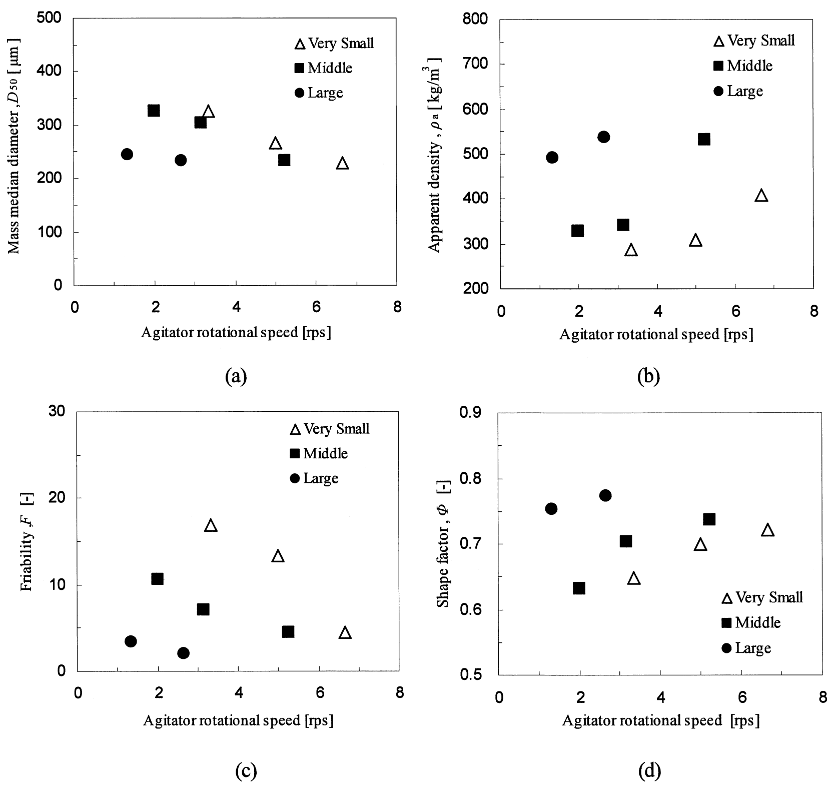


Fig. 3. Effect of Agitator Rotational Speed on the Granules' (a) Mass Median Diameter, (b) Apparent Density, (c) Friability, and (d) Shape Factor

Agitator blade height: very small, 7 mm; middle, 15 mm; large, 20 mm. Agitator blade angle: very small, 35°; middle, 35°; large, 35°.

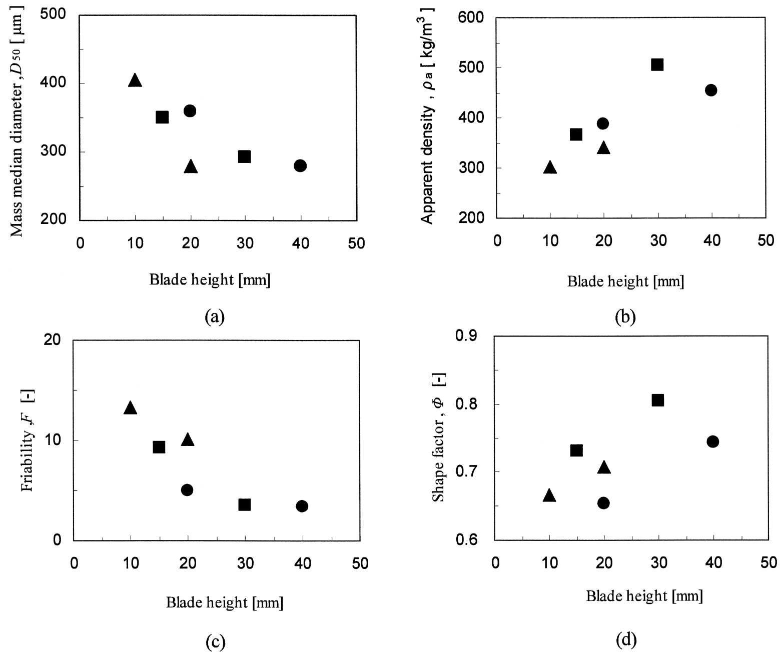


Fig. 4. Effect of Blade Height on Granules' (a) Mass Median Diameter, (b) Apparent Density, (c) Friability, and (d) Shape Factor
Agitator rotational speed: ▲ small $N$: 4.17 rps, ■ middle $N$: 3.17 rps, ● large $N$: 2.67 rps.

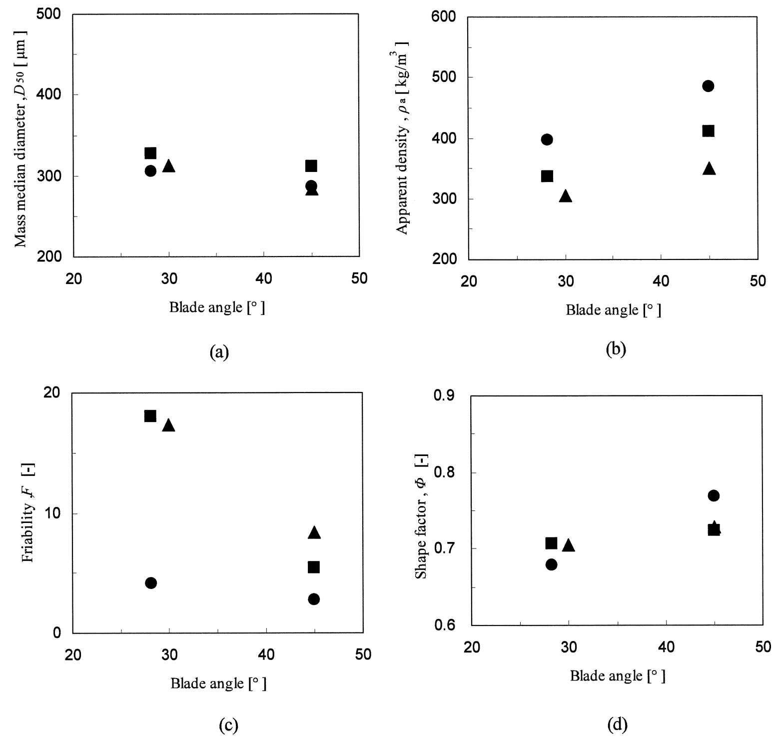


Fig. 5. Effect of Blade Angle on Granules' (a) Mass Median Diameter, (b) Apparent Density, (c) Friability, and (d) Shape Factor
Agitator rotational speed: ▲ small $N$: 4.17 rps, ■ middle $N$: 3.17 rps, ● large $N$: 2.67 rps.

The granules were sheared, compacted and rolled well as the blade height increased because of the increasing contact area between the granules and the agitator blade. Therefore, the granules became relatively small and thick, with a strong structure and spherical shape. A similar tendency was obtained when the vessel size was varied. Figures 5a—d illustrate the effects of the agitator blade angle on the granule mass median diameter, apparent density, friability and shape factor. As shown in Fig. 5, the granule physical properties were also affected by the agitator blade angle. The direction of the granules' movement was thought to change when the agitator blade angle was changed. When the agitator blade angle was large, the granules moved in a relatively horizontal direction because the agitator blade transferred a large amount of energy to the granules. Therefore, the granules became similar to the granules prepared using a high agitator rotational speed. On the other hand, the granules moved in a relatively vertical direction when the agitator blade was small; in this situation, the agitator blade minimally affected the granules. Therefore, the granules became similar to the granules prepared using a low agitator rotational speed. These results imply that an increase in the agitator blade height and its angle has a great impact on the granule properties. Based on these results obtained in this study, we concluded that the granule mass median diameter, apparent density, friability and shape factor obtained using agitation fluidized beds in several scales of granulators were influenced substantially by the agitator blade shape.

**Relations between Operating Conditions, Granulator Size and Granule Properties** Figures 6—9 show plots of dimensionless granule properties, such as dimensionless mass median diameter ($D_{50}/D_{P50}$), dimensionless apparent density ($\rho_a/\rho_{pa}$), friability ($F$) and shape factor ($\Phi$) against the dimensionless operating conditions parameter $(R\omega/u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$, $(R\omega/u)^2$. In these figures, $D_{P50}$ ($=20\,\mu$m) and $\rho_{pa}$ ($=370\,\text{kg/m}^3$) represent the mass median diameter and the apparent density of the powder sample before granulation, respectively.

As seen in Figs. 6—9, the dimensionless granule mass median diameter, apparent density, friability and shape factor show considerably better linear correlations with the novel dimensionless parameter, $(R\omega/u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$, than with the conventional dimensionless parameter, $(R\omega/u)^2$, proposed in a previous paper.[2)] Table 2 shows the coefficients of determination, $r^2$, both our novel scale-up theory and the conventional scale-up theory. Coefficients of determination, $r^2$, are involutions of correlation coefficients, $r$. As seen in this table, those coefficients of the novel scale-up theory were larger than those coefficients of the conventional scale-up theory. This outcome implies that the novel theory may be better at predicting the granule properties with greater accuracy than the conventional theory. The core particles' size influenced the coating film thickness because the surface areas of the particles depend on their diameters. The core particles' shape factor also affected the film thickness because of the difference in particle surface roughness. In addition, the core particles' apparent density was also important because the particles become more difficult to ingest when the powder volume increases. These physical properties might change the taste-masking level of the particles considerably. On the other hand, the core particles' friability did not dramatically change the ease at which the particles can be ingested when the core particles had sufficient strength not to be broken during the coating process. As mentioned above, our novel theory was capable of accurately predicting these properties. Therefore, the core particles could be produced with controlling these physical properties in any scale of granulator by adjusting the operating conditions and the shape of the agitator blade. Thus, this novel theory is expected to be useful for producing high-quality, taste-masking particles.

During agitation fluidized bed granulation, the agitator rotational speed and airflow velocity control particle movement. In addition, the agitator blade shape also affects particle movement substantially because the agitator blade comes in contact with the particles and transfers energy to them. For this reason, the granule structure varied extremely when the operating conditions, such as agitator rotational speed, air-

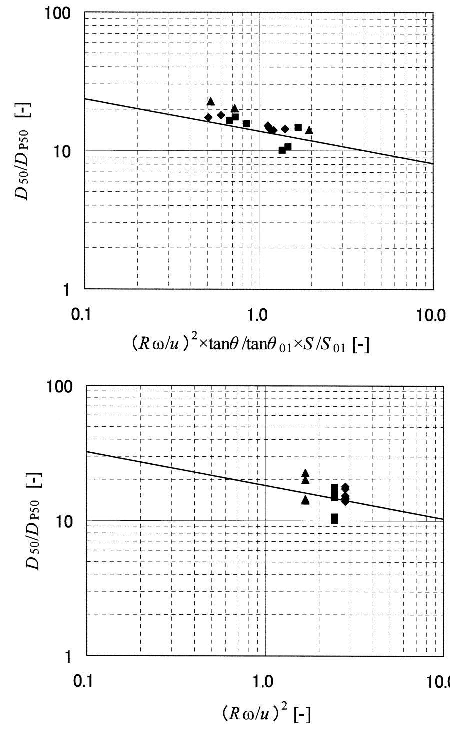


Fig. 6. Plots of Dimensionless Granule Mass Median Diameter against $(R\omega//u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$, $(R\omega/u)^2$

Vessel size: ▲ small, ■ middle, ● large.

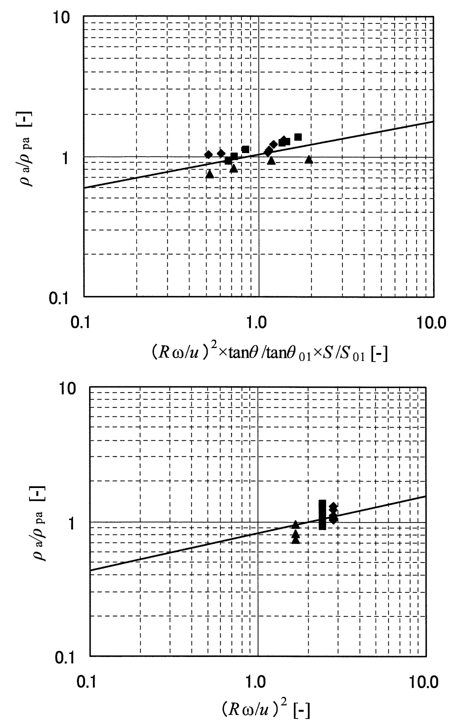


Fig. 7. Plots of Dimensionless Granule Apparent Density against $(R\omega/u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$, $(R\omega/u)^2$

Vessel size: ▲ small, ■ middle, ● large.

flow velocity and agitator blade shape, were changed. To prepare the same core particles using different scales of granulators, these operating conditions should be considered carefully. The agitator blade surface area and its angle are as important as the other operating conditions, such as the agitator

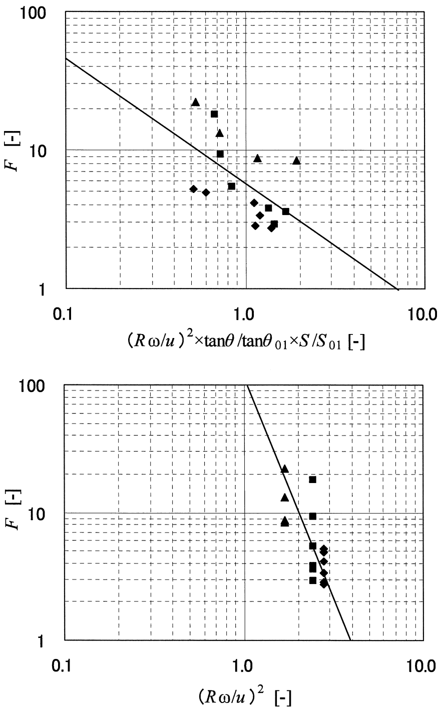


Fig. 8. Plots of Dimensionless Granule Friability against $(R\omega/u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$, $(R\omega/u)^2$

Vessel size: ▲ small, ■ middle, ● large.

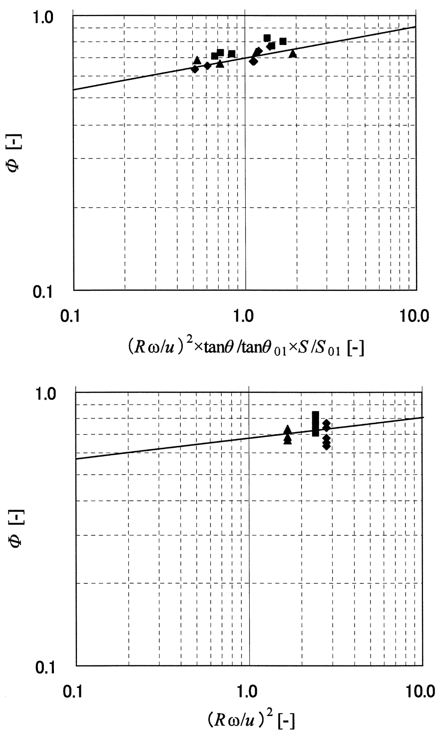


Fig. 9. Plots of Dimensionless Granule Shape Factor against $(R\omega/u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$, $(R\omega/u)^2$

Vessel size: ▲ small, ■ middle, ● large.

rotational speed, airflow velocity and vessel diameter. Therefore, the granule properties should be predicted under different operating conditions in any scale of granulator using the novel dimensionless parameter $(R\omega/u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$.

As shown in Figs. 6 and 8, when $(R\omega/u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$ increased, the granules' dimensionless mass median diameter and friability decreased. On the other hand, as shown in Figs. 7 and 9, the granules' dimensionless apparent density and shape factor increased when $(R\omega/u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$ increased. An increase in $(R\omega/u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$ represents an increase in the horizontal kinetic energy; in other words, the effects of the agitator rotational speed and the agitator blade shape on the granules increase. Therefore, the granules' size and friability decrease, while the apparent density and shape factor increase because the granules are sheared, compressed, compacted and rolled well. On the other hand, a decrease in $(R\omega/u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$ represents an increase in vertical kinetic energy; in other words, the effects of airflow velocity on the granules increase. Under these operating conditions, the movement of the granules resembles that in a conventional fluidized bed, and the agitator blade does not affect the granules' movement. As a result, the granules' size and friability increase, while their apparent density and shape factor decrease. Thus, the granules' physical properties, such as size, apparent density, friability, and shape factor, can be predicted under several operating conditions with any shape of agitator blade and in different scales of granulators using dimensionless parameter, $(R\omega/u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$.

To prepare core particles with approximately the same physical properties using granulators with different vessel sizes, the optimum operating conditions can be determined based on the novel dimensionless parameter, $(R\omega/u)^2\times\tan\theta/\tan\theta_{01}\times S/S_{01}$.

Table 2. Comparison of Coefficients of Determination, $r^2$, of Novel Scale-Up Theory and Conventional Scale-Up Theory

| | $D_{50}/D_{P50}$ | $\rho_a/\rho_{pa}$ | $F$ | $\Phi$ |
|---|---|---|---|---|
| Novel theory | 0.6949 | 0.5921 | 0.4123 | 0.6090 |
| Conventional theory | 0.1214 | 0.4303 | 0.4058 | 0.0006 |

## Conclusions

Core particle granulation using an agitation fluidized bed to produce granules suitable for subsequent coating was studied. The granule size became smaller, the density became larger, and the friability decreased with the spherical shape as the agitator rotation speed and the agitator blade height and angle were increased in agitation fluidized bed granulation. These results enabled the better understanding of the effects of the agitator rotational speed, the agitator blade shape, and the vessel size on the granules' properties. We also confirmed that core particles with the same properties can be obtained by adjusting the operating conditions, agitator blade shape and the vessel size of the granulator using our novel scale-up theory, which is based on kinetic energy similarities and included the effects of agitator blade shape factors.

**References**

1) Hamashita T., Ono T., Ito M., Nakagawa Y., Aketo T., Watano S., Proc. of the 126th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, on 30 March, 2006.
2) Watano S., Sato Y., Miyanami K., *Chem. Pharm. Bull.*, **43**, 1227—1230 (1995).
3) Hamashita T., Ono T., Ono M., Tsunenari Y., Aketo T., Watano S., Proc. of the third Asian Particle Technology Symposium, Beijing, on 3rd September, 2007.

4) Hashida M., *Formulation Design of Oral Dosage Forms*, **1998**, 32—34 (1998).
5) Hamashita T., Nakagawa Y., Aketo T., Watano S., *Chem. Pharm. Bull.*, **55**, 1169—1175 (2007).
6) Hamashita T., Matstuzaki M., Ono T., Ono M., Tsunenari Y., Aketo T., Watano S., *Chem. Pharm. Bull.*, **56**, 883—887 (2008).
7) Biswas P. K., Dev S. C., Godiwalla K. M., Sivaramakrishnan C. S., *Mater. Des.*, **20**, 253—265 (1999).
8) Gotoh K., Asaoka H., Masuda H., *Adv. Powder Technol.*, **5**, 353—364 (1994).
9) Terashita K., Tanida M., Miyanami K., *J. Soc. Powder Technol. Jpn.*, **36**, 698—705 (1999).
10) Watano S., Sato Y., Miyanami K., Ito Y., Kamata T., *Chem. Pharm. Bull.*, **43**, 1224—1226 (1995).
11) Faure A., York P., Rowe C. R., *Eur. J. Pharm. Biopharm.*, **52**, 269—277 (2001).
12) Wehrle P., Nobelis Ph., Cuine A., Stamm A., *Drug Dev. Ind. Pharm.*, **19**, 1983—1997 (1993).
13) Lipps D. M., Sakr A. M., *J. Pharm. Sci.*, **83**, 937—947 (1994).
14) Rambali B., Baert L., Massart L. D., *Int. J. Pharm.*, **252**, 197—206 (2003).
15) Watano S., Sato Y., Miyanami K., *Chem. Pharm. Bull.*, **44**, 1556—1560 (1996).
16) Watano S., Takashima H., Miyanami K., *Chem. Pharm. Bull.*, **45**, 1193—1197 (1997).
17) Cryer S. A., *AIChE J.*, **45**, 2069—2078 (1999).
18) Association of Powder Process Industry & Engineering Japan, "Fluidization Handbook," ed. by Horio M., Mori S., BAIFUKAN, Tokyo, 1999.