Regular Article*Highlighted Paper selected by Editor-in-Chief***Scale-Up of Lubricant Mixing Process by Using V-Type Blender Based on Discrete Element Method**Masashi Horibe,*^a Ryoichi Sonoda,^a and Satoru Watano^b^aFormulation Department, CMC Center, Kaken Pharmaceutical Co., Ltd.; 301 Gensuke, Fujieda, Shizuoka 426–8646, Japan; and ^bDepartment of Chemical Engineering, Graduate School of Engineering, Osaka Prefecture University; 1–1 Gakuen-cho, Naka-ku, Sakai 599–8531, Japan.

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A method for scale-up of a lubricant mixing process in a V-type blender was proposed. Magnesium stearate was used for the lubricant, and the lubricant mixing experiment was conducted using three scales of V-type blenders (1.45, 21 and 130 L) under the same fill level and Froude (*Fr*) number. However, the properties of lubricated mixtures and tablets could not correspond with the mixing time or the total revolution number. To find the optimum scale-up factor, discrete element method (DEM) simulations of three scales of V-type blender mixing were conducted, and the total travel distance of particles under the different scales was calculated. The properties of the lubricated mixture and tablets obtained from the scale-up experiment were well correlated with the mixing time determined by the total travel distance. It was found that a scale-up simulation based on the travel distance of particles is valid for the lubricant mixing scale-up processes.

Key words lubricant mixing; scale-up; numerical simulation; discrete element method

Scale-up in the pharmaceutical manufacturing processes is very important for controlling the quality of pharmaceutical products. In the manufacturing process of solid dosage forms, control of granule properties for tablet manufacturing is particularly important to obtain good quality tablets. In particular, the flowability of granules is a critical factor, and a poor powder flow causes several problems during tableting, such as capping, sticking, binding, and lamination. Additives for direct compression and lubricants are useful for avoiding these troubles and improving the flowability of granules. Magnesium stearate is the most frequently used lubricant to improve the flowability of granules,¹⁾ but magnesium stearate has a negative effect on the tensile strength and dissolution properties of tablets.^{2,3)} The effects of mixing conditions, such as rotational speed, fill level, and mixing time, on the mixing performance of a V-type blender have been investigated.^{4–6)} When the mixing time was too short, the frequency of sticking and binding generation were increased, and when the mixing time was too long, the frequency of capping and lamination generation were increased. The mixing time was inversely proportional to the rotation speed, and similar homogeneity was obtained for mixtures rotated for the same number of revolutions. In addition, the vessel fill level had a substantial effect on the mixing rate. As the vessel fill level increased, motion within the vessel was inhibited, leading to a decrease in the particle mobility across the symmetry plane and an increase in the mixing time.⁴⁾

Also, in laboratory and commercial scale operations, the optimization of mixing conditions such as mixing time and rotational number is important for achieving stable tablet production. The scale-up method of a rotating blender often uses a constant Froude (*Fr*) number,^{6,7)} a vessel tangential speed, or particle surface velocity.⁸⁾

The most commonly recommended scale-up method involves the use of the Froude number $Fr = rn^2/g$; where *r* (m) is the rotating radius of a V-type blender, *n* (rps) is the rotating speed, and *g* (m/s²) is the acceleration of gravity. *Fr* is widely

used in fluid mechanics to describe the balance between inertial and gravitational forces. Unfortunately, there is no such experimental data for scale-up of V-type blenders.

Numerical simulations using discrete element method (DEM) have been used to analyze solid dosage manufacturing.^{9–11)} The DEM simulations for scale-up of the mixing process have been reported in several studies.^{12–14)} However, there have been no studies using a DEM simulation for the lubricant mixing processes.

In this study, scale-up experiment and DEM simulation of the lubricant mixing processes were conducted for V-type blenders under the same condition of fill level and Froude number. Three scales of V-type blender (1.45, 21 and 130 L) were used for the scale-up experiment of lubricant mixing, and the physical properties of lubricated mixture and the tablet compressed by the lubricated mixture were evaluated. However, the physical properties of them were not corresponded either mixing time or number of revolution. Thus, the DEM simulations of three scales of V-type blender mixing were conducted to find the scale-up factor. As a result, the same physical properties of lubricated mixture and tablet could be obtained based on the travel distance of the particles between the scales.

Experimental

Materials Acetaminophen (Iwaki Pharmaceutical Co., Japan), lactose monohydrate (Dilactose S[®], Freund Corporation, Japan), microcrystalline cellulose (Ceolus[®] PH-301, Asahi Kasei Chemicals Co., Japan), carmellose calcium (E. C. G[®]-505, Gotoku Chemical Co., Ltd., Japan) and magnesium stearate (Nitto Kasei Kogyo K.K., Japan) were used in the experiments. Acetaminophen, lactose monohydrate, microcrystalline cellulose, carmellose calcium and magnesium stearate were mixed with 10:59:20:10:1 by weight.

Scale-Up Experiment Procedure The lubricant mixing was conducted by using three scales of V-type blenders based on the Froude number. So far, the scale-up method of a rotat-

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Table 1. Pharmaceutical Formulation for Lubricant Mixing Experiment

Components	Quantity [mg/tablet]
Acetaminophen	20
Lactose monohydrate	118
Microcrystalline cellulose	40
Carmellose calcium	20
Magnesium stearate	2
Total	200

Table 2. Experimental Conditions of Lubricant Mixing Experiment Based on Froude Numbers

	Type		
	V-1	V-10	V-60
Rotation speed [rpm]	60	40	28
Maximum rolling radius [m]	0.10	0.22	0.45
Froude number	0.40	0.39	0.39
Total amount of powder [kg]	0.223	3.23	20.0
Total mixing time [min]	25	15	11.5
Sampling time [min]	2, 5, 10, 16.5	1, 3, 6, 10	1, 2, 4.5, 7.5

ing blender has been reported using the *Fr*. Froude number is a scale-independent variable defined as:

$$Fr = rn^2/g$$

where r (m) is the rotating radius of a V-type blender, n (rps) is the rotating speed, and g (m/s²) is the acceleration of gravity. Pharmaceutical formulation for the lubricant mixing experiment is shown in Table 1. V-type blenders with their volumes of 1.45 L (Type S-3, Tsutsui Scientific Instruments Co., Japan), and 21 and 130 L (V-10 and -60, Tokujin Co., Japan) were used to prepare mixtures and tablets. The fill level of each blender was 30% vol to allow for the bulk density of a physical mixture of 520 kg/m³. The specifications and operational conditions used for the V-type blenders are summarized in Table 2. The mixing experiments using three scales of V-type blenders were conducted under the same Froude number that was adjusted by the rotation speed (60 rpm in the V-1, 40 rpm in the V-10 and 28 rpm in the V-60). The lubricated mixtures were compressed with 8.0 mm round punches with biconvex faces at 200 mg weight under 10 kN compression force per tablet using a 15 stations rotating tableting machine (HT-AP15SSII, Hata Iron Works Co., Ltd., Japan).

Evaluation of Lubricated Mixtures and Tablets Physical Properties Angle of repose and bulk and tapped densities of lubricated mixtures were measured using a powder tester (MT-1001T, Seishin Enterprise Co., Ltd., Japan). Compressibility was defined by the bulk and tapped densities of the lubricated mixtures as follows:

$$\text{Compressibility [\%]} = (\rho_T - \rho_B)/\rho_T \times 100$$

where ρ_T and ρ_B show tapped and bulk densities of lubricated mixtures (kg/m³), respectively.

The fracture load of tablets was measured using a tablet hardness tester (WPFHT-20N, Kiya Co., Japan). The thickness of each tablet was measured with a micrometer. The tensile strength of tablets was calculated as follows¹⁵⁾:

$$\sigma_t = \frac{2P}{\pi DT}$$

where σ_t (MPa) is the tensile strength, P (N) is the fracture load, D (mm) is the tablet diameter and T (mm) is the tablet thickness.

The disintegration time was measured using a tablet disintegration tester (NT-400, Toyama Sangyo, Japan) by the disintegration test method of the JP X3II. The test was performed using water at 37°C as the test fluid without auxiliary discs.

The pharmaceutical uniformity test (content uniformity test) of tablets was performed according to the JP XVII. The content was measured by HPLC. The analytical conditions were: Column, Sun Fire C18 (4.6×250 mm, particle size 5 μm, Waters); mobile phase, a mixture of water–acetonitrile–trifluoroacetic acid (800:200:1); flow rate, adjusted to make the retention time of acetaminophen about 5 min; and measurement wavelength, 243 nm.

Theory of DEM For modeling of particle motion in a V-type blender, a three-dimensional DEM was used. The DEM describes the motion of each particle based on the Newton's second law for individual particle, allowing for the external forces acting on the particle. The Newton's second laws of translational and rotational motions of each particle were numerically solved using an explicit finite difference scheme. The interactions between the particles were calculated based on the theories of contact mechanics. In this study, a soft sphere model originally proposed by Cundall and Stack¹⁶⁾ was used. In the soft sphere model, the Hertz–Mindlin contact model was employed to estimate the elastic rebound force, the viscous damping force, and the sliding friction force between contacting particles.¹⁷⁾ The contact model proposed by Zhou *et al.*¹⁸⁾ was also employed to estimate the rolling friction torque between contacting particles. The DEM simulation was performed using a commercial simulator EDEM ver.3.1 (DEM Solutions Ltd.). In this study, two contact models were used for the simulation. One was the Hertz–Mindlin (no-slip) contact model that is the default model used in EDEM, and the other was the Hertz–Mindlin contact model combined with the Johnson–Kendall–Roberts (JKR) cohesive model that is used to account for the cohesive force in particles collisions.¹⁹⁾ The EDEM can import a three-dimensional computer-aided design (3D-CAD) drawing and reflect it as the boundary conditions.

Model Equipment Vessel dimensions are shown in Table 3 along with a schematic in Fig. 1. The 3D-CAD models of three scales of V-type blenders were created by an ANSYS Design modeler. The vessel dimension and vessel volumes were all matched as closely as possible to the actual experimental equipment. These models were imported into the EDEM ver.3.1.

Model Particle The model particle was created based on the bulk density of the physical mixture used for the experiment. Bulk density of the model particles was calculated based on the mass of particles inside a cylinder of which the radius is 25 mm and height is 50 mm. This simulation was conducted by the Hertz–Mindlin (no-slip) contact model. At first, spherical model particles were used for this simulation, however, the shape of these particles could not match the bulk density of the actual powder. Therefore, a new model particle composed of six particles was created. The shape and the property of this particle are shown in Fig. 2 and Table 4.

Table 3. Vessel Dimensions of V-Type Blenders

Type	Vessel volume [L]	L [m]	R [m]	D [m]
V-1	1.45	0.12	0.10	0.08
V-10	21	0.26	0.22	0.22
V-60	130	0.50	0.45	0.41

Fig. 1. Plane Geometry of a V-Type Blender for a DEM Simulation

Fig. 2. Model Particle for a DEM Simulation

Table 4. Model Particle Parameters Used for the DEM Simulation

Particle density [kg/m ³]	1070
Particle diameter [mm]	7
Sliding friction coefficient [—]	0.50
Rolling friction coefficient [m]	2.5×10^{-5}
Poisson's ratio [—]	0.30
Shear modulus [Pa]	2.16×10^6
Damping coefficient [—]	0.30
Contact model	Hertz–Mindlin (no-slip)

Table 5. The Scale-Up DEM Simulation Conditions of V-Type Blenders

Type	V-1	V-10	V-60
Total number of particle	1329	19445	120576
Total amount of powder [kg]	0.223	3.23	20.0
Loose bulk density [kg/m ³]		520	
Particle fill level [vol%]		30	
Rotational speed [rpm]	60	40	28
Calculation time step [s]		1.0×10^{-4}	
Simulation time [s]		10	
Contact model		Hertz–Mindlin (no-slip) or Hertz–Mindlin (JKR)	

Scale-Up DEM Simulation of V-Type Blender Mixing

The conditions of the V-type blender scale-up simulation used in the two contact models are shown in Table 5. The particle fill level and rotational speed were matched to the experimental conditions. The number of particle used for V-1, -10 and -60 DEM simulation was 1329, 19445 and 120576 particles, respectively.

(a)

(b)

Fig. 3. The Physical Properties of Lubricated Mixtures at a (a) Mixing Time and (b) Number of Revolutions

Results and Discussion

Experimental Results of Lubricated Mixtures and Tablets The flowability of the lubricated mixtures was evaluated by compression degree and angle of repose. The magnesium stearate could reduce the friction of the powders,¹⁾ so the flowability of the lubricated mixture was gradually improved during the lubricant mixing. If the flowability of the lubricated mixture was improved, the compression degree and angle of repose were decreased. Figure 3(a) shows the compression degree and angle of repose of lubricated mixtures *versus* mixing time. The compression degree of lubricated mixtures indicated similar properties between each scale; however, the angle of repose of the V-1 lubricated mixtures was different compared with another scale. Figure 3(b) shows the compression degree and the angle of repose of the lubricated mixtures *versus* number of revolutions. These physical properties that were obtained by the large scale were improved with a smaller number of revolutions, and the compression degree and angle of repose were reduced faster than that of the small scale. As a result, the flowability of particles obtained by the large scale was improved in a shorter mixing time and number of revolutions than the small scale.

Figure 4 shows the content uniformity and the disintegration test of tablets *versus* mixing time. The acceptance criterion of the JP XVII pharmaceutical uniformity test (content uniformity test) is “not exceeding 15.0%,” and the value obtained in this scale-up experiment was much better than this criterion. Disintegration time of tablets was not changed

regardless of scale or mixing time and these tablets were disintegrated about 120 s. This result suggested that dissolution profile of the tablets were not affected by the scale and mixing time.

The compression moldability of tablets was evaluated by the tensile strength. Figure 5 shows the tensile strength of tablets *versus* mixing time or number of revolutions. The tensile strength of tablets decreased in the small scale slower than in the large scale under the same mixing time or number of revolutions. This difference of properties was more strongly apparent in the tablets than in the lubricated mixtures. These results indicated that the scale-up could not achieve the desired result using the mixing time or number of revolutions under the same Froude number condition. Therefore, we tried to use a DEM simulation to find the scale-up factor.

Confirmation of Optimal Rotational Speed by DEM Simulation To confirm whether the experimental conditions were appropriate or not, the optimal rotation speed of V-10 was determined by DEM simulation. The rotation speed of a blender affects the particles motion, so if all the particles could be moved similarly during V-type blender mixing, flowability of the particles would effectively be improved. To confirm whether the movements of each particle were similar or not, the travel distance of particles during the V-type blender mixing simulation was analyzed. The travel distance (TD) was calculated based on subtracting the three-dimensional coordinates (x , y , z) of a particle at a certain time step from that of the previous time step.

Fig. 4. The Content Uniformity and Disintegration Test of Tablets Analyzed by Mixing Time

(a) Content uniformity of tablet; (b) Disintegration test of tablet

Fig. 5. The Tensile Strength of Tablets Analyzed by Mixing Time and Number of Revolutions

Fig. 6. Relationship between CV Value of Travel Distance and Rotational Speed

Fig. 7. Snapshots of Particles in a V-Type Blender (21 L) at Different Rotational Speed

Fig. 8. Snapshots of Particles in a V-Type Blender (21 L) at Different Contact Model in the 40rpm Simulation Condition

Table 6. Analysis of Particle Travel Distance

Contact model	Hertz–Mindlin (no-slip)			Hertz–Mindlin (JKR)		
Type	V-1	V-10	V-60	V-1	V-10	V-60
Fill level [%]		30			30	
Travel distance / time [m/min]	18.6	30.7	40.2	17.6	28.3	36.5
Mixing time [min]	16.5	10.0	7.6	16.1	10.0	7.8
Total travel distance [m]		307			283	

$$TD = \sum_{i=1}^m \|\bar{P}_i - \bar{P}_{i-1}\|$$

$$\text{Where } \bar{P}_i = \begin{pmatrix} x_i \\ y_i \\ z_i \end{pmatrix}$$

And therefore,

$$TD = \sum_{i=1}^m \sqrt{(x_i - x_{i-1})^2 + (y_i - y_{i-1})^2 + (z_i - z_{i-1})^2}$$

where m and P_i denote the total number of time steps and the three-dimensional coordinates (x , y , z) of the particle i , respectively. The travel distance of particles was coded in C++ with EDEM's Application Programming Interface (API) and

Fig. 9. The Physical Properties of Lubricated Mixtures Analyzed by Travel Distance for a No-slip Contact Model

Fig. 10. The Tensile Strength of Tablets Analyzed by Travel Distance for a (a) No-slip Contact Model and (b) JKR Contact Model

used directly in EDEM. The V-type blender mixing simulation was conducted under the same conditions as shown in Table 5 except for the rotational speed. The travel distances of all particles were evaluated based on the coefficient of variation (CV) value to confirm the difference of each particle travel distance. The relationship between CV value of travel distance and rotational speed is shown in Fig. 6. The CV value of travel distance in 40rpm was smaller than that of other rotation speeds, and it is assumed that particle motion was uniform in the 40rpm simulation condition. This simulation result indicated that the experimental condition of the scale-up experiment was appropriate. On the other hand, the CV value of 80rpm rotational speed was higher than the other conditions, which suggested that particle motion was restricted by the centrifugal force (Fig. 7).

DEM Simulation Result of V-Type Blender Mixing The result of scale-up DEM simulation is shown in Table 6 and Fig. 8. The JKR contact model provides higher friction force than the no-slip contact model. The flowability of the particles simulated by the Hertz–Mindlin (JKR) contact model was worse than that of the Hertz–Mindlin (no-slip) contact model. Hence, the travel distance simulated by the Hertz–Mindlin (JKR) contact model was shorter than that of the Hertz–Mindlin (no-slip) contact model. In this study, model particle diameter of DEM simulation was bigger than actual particle diameter. However, this scale-up simulation were conducted under the same fill level, therefore, the ratio of the travel distance of particles to the scales was not affected by the particle size.

The travel distance per unit time in the large V-type blender was longer than in the small V-type blender. If the particles moved farther distances in the unit time, the lubricant mixing effect could be achieved with a shorter time. Therefore, corresponding the total travel distance between the scales was important, and the same travel distance in the three scales was calculated to adjust for the mixing time.

Figure 9 shows the compression degree and the angle of repose of lubricated mixtures *versus* travel distance and Fig. 10 shows the tensile strength of tablets *versus* travel distance. The compression degree of lubricated mixtures and the tensile strength values of tablets corresponded well with the total travel distance.

Conclusion

The scale-up experiment and simulation of the lubricant mixing process were conducted using V-type blenders under the same fill level and Froude number condition. As a result, properties of lubricated mixtures and tablets obtained from the scale-up experiment were related to the mixing time determined by the total travel distance calculated by the DEM simulation. It was found that a scale-up simulation based on the travel distance of particles is valid for lubricant mixing scale-up processes.

Conflict of Interest The authors declare no conflict of interest.

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