Optimization of Operating Conditions in a High-Shear Mixer Using DEM Model: Determination of Optimal Fill Level

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For the purpose of evaluating optimal fill level of starting materials in a high-shear mixer, discrete element method (DEM) simulation was conducted to visualize kinetic status between particles. The simulation results obtained by changing fill levels were used to determine solid fraction of particles, particle velocity, particle velocity vector, and kinetic energy and discuss the flow pattern. Optimal fill level was obtained from the information on these matters. It was pointed out that understanding the kinetic energy between particles in an agitating vessel was effective in determining the optimal fill level. Granulation experiment was conducted to validate the optimal fill level obtained by the simulation, confirming the good agreement between these two results. It was pointed out that determination of kinetic energy between particles through the simulation was effective in obtaining an index of the kinetic status of particles. Further, it was confirmed that the simulation could provide more information than conventional granulation experiments could provide and also helpful in optimizing the operating conditions.

Key words discrete element method; high-shear mixer; optimization; fill level; kinetic energy; granulation

It is well known that, besides fluidized-bed granulation, agitating granulation has been commonly used to produce solid pharmaceuticals. Research works reported about agitating granulation included determination of optimal added ratio of granulation liquid,¹⁾ discussion of granulation process based on measurement of power consumption, determination of granulation end points^{1—8)} and the relationship between granule yield and operating conditions.^{1,9)} However, these research works were evaluated on the basis of experiments, thus needing much time and labor.

In association with the recent development of informationrelated technology, research with attention given to computer simulation has been actively performed. Computer simulation is characterized by easy realization of various works such as equipment design of machineries used in the pharmaceutical industry, optimization of operating conditions and analysis of kinetic status of particles. It has been pointed out that the computer simulation could extract various information that would be otherwise unavailable by conventional tryand-error experiments, thus eliminating enormous cost, labor and time so far wasted.

Reportedly, machineries used in the pharmaceutical industry are subjected to assessment by the simulation, yielding beneficial results. Such reported examples included particle behavior in fluidized bed,^{10,11}) as well as kinetic motion of particles and mixing processes¹²⁾ in a coating drum,^{13,14)} Vbender¹⁵⁾ and double corn bender.^{15,16)} However, there seem to be no reports available about the simulation of kinetic motion and mixing processes, with attention given to a highshear mixer frequently used in preparation of pharmaceuticals or about the research on optimization of operating conditions on the basis of discrete element method. Thus, we assessed the kinetic motion of particles in a high-shear mixer by discrete element method and determined optimal rotation speed as well. We also gave discussion to optimal rotation speed of an agitating blade based on the granulation experi $ment.¹⁷$

In this study, attention was given to fill level of starting

mal operating conditions of the high-shear mixer by referring to the discrete element method (DEM) simulation. The simulation was conducted by changing the fill level of starting materials to not only visualize the kinetic motion of particles in an agitating vessel but also make numerical assessment. In particular, the fill level in the agitation granulation was optimized on the basis of the results obtained from solid fraction of particles, particle velocity, particle velocity vector, kinetic energy and flow patterns. An agitating granulation experiment was conducted to validate the simulation results. Consequently, it was found that small grains with a target diameter (granules for tableting) could be obtained in a high yield when granulation was conducted at the optimal fill level predicted by the simulation. Further, we confirmed that the simulation was effective in optimizing the operating conditions and hereby report the details.

materials so that additional discussion can be made for opti-

Simulation

Simulation Method Discrete element method (soft sphere model)^{18—20)} was adopted in the simulation of this study. This method enabled us to understand the overall behavior of particles by following individual particle behaviors. Namely, it is possible to analyze an entire particle behavior as bulk by collecting each particle motion. An individual particle motion can be calculated by solving the Newton's equation of motion, if magnitude of the force exerted on the said particle is to be determined. The equation used in this simulation was given in the Eq. 1.

$$
m\frac{dv}{dt} = mg + F_{\text{collision}} + F_{\text{wall}} \tag{1}
$$

Wherein *m* represents mass of a single particle; *g*, gravitational acceleration; $F_{\text{collision}}$, contact force between particles exerting on a given particle; F_{wall} , contact force exerting on between wall surface/agitating blade and target particles. In this simulation, drag force exerting on a particle was omitted.

It is necessary to determine the contact force exerting on a

Fig. 1. Model of Contact Force

Fig. 2. Schematic Diagram of a High-Shear Mixer

particle as shown in the Eq. 1 in order to determine the motion of the particle. Therefore, the contact force between particles and particle/wall surface was calculated by referring to the model of the contact force as shown in Figure 1. The contact force between particle and wall surface was calculated on the assumption that the contact was made between particles. In this model, the contact force was expressed using actions of the fundamental elements in mechanical physics consisting of the linear spring giving repulsion force in proportion to displacement, dashpot for taking into account the energy attenuation on contact and friction slider. External forces exerting on particles included gravitational force in addition to contact force received from other particles. The overall behavior of particles was determined by repeating numerical integration by every time step for all individual particles. The time step was regarded as 20% of duration of collision contact.¹⁹⁾ Further, the duration of collision contact, T_d , was given as follows.

$$
T_{\rm d} = \pi \sqrt{m/k} = \sqrt{(\pi d_{\rm p})^3 \rho_{\rm p}/6k} \tag{2}
$$

Wherein d_p represents particle diameter; ρ_p , density of particle; and *k*, spring constant.

Simulation Conditions Figure 2 showed a schematic diagram of the high-shear mixer (VG-01 by Powrex Corp.) used in this study. The same machine was used both in the simulation and in the granulation experiment. This machine was provided with a 0.16 m-across vessel and the effective volume was 1.5×10^{-3} m³. An agitating blade (triple blades) rotating horizontally at high speed was mounted on the base of the machine to agitate particles while it was rotated.

Fig. 3. Fill Levels in Simulation and Experiment

Table 1. Simulation Conditions

Model	DEM (soft sphere model)		
Particle diameter (m)	3×10^{-3}		
Particle density $(kg/m3)$	1500		
Spring constant (N/m)	800		
Restitution coefficient $(-)$	0.9		
Friction coefficient $(-)$	0 ³		
Time step (s)	1.0×10^{-4}		
Rotational speed of the agitating blade (rps)	8(2, 4, 6)		
Fill percentage $(\%)$	13.0	26.8	41.6
	53.7	67.2	80
Number of particles $(-)$	8069	16607	25826
	33354	41709	49660

Table 1 showed the simulation conditions. The simulation was conducted three-dimensionally. In this study, fill level (the number of particles) was varied at 6 levels to conduct numerical calculation in order to predict an optimal fill level by the simulation. The particle size, particle density, spring constant and restitution coefficient were kept unchanged, because fill level was of particular importance. Further, a high shear mixer was often equipped with a chopper, but this study was performed, with attention given to the agitating blade alone in order to avoid complex in particle motion and assessment and to simulate a simple agitating granulation. Figure 3 showed a summary of the simulation and filling status in the machine used in this granulation experiment.

In order to validate the simulation conducted under the conditions, animation was prepared to observe the particle motion in the agitating vessel. The observation results have confirmed that the particle motion reproduced by the simulation was similar to that found in the granulation experiment.

Results and Discussion in Simulation

Relationship between Solid Fraction of Particles and Fill Level The simulation was conducted by allowing the fill level to change as shown in Fig. 3 to determine the solid fraction of particles so as to examine space distribution and arrangement of particles in space inside the agitating vessel. In this study, the agitating vessel was divided into multiple cells to calculate the volume fraction of particles occupied in a given cell, the value of which was designated as solid fraction of particles. The darker red in the displayed result represented densely packed state of particles while the darker blue represented loosely packed state of particles.

Solid fraction of particles during the agitating operation was examined and the results were exemplified in Figs. 4a to c. These Figures showed the results at the instant when the particles were in a dynamic state, which were visualized by expressing the solid fraction of particles numerically. In the cross-section view of the agitation vessel, the right side showed a state of particles moving together with a blade, while the left side showed a state of the particles after passage of the blade. The cross-section view of the blade was shown in a thick line on the bottom of the right-side cross section. Further, Figs. 4a, b and c respectively showed the fill levels, 26.8, 53.7 and 80%, which were obtained from the simulation results. Figure 4b showed the result obtained at around optimal fill level, the details of which will be described later. On the other hand, Figs. 4a and c respectively showed the results of lower and higher fill levels.

The results of Fig. 4 confirmed that increased fill level of starting materials from 26.8 to 80% led to spread of areas having particles (shown in green and red). It was found that at lower fill level (as shown in Fig. 4a), the blue area where particles were in a loosely packed state was observed broadly, gaining a wide free space. It was also found that if the fill level shown in Fig. 4c reached 80%, the particles occupied almost all space of the agitating vessel at the instant of being a dynamic state when the blade was rotating.

At any fill level, found was the red area indicating a densely packed state of particles at upper part of the cross section of the agitating blade. This finding was interpreted that the agitating blade caused shearing action, which then gave densification to particles. An area where particles were in a densely packed state was also found at the inner part of particle bed in the agitating vessel while the fill level was increased. When the fill level was increased, an area having particles was not only widely spread but the particles were densely packed inside the particle bed. It was considered on the basis of this result that increase in the fill level led to decrease in free space of the particles in the agitating vessel and facilitated densification between particles.

The results so far discussed about the simulation of solid fraction of particles revealed that distribution and packed state of particles in the agitating vessel could be visualized easily and expressed in a numerical fashion.

Relationship between Particles Velocity Vector and Fill Level Particle velocity vector at the cross section of the agitating vessel was determined to grasp details of kinetic motion in the agitating vessel. The results were shown in Figs. 5a to c. More particularly, Figs. 5a, b and c respectively showed the simulation results obtained at low fill level, at around optimal fill level, and at high fill level. In the crosssection view of the agitating vessel, the right side showed a state of particles moving together with a blade, while the left side showed a state of the particles after passage of the blade. The arrows showed the results obtained by projecting the particle velocity vector on the cross section of the agitating vessel. The arrow given above Fig. 5a represented particle velocity 2 m/s, showing that a longer vector arrow meant a faster particle velocity. In Fig. 5, darker red arrows showed faster particle velocity while darker blue arrows showed slower particle velocity.

It was found that at the fill level of 53.7% indicated in Fig. 5b, particles formed a smooth circulation, rising along the wall of the agitating vessel around the tip of the blade and then descending. Also confirmed was a smooth circulation of particles in circumferential direction all around the vessel. This smooth circulation of particles was considered to give a favorable effect on mixing and granulation. At a low fill level of 26.8% (as shown in Fig. 5a), the circulation was obtained on the cross section including the agitating blade. However, as compared with the results of Fig. 5b, favorable circulation of particles was not obtained in view of overall circulation flow in the agitating vessel. At a fill level of 80%, a great circulation flow moving to the upper part of the agitating vessel was obtained, but at the tapered part of the vessel the particle velocity was reduced as shown by the blue arrow of particle velocity vector. Circulation flow was obtained but the particle velocity was slow at the upper part of the vessel and almost in a stagnant area. This result showed that increased fill level would lead to decrease in free space of particles to reduce particle motion from the middle to upper part of the vessel, thus causing circulation of particles to slow. Such relationship between fill level and circulation of particles was also confirmed by visual observation of the upper part of the vessel in a granulation experiment discussed later.

The results and discussion made so far about the particle velocity vector have revealed that an optimal circulation flow was obtained at the fill level of 53.7% and there was no stagnant area showing a sluggish motion of particles. In addition to convective mixing, diffusive mixing was done effectively to attain a favorable mixed state.

Relationship between Particle Velocity and Fill Level Particle velocity on the vertical section of the agitating vessel was expressed in a contour line to grasp the particle velocity in the vessel according to fill levels, the results of which were shown in Figs. 6a and b. In these Figures, darker red showed a greater particle velocity while darker blue showed a lower particle velocity. Figure 6a showed that at the level of 53.8%, a greater particle velocity was found at the tip of the agitating blade whereas the particle velocity gradually reduced as the particle moved upward. At the higher fill level as shown in Fig. 6b, an area indicated by green (particle velocity around 1.5 m/s) was decreased at the lower part of the agitating vessel. The contour lines were spaced at relatively narrow intervals from the tapered part to the lower part of the vessel, suggesting a greater reduction in the particle velocity. Further, the particle velocity was greatly reduced at areas from the tapered part to the upper part, suggesting a sluggish particle motion.

The results and discussion made so far have revealed that the level of 53.7% provided particles with free space and enabled most of the particles in the agitating vessel to keep the velocity of around 1.5 m/s and to show an active particle motion. In other words, an optimal condition for mixing and granulation was obtained at the fill level of around 53.7%. It was reconfirmed that increased fill level resulted in decrease in free space, causing particle motion in the upper part of the vessel to slow, thus impeding smooth operation of mixing and granulation.

Particle velocity distribution was examined by referring to particles not only on the vertical section in the agitating vessel (*xz* and *yz* planes) but also on the horizontal section at a given height (*xy* plane) in order to grasp the particle motion three-dimensionally. Figures 7a to c showed the results ob-

Fig. 4. Relationship between Solid Fraction of Particles and Fill Level (a), 26.8%; (b), 53.7%; (c), 80%.

Fig. 5. Relationship between Particle Velocity Vector and Fill Level (a), 26.8%; (b), 53.7%; (c), 80%.

tained when attention was given to an optimal fill level of 53.7%. More particularly, Figs. 7a, b and c respectively showed the results of particle velocity distribution at the height of 7.5, 30 and 80 mm above the horizontal section from the base of the agitating vessel.

Figure 7a showed that the particle velocity was high due to centrifugal force at the tip of the agitating blade. It was found that the particle velocity was broadly distributed on the horizontal section. The particle velocity distribution on the cross section including the blade was confirmed to be similar to that found in Fig. 7a, regardless of difference in fill levels.

Since particles near the agitating blade were most heavily influenced by the action of the blade despite any difference in fill levels, no substantial difference was found in the particle velocity distribution.

The particle velocity distribution on the horizontal section (30 mm high) near the tapered part as indicated in Fig. 7b exhibited a greater particle velocity above the agitating blade on the same horizontal section. This area above the blade where the particle velocity was great was confirmed when fill level was changed. However, the velocity obtained at an area above the blade where the velocity was great tended to de-

Fig. 6. Relationship between Particle Velocity and Fill Level (a), 53.7%; (b), 80%.

Fig. 7. Particle Velocity Distribution at Various Height above the Horizontal Section from the Base of the Agitating Vessel (a), 7.5 mm; (b), 30 mm; (c), 80 mm.

crease with changing fill levels, particularly from 53.7 to 80%. This trend was considered due to decrease in free space along with increased fill level, which subsequently inhibited particle motion.

Figure 7c showed the horizontal section at the height of 80 mm near the surface of particles. Here, the results of velocity distribution of particles were expressed differently from those at the heights of 7.5 and 30 mm. The length of vector arrow expressed the velocity of particles, and the color shown in Fig. 7c visualized solid fraction of particles. A longer arrow given in the Figure showed a greater velocity. The color in the Figure indicated solid fraction of particles, showing darker red representing a densely packed state of particles while darker blue representing a loosely packed state.

Figure 7c showed that at the fill level of 53.7% hollow part

indicated by blue was present at the center of the vessel, suggesting the presence of sufficient free space. Here, when attention was given to the particle velocity in circumferential direction as indicated by the arrow, it was confirmed that at the fill level of 53.7% particles near the surface of the particle bed were provided with the velocity in a circumferential direction. It was also confirmed that at the fill level of 80% almost all the areas of the horizontal section at the height of 80 mm were filled with particles and the particles hardly moved in a circumferential direction.

Thus, it was clarified that at the fill level of 53.7% where a smooth particle circulation was obtained, the particles from the base of the agitating vessel to the surface of the particles did not form a stagnant area, showing an actively fluidizing motion.

Relationship between Kinetic Energy and Fill Level It is extremely important to obtain a smooth circulation of particles in conducting the operations of mixing and granulation. It can be easily assumed that kinetic status of particles will influence the results of mixing and granulation. The findings so far discussed revealed that at the fill level of 53.7% particles yielded a smooth circulation of particles. However, there is a certain limit in grasping visually the smooth particle motion and circulation for discussion. Hence, average kinetic energy of particles is determined to obtain a quantitative understanding of the kinetic status of particles and smooth circulation of particles. We believe that larger kinetic energy can be obtained as particle motion and particle circulation become smoother.

Figure 8 showed the relationship between average kinetic energy in the agitating vessel and the fill level. As shown in the Eq. 3, the vertical axis of the Figure represented the average kinetic energy per particle obtained by summing the kinetic energy of all the particles present in the agitating vessel.

$$
E_{\rm av} = \frac{1}{2} m \langle v^2 \rangle = \frac{1}{2} m \frac{1}{n} \sum_{i=1}^n v_i^2
$$
 (3)

Wherein *m* represents mass of a single particle; *n*, number of particles; $\langle v \rangle$, average particle velocity; and v_i , velocity of a given particle.

At individual fill levels, average kinetic energy was calculated by referring to rotational speed of an agitating blade at various levels, since the simulation was conducted by allowing the rotational speed of the blade to vary. The results were also shown in Fig. 8.

Figure 8 showed that the kinetic energy increased with fill levels, exhibiting a maximum value at fill levels of about 50 to 60%. It was also found that increased fill levels $(>60\%)$ resulted in reduced kinetic energy. This tendency was more markedly found when the rotational speed was raised.

Variation in kinetic energy against fill level, or gradient in kinetic energy ($\Delta_{E/F} = \Delta_{E}/\Delta_{E}$), increased with increasing the rotational speed (8 rps). In other words, it was found that the kinetic status of particles was more vulnerable to the influence of fill levels when the rotational speed was raised. Particularly, at the rotational speed of 6 or 8 rps, the gradient in kinetic energy at the fill levels of 60 to 80% ($\Delta_{\text{E/F(60-80%)}}$) was found greater in relation to $\Delta_{E/F(15, -50\%)}$ at the fill level of 15 to 50%. It was revealed that the kinetic status of particles

Fig. 8. Relationship between Average Kinetic Energy in the Agitating Vessel and Fill Level

 \blacklozenge , 2 rps; \blacksquare , 4 rps; \blacktriangle , 6 rps; \blacklozenge , 8 rps.

due to change in fill levels would be more markedly influenced at a higher fill level rather than a lower fill level. Excess charge at high-speed rotation should be handled with care, because it may slow the motion of particles, preventing a smooth particle motion.

A condition where the agitation blade was rotated at 8 rps was compared with that in the granulation experiment to be discussed later, suggesting that the average kinetic energy reached its peak around the fill level of around 60%. It is assumed that at a maximum-value yielding fill level the agitation blade acted on particles most effectively. We interpreted this finding as provided by a smooth particle circulation as explained previously.

The simulation results and discussion made so far confirmed that an optimal fill level when the blade was rotated at 8 rps was around 60% (50 to 65%) where a smooth particle circulation was obtained in the agitating vessel and the average kinetic energy of particles showed a maximum value.

The next section deals with a granulation experiment conducted by changing fill levels in order to validate the optimal fill level obtained by the simulation and the discussion of the results as well.

Granulation Experiment

Materials and Experimentation Granulation was done using the same high-shear mixer used in the simulation. Table 2 showed types of powder and formulation. In this experiment, a powder binder was added. Purified water was used as a binder solution and 23 wt% binder solution was added all at once. On the basis of the simulation results, the agitating blade was rotated at 8 rps during granulation. The operating time for granulation was 900 s. Thus-obtained granules were subjected to fluidized-bed drying until exhaust air temperature was 310 K. In the granulation experiment, fill level was varied at 5 levels to discuss the optimal fill level.

In this study, we performed the experiment, giving attention to the fill level of starting materials which enabled us to obtain small grains with about 200μ m diameter at a high yield because these grains are known suitable for granules for tableting.

Particle size of granules was determined by sieving (row tap shaker), mass median diameter D_{50} and geometric standard deviation σ_{φ} were calculated on the basis of the particle size distribution. Yields were obtained respectively for small grains (75 to 500 μ m), granules with about 200 μ m diameter (106 to 300 μ m), and substances other than granules (less than 75 μ m).

Table 2. Types of Powder and Formulation

Material	Manufacturer	Ratio ($wt\%$)	Remark
Lactose 200M	DMV Inc.	57.9	
Cornstarch	Matsutani Chemical Industry Co., Ltd.	28.95	
Avicel PH101	Asahi Chemical Industry Co., Ltd.	9.65	Crystalline cellulose
$HPC-L$	Shin-Etsu Chemical Co., Ltd.		Binder

Fig. 9. Relationship between Yield of Target Granules, Small Grain and Fill Level

j, target granules with about 200 μ m diameter (106 to 300 μ m); \blacklozenge , small grain (75 to 500 μ m), \blacktriangle , substances other than granules (less than 75 μ m); \blacklozenge , recovery rate.

Results and Discussion in Granulation Experiment

Relationship between Yield of Target Granules, Small Grain and Fill Level Figure 9 showed the relationship between the yields of 200 μ m granules (106 to 300 μ m)/small grains and fill level. It was found that, at the optimal fill level of around 50%, target granules with 200 μ m diameter (106 to $300 \,\mu$ m) were abundantly obtained and the small grains were also obtained at a high yield. Granules with target size diameter and small grains were also obtained at a favorable yield at the optimal fill level of around 60% (50 to 65%), which was predicted by the simulation. Further, it was experimentally revealed that small grains were obtained at a high yield as the fill level was increased, showing a constantly high yield (85%) when the fill level attained 50% or higher.

From the granulation experiment results so far discussed, it was considered that 50% fill level would be where granules with target diameter were obtained abundantly and in a high yield. Further, at the optimal fill level of around 60% (50 to 65%) predicted by the simulation, granules with target diameter were obtained relatively abundantly. Namely, the optimal fill level predicted by the simulation was in good agreement with that obtained as a result of the granulation experiment. This result showed that the particle circulation could be properly expressed by kinetic energy, and grasping the kinetic energy of particles in the agitating vessel would be effective in deciding an optimal fill level.

Relationship between Median Diameter and Fill Level The granulation experiment was conducted by changing fill level of starting materials to determine the relationship between mass median diameter/geometric standard deviation of the granules obtained and the fill level, which was shown in Fig. 10. The fill level of 16.3% failed to provide a smooth particle circulation, giving less energy to particles, thus resulting in small granules with median diameter of about 100

Fig. 10. Relationship between Median Diameter of Granules, Geometric Standard Deviation and Fill Level

 \blacklozenge , D₅₀ μ m; \blacksquare , σ_{α} .

 μ m. However, the fill level of 35 to 65% provided granules having target median diameter of 200 μ m at a relatively high yield. This was considered due to a favorable action of the blade energy on particles, thus providing relatively smooth circulation of particles. Further, the fill level of around 80% provided granules with median diameter of about up to 270μ m. As indicated in the results of Fig. 4, this was considered due to the fact that free space decreased with increasing fill level, thus resulting in increased particles susceptible to densification. The geometric standard deviation did not vary greatly although slightly decreased with increasing fill level.

The results of the granulation experiment so far explained have revealed that 50% fill level was an optimal level where granules with target median diameter of about $200 \mu m$ were obtained abundantly. The optimal fill level indicated by this experiment was in good agreement with that predicted by the simulation where particles showed favorable flow pattern and the kinetic energy attained a maximum value. In other words, the simulation was effective in optimizing operating conditions (fill level).

Conclusion

For the purpose of evaluating an optimal fill level of starting materials in a high-shear mixer, discrete element method was employed to conduct simulation to visualize the kinetic status of particles. The simulation results obtained by changing fill levels were used to determine solid fraction of particles, particle velocity, particle velocity vector and kinetic energy and discuss the flow pattern as well. Thus-obtained information was used to evaluate an optimal fill level. Further, the simulation was validated by the granulation experiment. The following matters were clarified from the above results.

(1) An optimal fill level for starting materials was found to be around 50% in a high-shear mixer. This optimal fill level provided particles with free space in the agitating vessel, allowing most of the particles to maintain adequate particle velocity and to conduct particle motion. It was also found that particles formed a smooth circulation rising upward along with the wall of the vessel and then descending.

(2) The simulation has revealed that it was effective to obtain the kinetic energy of particles as an index for expressing the kinetic status of particles. It was found that the fill level of 50 to 65% was where the kinetic energy attained a maximum value and formed smooth particle circulation. It was pointed out that the kinetic energy of particles was susceptible to fill levels, since the kinetic energy varied greatly in relation to fill levels as the rotational speed was raised.

(3) The granulation experiment was conducted by changing fill levels to validate the simulation results. Consequently, small grains (75 to 500 μ m) abundantly containing granules (106 to 300 μ m) with target diameter of about 200 μ m were obtained at a high yield at the fill level of around 50%.

(4) The optimal fill level predicted by the simulation results was found to be in good agreement with the result obtained experimentally. It was pointed out from the consistency between the simulation and the experiment that grasping the kinetic energy of particles in the vessel was effective in deciding the optimal fill level. Further, the simulation was confirmed to be effective in providing more information than conventional granulation experiments could provide and also helpful in optimizing the operating conditions.

References

1) Terashita K., Kato M., Ohike A., Miyanami K., *Chem. Pharm. Bull.*, **38**, 1977—1982 (1990).

- 2) Leuenberger H., *Pharm. Acta. Helv.*, **57**, 72—82 (1982).
- 3) Lindberg N. D., *Drug Dev. Ind. Pharm.*, **10**, 45—56 (1984).
- 4) Holm P., Schaefer T., Kristensen H. G., *Powder Technol.*, **43**, 213— 223 (1985).
- 5) Holm P., Schaefer T., Kristensen H. G., *Powder Technol.*, **43**, 225— 233 (1985).
- 6) Timko R. J., Barrett J. S., Mchugh P. A., Chen S. T., Rosenberg H. A., *Drug Dev. Ind. Pharm.*, **13**, 405—435 (1987).
- 7) Terashita K., Watano S., Miyanami K., *Chem. Pharm. Bull.*, **38**, 3120—3123 (1990).
- 8) Watano S., Keijiro T., Miyanami K., *Chem. Pharm. Bull.*, **40**, 269— 271 (1992).
- 9) Terashita K., Ohike A., Kato M., Miyanami K., *Yakugaku Zasshi*, **107**, 377—383 (1987).
- 10) Terashita K., Natsuyama S., Nishimura T., Sakamoto H., *J. Japan Soc. Powder and Powder Metall.*, **47**, 1306—1311 (2000).
- 11) Rhodes M. J., Wang X. S., Nguyen N., Stewart P., Liffman K., *Chem. Eng. Sci.*, **56**, 2859—2866 (2001).
- 12) Muguruma Y., Tanaka T., Kawatake S., Tsuji Y., *Powder Technol.*, **93**, 261—266 (1997).
- 13) Yamane K., Sato T., Tanaka T., Tsuji Y., *Pharmaceutical Research*, **12**, 1264—1268 (1995).
- 14) Wightman C., Moakher M., Muzzio F. J., Walton O., *AIChE J.*, **44**, 1266—1276 (1998).
- 15) Moakher M., Shinbrot T., Muzzio F. J., *Powder Technol.*, **109**, 58—71 (2000).
- 16) Alexander A. W., Shinbrot T., Muzzio F. J., *Phys. of Fluid*, **13**, 578— 587 (2001).
- 17) Terashita K., Natsuyama S., Nishimura T., Kojima H., *J. Japan Soc. Powder and Powder Metall.*, **47**, 1300—1305 (2000).
- 18) Cundall P. A., Strack O. D. L., *Geotechnique*, **29**, 47—65 (1979).
- 19) Tsuji Y., Kawaguchi T., Tanaka T., *Powder Technol.*, **77**, 79—87 (1993).
- 20) Muguruma Y., Tanaka T., Tsuji Y., *Powder Technol.*, **109**, 49—57 (2000).