Drug Development and Industrial Pharmacy, 26(2), 149–158 (2000)

RESEARCH PAPER

Measurement of the Adhesive Force of Fine Particles on Tablet Surfaces and Method of Their Removal

Y. Shimada,[1] M. Sunada,[1] M. Mizuno,[1] Y. Yonezawa,[1] H. Sunada,[1] M. Yokosuka,[2] H. Kimura,[2] and H. Takebayashi[2]

[1] *Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya 468-8503, Japan*
[2] *Matsui MFG Company, Limited, R&D Center, 1-10-4 Nagaokagu-cho, Hirakata, 573-0102, Japan*

ABSTRACT

The adhesion force of fine particles on the surface of tablets was measured by a centrifugal force and impact separation method. A Finededuster (FDD) was employed to remove fine particles from the tablet surface. The centrifugal force and impact separation method was suggested to be effective for measuring the adhesive forces between particles and the tablet surface, and effective disjoining force in the FDD could be estimated by comparison of the results obtained using these two methods. The FDD showed high removal efficiency regardless of how many tablets were processed at the same time. In either of these methods, critical particle size was about 10–20 μm, and larger particles were removed more efficiently. This critical particle size was similar to that observed for other mechanical properties of powders, such as angle of repose and flowability. We simulated particle residual percentage under various operation conditions by ANN (artificial neural network) analysis and multiple regression analysis. This simulation enabled us to predict how the efficiency of particle removal is affected by the interaction of the experimental and material factors.

Key Words: *Adhesive free; Artificial neural network; Centrifugal separation method; Finededuster; Tablet surfaces.*

INTRODUCTION

Organic drug powders are highly adhesive and undergo particle cohesion during manufacturing processes such as fractionation, filling, and compression, thus preventing smooth automation of these procedures. Hence, removal of excess microparticles from the surface of tablets is desirable for automatic tableting systems. Microparticles attached to the tablet surface were removed using a Finededuster (FDD) powder-removing apparatus, and the results obtained were compared with the adhesive forces of microparticles measured using the centrifugal force method (1–3) and impact separation method (4) to estimate the effective disjoining force of the FDD.

EXPERIMENTAL

Materials

The powder sample used was Microcelac, a lactose–crystalline cellulose combined-type excipient for direct tableting (MC; Meggle Co., Germany). Microcelac tablets were obtained by directly tableting MC at 800 kg with a rotary tableting machine (Cleanpress Correct HVK-12, Kikusui Manufacturing Co., Kyoto, Japan) and had an even-cornered flat-beveled shape with a diameter of 8 mm and weighing 180 mg.

Methods

Adhesion Force Measurement of Fine Particles on the Tablet Surface and Their Removal

The adhesion force between particles and the tablet surface was measured by centrifugal separation and impact separation methods. Particles adhering to the tablet surfaces were separated from the tablets by the action of centrifugal or impact force. The adhesive force was estimated from the data obtained after statistical analysis in these methods and following use of a Finededuster (FDD-104, Matsui Manufacturing Co., Osaka, Japan) to remove fine particles from the surface of the tablets.

Centrifugal Separation Method

The tablets with adhering particles were fixed in a cell mounted in a centrifuge (KH-180, Kubota Manufacturing Co., Tokyo, Japan). The velocity of rotation was measured with a stroboscope (SS-5, Toshiba Co., Tokyo, Japan), and the centrifuge was kept rotating for 5 min after it attained a given rotation velocity. The centrifugal force acting on individual particles f_1 is given by Eq. 1 if the particles are assumed to be spherical:

$$f_1 = (\pi/6) \cdot \rho \cdot d^3 \cdot r \cdot \omega^2 \qquad (1)$$

where d is the diameter of particles, ρ is the true density of particles, r is the radius of rotation, and ω is the angular velocity of rotation.

Impact Separation Method

The tablets with adhering particles were fixed in a cell and mounted in a pendulum impact testing machine (PST-300, Yoshida Seiki Co., Tokyo, Japan). Then, particles were detached from the tablets by impact force. The impact acceleration α generated by the impact was measured with an acceleration pickup. The impact separation force f_2 acting on each particle is expressed as

$$f_2 = (\pi/6) \cdot \rho \cdot d^3 \cdot \alpha \qquad (2)$$

Powder-Removing Apparatus for Tablets: Finededuster Method

Figure 1 shows the powder-removing apparatus for tablets (FDD). Revolution of the rotor periodically blocks the air inlet of the blower to permit accumulation of potential energy (increase in static pressure), and this energy is converted into kinetic energy (suction of air) when the air inlet is open, thereby generating a pulsating airflow. The generated pulsating suction force causes fine particles to detach from the tablet surface, and the separated particles are collected by suction. Figure 2 shows vibration plates (wave and flat). Vibration of the oscillation plate provided light impact on the fine particles, thus enhancing their detachment from the tablet surface.

Residence Time in the Finededuster Unit

The residence time of tablets in the FDD unit was measured at an FDD rotor pulse frequency of 15 Hz and at two power source frequencies (50 and 60 Hz) of the blower with two types of vibration plate.

Residual Percentage of Fine Particles on the Tablets

Direct microscopic measurement of fine particles on tablet surfaces is very difficult. In particular, measurement with an image analyzer is difficult because it hardly permits particle contours to be clearly distinguished from tablet surface roughness. Hence, fine particles were separated from the tablet surface and attached to the wall of a disk-shaped transparent plastic container (45 mm in di-

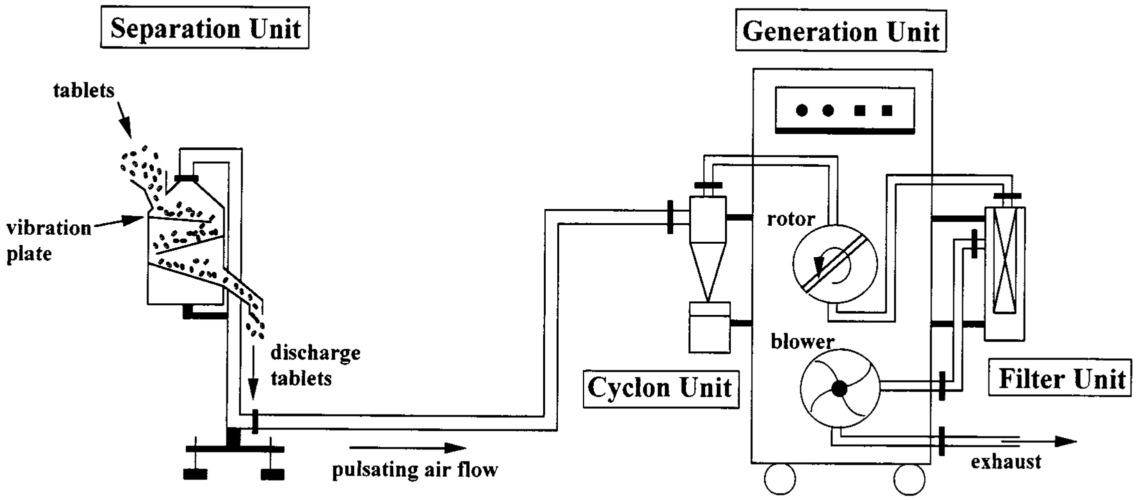

Figure 1. Schematic diagram of Finededuster apparatus.

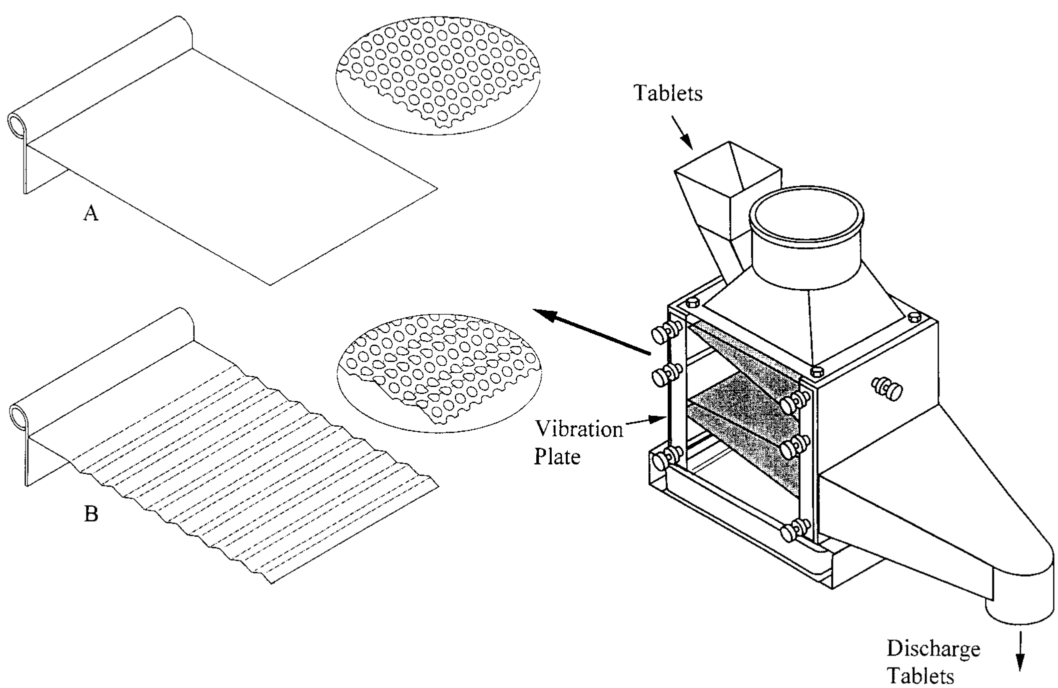

Figure 2. Two shapes of vibration plate: A, flat; B, wave.

ameter). The container consisted of a cap and a receptacle, and its inside could be easily observed with a microscope, facilitating particle measurement. To transfer fine particles from the tablet surface to the container and attach them to its wall, an external force was applied to the tablets by revolution.

Revolution Method

For the revolution method, 10 tablets were put in the transparent receptacle. The receptacle was covered with the cap and then fixed with double-coated tape at the side of the rotating shaft at the center of the rotating box of an abrader (Kayagaki Rika Co., Tokyo, Japan). The transparent container, fixed to the wall of the rotating box, rotates with the box, thereby exerting an external force on the tablets. Rotation of the box continued for 60 sec, during which time fine particles detached from the tablet surface and attached to the container wall. Tablets from which fine particles had previously been largely removed by centrifugal force, impact force, and FDD methods were also subjected to the same treatment (Fig. 3). Fine particles still remaining on the tablet surface were attached to the container wall using the revolution method.

Diameter measurements were conducted on the particles attached to the container wall with an image analyzer connected to a microscope. Particle number was counted at each particle size before and after removal, and residual percentage of particles was calculated from the data obtained. The number and Heywood diameter of fine particles remaining in an area on the tablet surface were measured with an image analyzer (Luzex FS, Nireko Co., Tokyo, Japan). The particle numbers before a_{i0} and after a_i separation were counted for each diameter. The percentage of residual particles was calculated using the following equation:

$$R\ (\%) = 100 + a_i/a_{i0}$$

Simulation of Particle Residual Rate by Artificial Neural Network and Multiple Regression Analysis for the Finededuster Method

Three-dimensional graphical representation of the experimental data obtained in this study enabled us, through simulation, to predict how the efficiency of particle removal is affected by interactions among the experimental factors involved. Multiple regression analysis and artificial neural network (ANN) analysis were used as the analytical methods. ANN analysis is a means of analyzing nonlinearity and is known to give a better fit to experimental data than conventional statistical methods, including multiple regression analysis. While ANN analysis has been improved by such technology as the partition construction technique (5) to produce more accurate results,

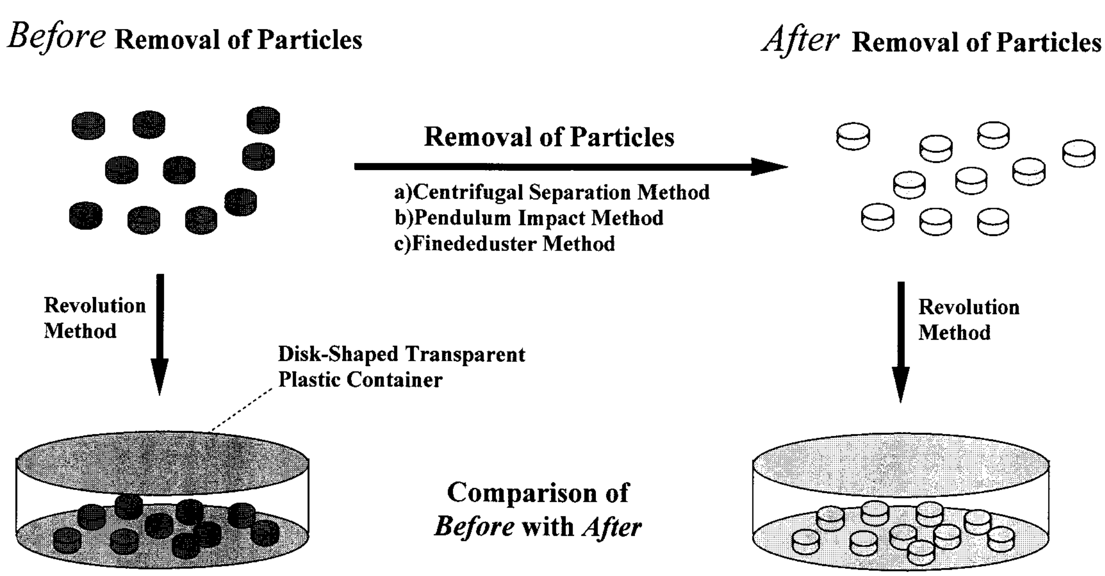

Figure 3. Measurement of fine particles on tablet surface.

it may run into local minima and give inappropriate results due to overlearning or dependence on the operation conditions. Hence, multiple regression analysis was used together with ANN analysis to analyze the data, thereby increasing the reliability of the simulation.

The simulation structure of ANN is similar to the neural structure of the human brain. ANN analysis is an imitation of artificial intelligence and constructs an artificial neuron structure through learning the existing data obtained so far; it enables prediction of unknown results under new conditions. In the present study, we conducted ANN analysis and multiple regression analysis according to the method of Takahara et al. (6). An attempt was then made to predict and examine changes in the efficiency of particle removal by the FDD based on the results of the simulation.

Method of Simulation

We analyzed the relations among three factors (particle residual percentage, particle size, and blower frequency) in the removal of fine particles attached to tablets in the FDD. The ANN analytical method used here employed a technique using the Kalman filter (7), thus markedly reducing the time of simulation. Table 1 shows the operational conditions of ANN analysis. Six-unit branching was adopted as the hidden layer unit (the middle part of the second layer of the three-layer neuron layer). Reconstruction was performed 10 times (to optimize the neuron structure and make its constitution more suitable). Equation 3 gives the general form of multiple regression equation for the cases in which flat and wave vibration plates were used, respectively, for the treatment of many tablets.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2 \tag{3}$$

Table 1

Operation Conditions in Artificial Neural Network

	Flat	Wave	Many Tablets (Flat Vibration Plate)
Hidden layer unit	6	6	6
Reconstruction	10	10	10
Sigmoid curve	2	2	2
Initial UD matrix	1	1	1
Mean error	0.08	0.04	0.08
Neuron weight	18	18	18

UD = U-D filter algorithm parameter (7).

Table 2

Coefficients of Optimal Regression Equation in Multiple Regression Analysis (Eq. 3)

Coefficient	Flat	Wave	Many Tablets (Used Flat Vibration Plate)
b_0	88.761	98.681	90.245
b_1	—	−1.210	−0.264
b_2	−3.724	−3.678	−6.148
b_3	0.008	0.036	0.013
b_4	−0.010	—	—
b_5	0.052	0.023	0.096
r	0.977	0.978	0.975
F	88.937	95.405	83.265
SD	4.387	2.531	6.319
r^2	0.944	0.947	0.940
Sample number	22	22	22

r = correlation coefficient; SD = standard deviation; F = F value; r^2 = decision coefficient.

where Y is the residual percentage, X_1 is the blower frequency (Hz), X_2 is the particle diameter (μm), and b_0–b_5 are regression equation coefficients.

Table 2 summarizes the calculated values in each case for the coefficients of regression, correlation coefficient, F value, standard deviation, determination coefficient, and sample number.

RESULTS AND DISCUSSION

Comparison Among Centrifugal Force, Pendulum Impact, and Finededuster Methods in Particle Removal from the Tablet Surface

Figure 4 shows the relation between residual percentage of particles and particle diameter obtained by centrifugal force, pendulum impact, and FDD methods (60/15 Hz). The disjoining force acting on fine particles on the tablet surface in the unit of the FDD was then estimated based on the results shown in Fig. 5. The data obtained by centrifugal force and impact separation methods were plotted (Fig. 5), and the force at which half of the particles were removed f_{50} (mean adhesion force) was calculated. The value of f_{50} was determined to be 1.07×10^{-7} (N). The mean particle diameter d was 15.8 μm in this case. Then, residual percentage of particles was estimated at a particle size of 15.8 μm for the three separation methods. The FDD method was found to give the lowest resid-

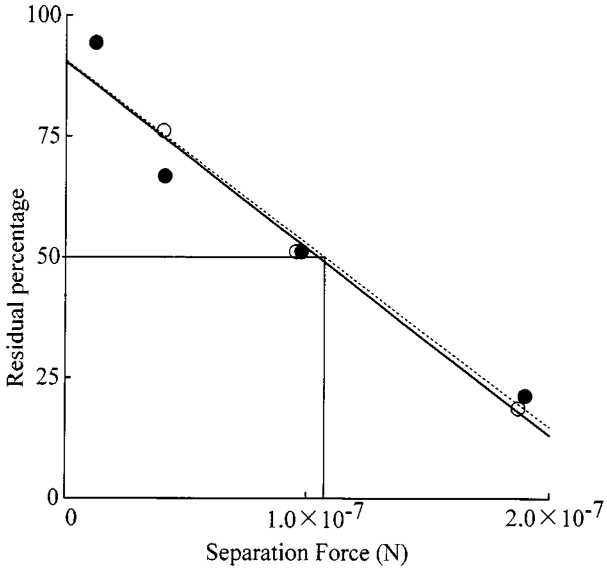

Figure 4. Residual percentage versus separation force of Microcelac tablet system. ○, pendulum impact method; ●, centrifugal separation method.

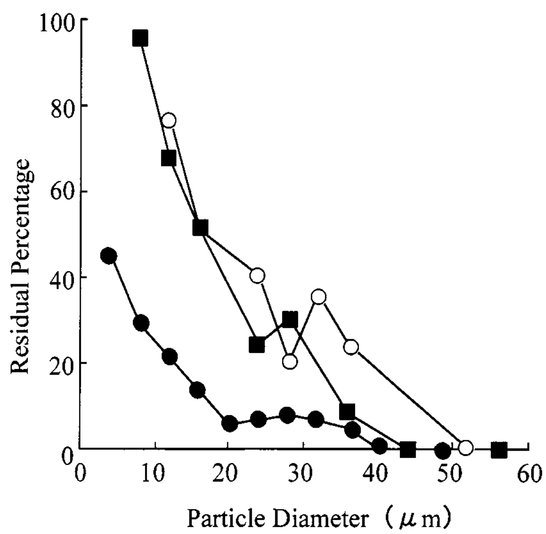

Figure 5. Comparison of centrifugal separation method, pendulum impact method, and Finededuster (revolution method). ●, Finededuster 60-Hz blower frequency, 15-Hz rotor frequency; ○, centrifugal method; ■, pendulum impact method.

ual percentage, about 30%, suggesting that a disjoining force higher than 1.07×10^{-7} (N) acts on fine particles on the tablet surface in the FDD under the conditions indicated in Fig. 4. Residual percentage of particles decreased suddenly at a particle diameter of about 10–20 μm (Fig. 4), indicating the existence of a critical particle size at around this size.

Effects of Blower Frequency, Shape of Vibration Plate, and Residence Time on Residual Percentage for the Finededuster Method

Figure 6 shows the effects of vibration plate shape and blower frequency on residual percentage. The shape of the vibration plate was shown to affect the removal efficiency of particles. When a wave vibration plate was used, more efficient removal was observed compared with the use of a flat plate. Table 3 shows the residence time of tablets in FDD. As the blower frequency increased, residence time decreased. As air pressure in the FDD became greater as the blower frequency increased, tablets moved more quickly than under lower frequency, and residence time became shorter. The wave plate used in this study gave a longer residence time compared with the flat plate. This result indicated that, although residence time is important, blower frequency is a more important factor in the regulation of removal efficiency. The generated pulsating suction air force in FDD was the most important factor for particle removal, and use of a wave vibration plate and long residence time resulted in more efficient removal. Table 4 shows the results of average air velocity in the FDD unit. With an FDD blower frequency of 60 Hz and rotor frequency of 15 Hz, the difference between static pressure (maximum) and static pressure (minimum) reached the largest value. This result corresponded well to those shown in Fig. 6. In either of the cases shown in Fig. 6, a critical particle size of about 10–20 μm was found to exist, and larger particles were removed more efficiently.

Residual Percentage When Dealing with a Number of Tablets

Figure 7 shows residual percentage plotted against particle diameter when dealing with a number of tablets at the same time. The FDD showed almost the same capacity for dealing with one or a number of tablets under our experimental conditions. A critical particle size of about 10–20 μm was found to exist, and larger particles were removed more efficiently.

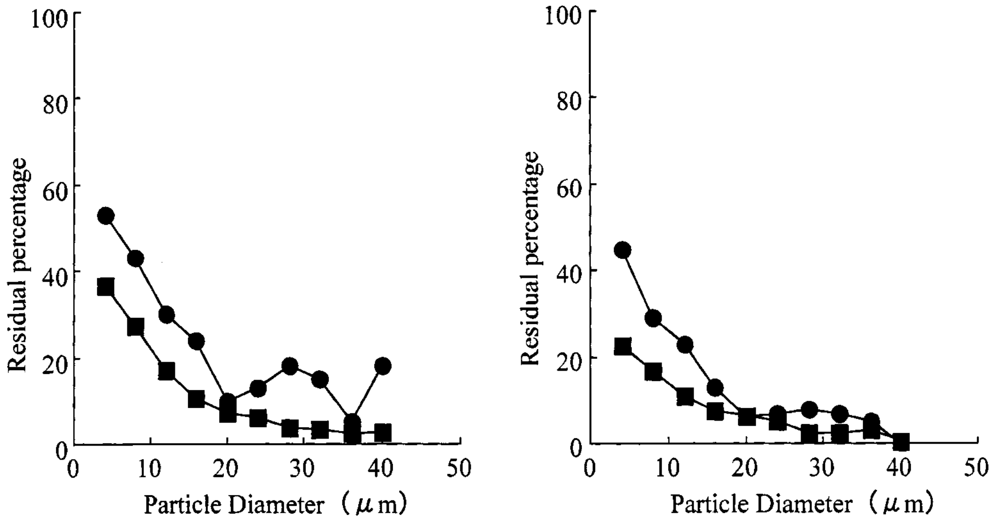

Figure 6. Effect of vibration plate shape on residual percentage. ●, flat vibration plate method; ■, wave vibration plate method. Left: 50-Hz blower frequency, 15-Hz rotor frequency. Right: 60-Hz blower frequency; 15-Hz rotor frequency.

Table 3

Measurement of Residence Time in Finededuster

Blower (Hz)	Rotor (Hz)	Residence Time (sec)	
		Flat Plate	Wave Plate
50	15	4.39	5.51
60	15	3.74	4.30

Simulation Results for Particle Residual Rate by Artificial Neural Network and Multiple Regression Analyses for the Finededuster Method

Flat Vibration Plate

Figure 8 shows the results of simulation using the data shown in Fig. 6, which were obtained by the rotation method with the tablets allowed to pass through the unit one by one. Analysis by ANN gave values similar to

Table 4

Measurement of Average Air Velocity and Static Pressure in Finededuster Unit

Blower (Hz)	Rotor (Hz)	Average Air Velocity (m/sec)	Static Pressure Maximum (Pa)	Static Pressure Minimum (Pa)
50				
	0	2.6	0.0	0.0
	13	2.2	80.7	−89.3
	15	3.1	114.7	−147.0
	20	3.1	67.4	−92.9
60				
	0	3.1	0.0	0.0
	13	3.5	93.8	−126.4
	15	3.6	141.1	−185.2
	20	3.0	83.0	−127.4

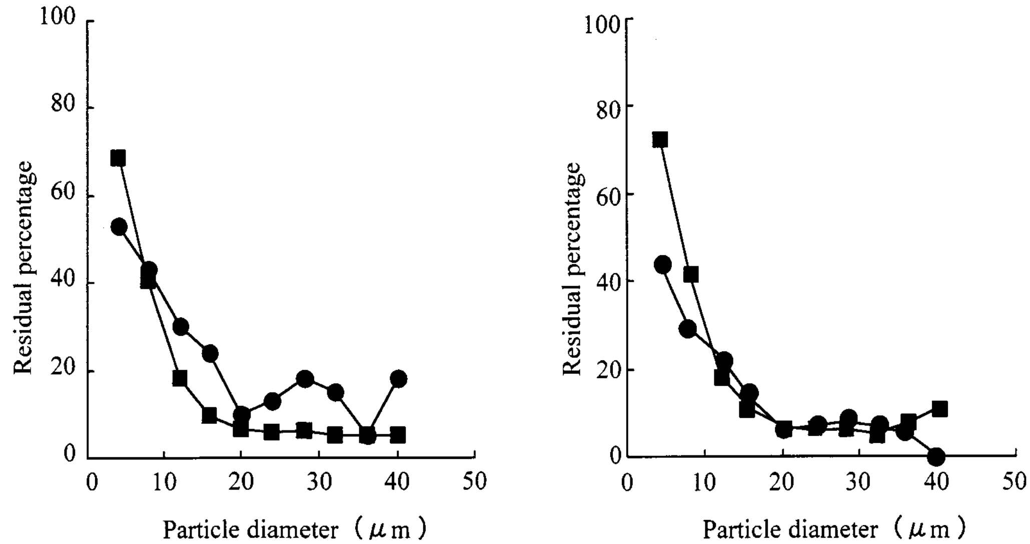

Figure 7. Residual percentage when dealing with a number of tablets (flat vibration plate). ●, 1 tablet; ■, 3000 tablets. Left: 50-Hz blower frequency; 15-Hz rotor frequency. Right: 60-Hz blower frequency; 15-Hz rotor frequency.

those obtained by multiple regression analysis. Thus, the particle residual percentage tended to decrease as the blower frequency or particle size increased.

Wave Vibration Plate

Figure 9 shows the results of simulation using the data shown in Fig. 6. When a wave vibration plate was used, the residual percentage was more than 30% lower than that for the flat vibration plate, as shown in Fig. 8. This was due to the improvement in the efficiency of particle removal achieved using a wave vibration plate. The results of simulation also predicted that a wave vibration plate provides higher removal efficiencies than the flat vibration plate.

Large-Scale Treatment (Flat Vibration Plate)

Figure 10 shows the results of simulation using the data shown in Fig. 7. ANN analysis and multiple regres-

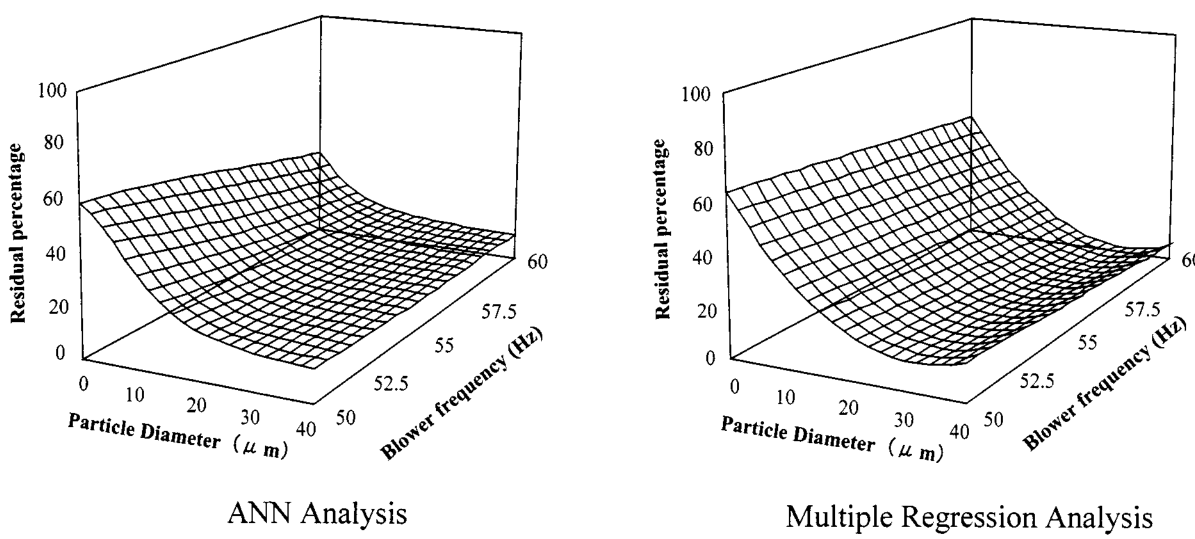

Figure 8. Simulation of particle residual percentage (flat vibration plate).

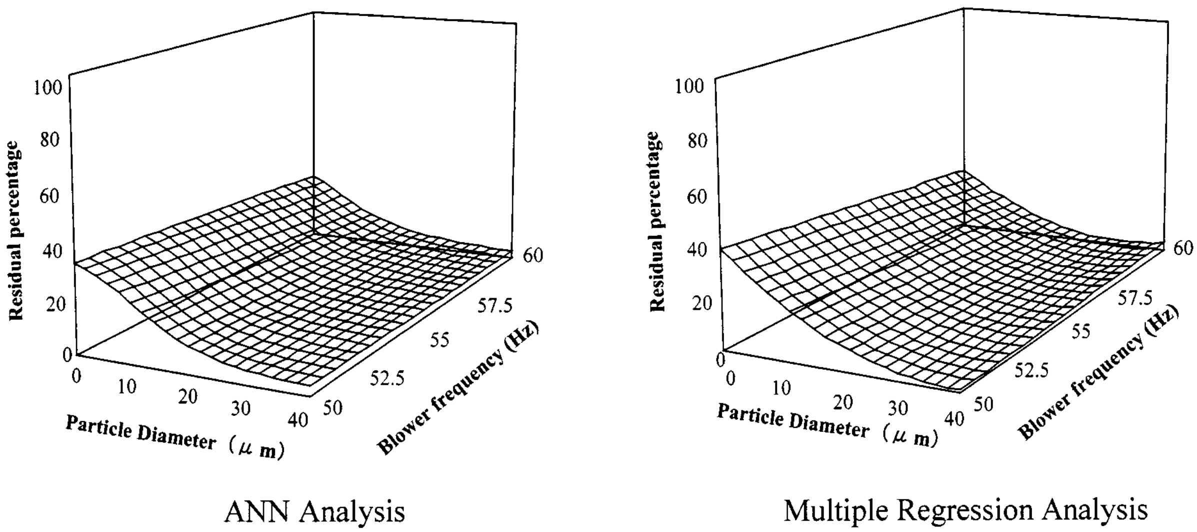

Figure 9. Simulation of particle residual percentage (wave vibration plate).

sion analysis gave somewhat different predicted values, as indicated by the graphs in Fig. 10. The experimentally obtained values were then compared with the values predicted by ANN analysis and those calculated using the multiple regression equation (Eq. 3). Significant differences were found between the experimentally obtained and calculated values in multiple regression analysis, whereas the difference was insignificant in ANN analysis. Figure 10 also indicates that the values predicted by multiple regression analysis for particles smaller than 10 μm and larger than 20 μm differed significantly from those observed, while the agreement between the observed and predicted values in ANN was good. The large-scale tablet treatment generally gave somewhat higher residual rates than for the flat vibration plate and wave vibration plate treatments, for which tablets were treated one by one. Nevertheless, this treatment was found to be very effective for removing particles larger than about 15 μm, as demonstrated by the experimental results as well as the simulation.

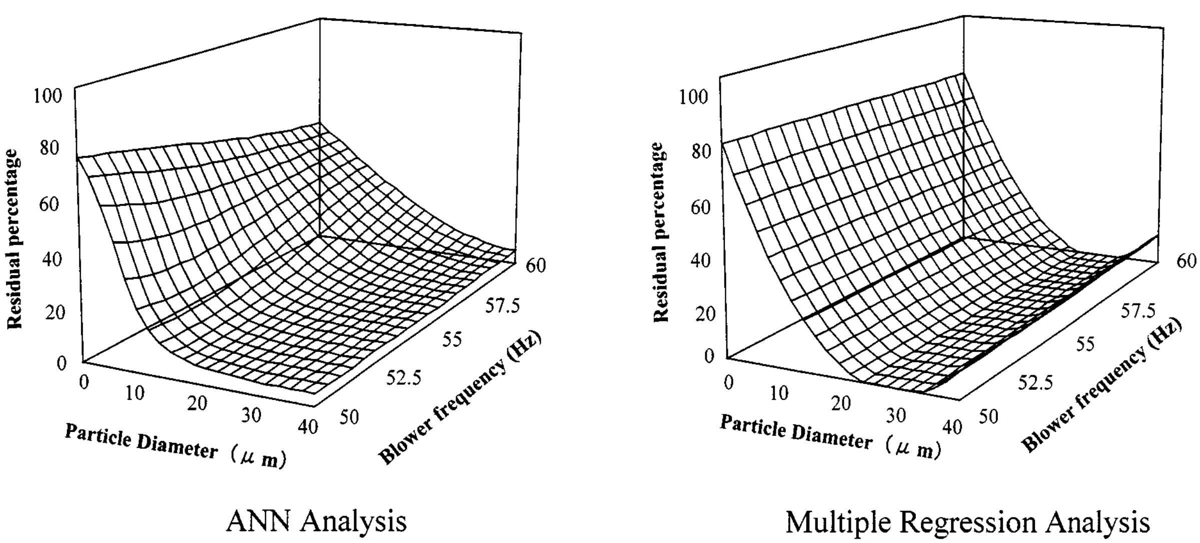

Figure 10. Simulation of particle residual percentage in large-scale tablet treatment.

Table 5

Comparison of Observed and Predicted Values of Particle Residual Percentage

Particle Diameter	Blower Frequency	Observed Values	Predicted Values (ANN)	Δ	Predicted Values (MRA)	Δ′
4	50	65.25	65.26	0.01	56.46	8.79
4	60	58.57	58.73	0.16	54.32	4.25
16	50	7.00	6.95	0.05	13.24	6.24
16	60	8.25	8.61	0.36	12.60	4.35
28	50	3.75	3.43	0.32	−2.36	6.11
28	60	5.25	4.35	0.90	−1.49	6.74
40	50	4.50	4.38	0.12	9.67	5.17
40	60	3.50	3.66	0.16	12.04	8.54
			ANN of average	0.26	MRA of average	6.27

Δ = Difference between the values obtained experimentally and those predicted by ANN analysis.
Δ′ = Difference between the values obtained experimentally and those predicted by multiple regression analysis (MRA).

CONCLUSIONS

Centrifugal force and pendulum impact methods were shown to be effective for measuring the adhesive forces between fine particles and the tablet surface. In either of these methods, the existence of a critical particle diameter of about 10–20 μm was found when fine particles were removed from the surface of the tablets. This is similar to the observations for other mechanical properties of powders, such as angle of repose and flowability. The disjoining force acting on the particles on the tablet surface in the FDD could be estimated from the results obtained by centrifugal force and pendulum impact methods. Moreover, particles larger than 20 μm were found to be removed very efficiently by the FDD method.

ACKNOWLEDGMENTS

We thank Professor Dr. K. Takayama and Dr. M. Fujikawa (Department of Pharmaceutics, Hoshi University) for providing the simulation program, Anna for ANN analysis, and ALCOLA for the multiple regression analysis.

REFERENCES

1. J. Okada, Y. Matsuda, and Y. Fukumori, Yakugaku Zasshi, 89, 1539–1544 (1969).
2. J. Okada, Y. Matsuda, and Y. Fukumori, Yakugaku Zasshi, 91, 1207–1210 (1971).
3. K. Iida, A. Otsuka, K. Danjo, and H. Sunada, Chem. Pharm. Bull., 40, 189–192 (1992).
4. A. Otsuka, K. Iida, K. Danjo, and H. Sunada, Chem. Pharm. Bull., 31, 4483–4488 (1983).
5. W. C. Carpenter and M. E. Hoffman, AI Expert, 31–33 (March 1995).
6. J. Takahara, K. Takayama, K. Isowa, and T. Nagai, Int. J. Pharm., 158, 203–210 (1997).
7. T. B. Blank and S. D. Brown, J. Chemom., 8, 391–407 (1994).