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RESEARCH PAPER

Preparation and Evaluation of High Drug Content Particles

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ABSTRACT

To determine how to prepare high drug content particles using a Wurster fluidized bed to determine realizing the miniaturization of solid dosage forms, aspirin was selected as the model drug and granulated without any additive. In this study, the emphasis was on evaluating the key operation factors of airflow rate and atomizing flow volume. The properties of the resulting particles, such as the average diameter, particle strength, appearance, and compressibility using different airflow rates and atomizing flow volumes, were investigated. Furthermore, detailed optimization of the operation conditions was conducted by artificial neural network (ANN) analysis. The relationship between the controlling factors (powder supplied, concentration of spray liquid, the amount of consumed spray liquid, and spray rate) and the response variables (product yield, median diameter, angle of repose, and degradation of aspirin) was investigated after evaluating the airflow rate and atomizing flow volume effects. The resulting granules under optimum operation conditions showed excellent physicochemical properties such as particle size uniformity, flowability, and compressibility.

Key Words: Miniaturization; Solid dosage forms; Wurster fluidized bed; Aspirin; Optimization; Artificial neural network (ANN); Flowability; Compressibility; Stability.

INTRODUCTION

The development of solid medicated excipients has attracted much interest for a long time because using a good excipent can improve the properties of the final solid preparations. However, in recent years, the preparation of particles with a high drug content and direct application of these particles to various solid dosage forms to decrease the amount of excipient required and miniaturize solid dosage

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forms have become a focus point in drug manufacture.[1,2] Aspirin, a traditional antipyretic analgesic drug, has been used in clinical treatment for over 100 years. However, because new remedial activities of aspirin are continuously being found either when used alone or as an active ingredient in combination preparations, it seems likely that aspirin will long continue to play a significant role in clinical practice.[3,4] However, because of its poor flowability, compressibility, and stability, aspirin often presents many difficulties in preparing and handling solid dosage forms containing aspirin. Furthermore, in combination preparations, the aspirin content is often very high[5,6] making the preparation of large volumes of drug with good physical properties difficult.

In this study, aspirin was granulated without any additives using a Wurster fluidized bed. The Wurster fluidized bed is an efficient granulating and coating apparatus and is generally used because many different operations, such as mixing, granulating, coating, and drying can be conducted in a single vessel at the same time, thus reducing the cost, space, and time.[7] Furthermore, its high drying efficiency is advantageous to the stability of drugs sensitive to the moisture. As we all know, degradation often occurs when aspirin is granulated with water solution because aspirin is easy to hydrolyze in the condition of high humidity. However, there are few reports about the degradation degree of aspirin during the granulation process. Aspirin is also difficult to compress directly, especially when it exists in the dosage forms with a high content, because the original aspirin powder or crystalline is of poor flowability and compressibility.

In this study, based on an analysis of the effects of airflow rate and atomizing flow volume on the resulting particle properties such as particle diameter distribution, strength, and compressibility, the other controllable operation conditions were optimized in detail by artificial neural network (ANN) analysis.[8] In the ANN analysis, the powder supplied, concentration of the binder, amount of binder used, and spray rate were selected as the controlling factors. The resulting particle yield, diameter, flowabilifiy (angle of repose), and the aspirin degradation in the process of granulation were selected as the response variables. The relationships between controlling factors and response variables were represented clearly by drawing contour figures, and the optimum operation conditions were determined by using the superimposed two-dimensional diagrams.[9]

The aspirin granules prepared under the optimized conditions were evaluated for particle size, flowability, compressibility, and disintegration. Through the investigation, the optimized aspirin granules showed excellent physicochemical properties, and many difficulties in the process of preparing aspirin-containing drugs could be overcome.

MATERIALS AND METHODS

Materials

Aspirin fine powder (acetylsalicylic acid $\geq$99.5%) was purchased from Sankyo Chemical Industries, Ltd. (Tokyo, Japan). Hydroxypropyl methyl cellulose (HPMC, TC-5E, 3 mm^2/g) as a binder was obtained from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan).

A Wurster fluidized bed (MP-01-SP, Powrex Corporation. Osaka, Japan) was used in the study.

Methods

Preparation of Aspirin High Content Granules

The basic operation conditions of aspirin granulation using a Wurster fluidized bed are shown in Table 1. The airflow rate and the atomizing flow volume were changed, and the effects of these two factors on the resulting granule yield, diameter, strength, and appearance were investigated.

Measurement of Particle Diameter

The particle diameter was determined by using a laser micron sizer (LMS-30, Seishin Enterprise Co., Ltd. Tokyo, Japan).

Table 1. Operation conditions of aspirin granulation.

Operation conditions	
Powder supplied (g)	600
Binder concentration (%)	5
Spraying rate (g/min)	5.0
Binder used (g)	1,000
Inlet temperature (°C)	75
Outlet temperature (°C)	25
Air flow rate ($\times 10^{-3}$ m^3/s)	5.56, 8.33, 11.1
Atomizing flow volume ($\times 10^{-4}$ m^3/s)	5.0, 6.7, 8.3

Measurement of Particle Strength

The strength of the resulting particles was determined by using a particle hardness tester (Grano, Okada Seiko Co., Ltd. Tokyo, Japan). The test speed of the upper punch with a load cell was set at 100 μm/s. Twenty particles of each kind were evaluated, and the particle strength was calculated by the equation as follows[10]:

$$S_t = \frac{4P}{\pi D^2} \tag{1}$$

where S_t is the granule strength, P is the crushing load when the particle is broken, and D is the particle diameter.

SEM Observation

The appearance of the resulting particles was observed by using SEM photographs (SEM, JSM-T20, JEOL Co., Ltd. Tokyo, Japan).

Investigation of Particle Compressing Properties

The granules samples were compressed on a universal tension and compression tester (AUTOGRAPH AG-5000D), Shimadzu Corporation, Kyoto, Japan) with 10-mm flat-face punches to tablet weight of 250 mg. The upper punch velocity was fixed at 0.5 mm/min, and the compression process could be recorded by the computer.

Moreover, the data collected by the computer were used to investigate the compressing properties of the particles prepared with different conditions and the following Kawakita equation was used.

$$\frac{P}{C} = \frac{1}{a}P + \frac{1}{ab} \tag{2}$$

where P denotes the compression force, C represents the compressed degree, and a, b are constants.

Measurement of Tablet Tensile Strength

To evaluate the effect of the resulting particles on the final dosage form, the tablet tensile strength was determined by using a tablet hardness tester (TS-50N, Okada Seiko Co., Ltd. Tokyo, Japan) after 250 mg of the resulting granules were compressed into tablets with 10-mm flat punches using AUTOGRAPH at about 13, 26, 39, 65, and 104 MPa. The plunger was driven down at a speed of 40 mm/min along the radial direction of the tablet, and the tensile strength (T_s) was calculated by using the following equation:

$$T_s = \frac{2F}{\pi \cdot d \cdot h} \tag{3}$$

where F is the crushing load, and d and h denote the diameter and thickness of the tablet, respectively.

Optimization of Operation Conditions with ANN Method

On the basis of the analysis of airflow rate and atomizing flow volume, these two factors were fixed at a relatively stable level. By changing other controllable factors, such as the binder solution concentration, the amount of powder supplied, the spray rate, and the amount of spray liquid added, the physical properties of the resulting granules could also be widely varied. The ANN analysis was used to optimize the operation conditions because ANN can analyze not only the linear relationship but also the nonlinear relationship and it has been verified to be the most powerful and effective optimizing method. [11,12] In the optimization process, median particle size (d_{50}), product yield (Y), the angle of repose (θ), and aspirin degradation during the process of granulation (D) were selected as the response variables. The binder solution concentration (C), the amount of powder supplied (F), the spray rate (V), and the amount of spray liquid added (W_s) were used controlling factors. The experimental data are listed in Table 2.

Evaluation of the Optimized Granules

The granules prepared under the optimized operation conditions were evaluated for their mean diameter by using a laser micron sizer; apparent density, tapping density, and angle of repose with a Multi Tester (LMS-30, Seishin Enterprise Co., Ltd. Tokyo, Japan).

The shape and surface of the original and optimized aspirin particles were observed by using the Scanning Electron Microscope.

The particles compressibility was evaluated by determining the tablet tensile strength because the tablet tensile strength was closely linked to the nature of compressed a particles[13]; 250 mg of the optimized granules were compressed into tablets

Table 2. List of data from practical experiments.

	Controlling factors				Experimental results			
Experiment no.	Powder supplied F (g)	Spray liquid concentration C (%)	Spray speed V (g/min)	Spray liquid used W_s (g)	Particle yield Y (%)	Median diameter d_{50} (μm)	Angle of repose θ (°)	Aspirin degradation D (%)
1	300	3	6	800	79.0	178.8	40	0.10
2	500	3	5	800	90.0	160.6	38	0.14
3	500	5	5	800	87.0	168.1	36	0.22
4	500	5	6	1200	90.5	180.8	35	0.25
5	500	5	7	800	92.4	171.7	34	0.21
6	500	5	7	1200	91.5	189.0	35	0.26
7	500	5	7	1500	92.6	202.6	36	0.28
8	800	5	7	1500	94.5	160.5	36	0.27
9	500	7	6	800	88.9	172.3	45	0.31
10	500	7	7	800	90.7	178.8	41	0.34
11	800	7	7	1500	95.2	198.5	37	0.33
12	600	7	7	1000	92.7	195.5	40	0.30
13	600	7	7	1200	93.8	217.0	39	0.34
14	600	7	8	1200	94.0	229.0	38	0.36

with 10-mm flat punches using AUTOGRAPH at pressures of 13, 26, 39, 65, and 104 MPa comparing with the original aspirin powder compressed at the same condition. The measuring method of the tablet tensile strength was the same to the measurement of that set forth above.

The disintegration time of the tablets compressed with the optimized aspirin granules at pressures of 13, 26, 39, 65, and 10 4MPa was determined by using a disintegration tester (Toyama Sanyo Co., Ltd. Tokyo, Japan) according to the disintegration test method described in JPX IV. The test solution was the distilled water maintained at $37 \pm 2^{\circ}$C.

RESULTS AND DISCUSSION

The effects of airflow rate and atomizing flow volume on the resulting particle yield and d_{50} are shown in Figs. 1(a) and (b). In Fig. 1(a), it is clear that the yield was higher when the airflow rate was kept in a suitable level because a suitable airflow rate could ensure the powder flow in the vessel fully. However, if the higher airflow rate was used from the start of granulation, the fine powder would scatter through the bag filters resulting in the loss of yield. As shown in (a), the yield decreased greatly when the airflow rate was increased from 8.33×10^{-3} to $11.1 \times 10^{-3}\,M^3/s$. The average particle diameter distribution indicated that at the lower airflow rate, the fine powder scattering was efficiently decreased, and the powder could flow around vessel and grow in diameter little by little. When the airflow rate was increased, the fine powder attached onto the bag filters and the vessel wall was also increased, so the fine powder could not grow smoothly. The existence of the fine powder in the resulting particles did not affect the yield but caused a decrease in the average diameter. When the airflow rate reached $11.1 \times 10^{-3}\,M^3/S$, a much finer powder was scattered from the bag filters, and only the larger powder particles were granulated, which led to a lower yield and a larger resulting diameter. Figure 1(b) shows that the atomizing flow hardly affected the yield, but the particle diameter was influenced by the atomizing flow volume. The atomizing flow volume determined the spray mist size and the higher the atomizing flow volume was, the smaller the spray mist. In general, the small spray mist can avoid the formation of liquid bridges between particles at contact point and thus avoid the agglomeration.[14]

Figures 2(a) and (b) show the effects of the airflow rate and atomizing flow volume on resulting particle strength. Figure 2(a) indicates that the airflow rate can hardly affect the resulting particle strength, whereas in Fig. 2(b), the resulting particles prepared with the lower atomizing air volume showed lower strength.

The appearances of resulting particles are shown in Figs. 3 and 4, from which it can be seen that the particles prepared with different airflow rates showed little difference in their appearance. However, the

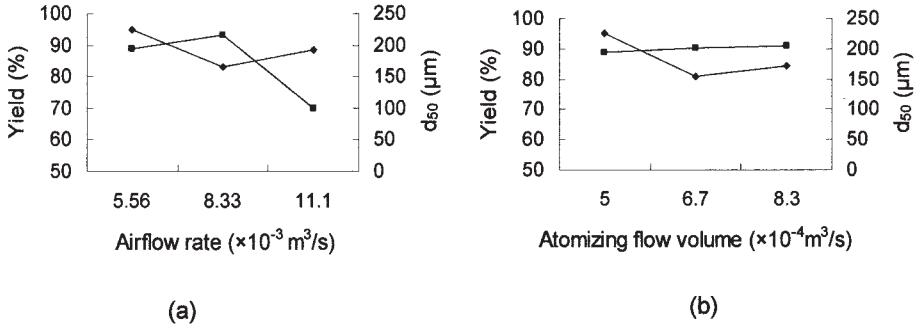

Figure 1. Effects of airflow rate and atomizing flow volume on yield and d_{50}. ■, yield; ◆, d_{50}. (a) Effect of airflow rate (atomizing flow volume $= 5.0 \times 10^{-4}\,m^3/s$). (b) Effect of atomizing flow volume (airflow rate $= 5.56 \times 10^{-3}\,m^3/s$).

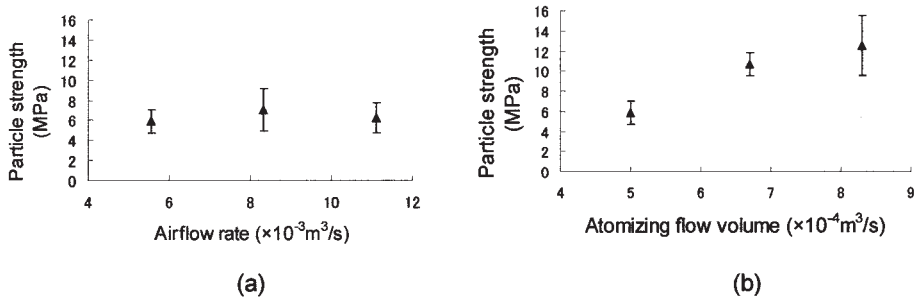

Figure 2. Effects of airflow rate and atomizing flow volume on the resulting particle hardness. (a) Effect of air flow rate (atomizing flow volume $= 5.0 \times 10^{-4}\,m^3/s$). (b) Effect of atomizing flow volume (airflow rate $= 5.56 \times 10^{-3}\,m^3/s$).

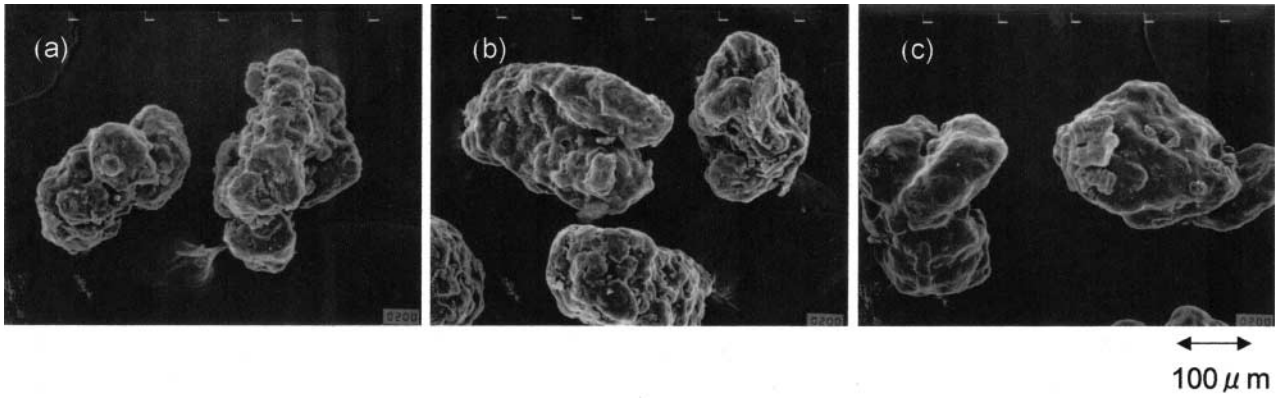

Figure 3. Effects of airflow rate on the resulting particle appearance (atomizing flow volume $= 5.0 \times 10^{-4}\,m^3/s$). (a) Airflow rate $= 5.56 \times 10^{-3}\,m^3/s$. (b) Airflow rate $= 8.33 \times 10^{-3}\,m^3/s$. (c) Airflow rate $= 11.1 \times 10^{-3}\,m^3/s$.

atomizing flow volume affected the appearance greatly. With the same airflow rate, at the lower atomizing volume, the particles were gathered in groups by the small particles linking one by one and the structure was looser. On the contrary, at the higher atomizing volume, the linkage of the small particles was intensive, the formed particles had a smoother surface, and they had a better spherical shape. From these figures, it can also be seen that the particle strength will increase with the increase in the atomizing flow volume, because at the higher atomizing flow volume, the formed particles are of more intensive structure. So through adjusting the atomizing flow volume, particles with a relatively stronger strength and more spherical appearance can be obtained.

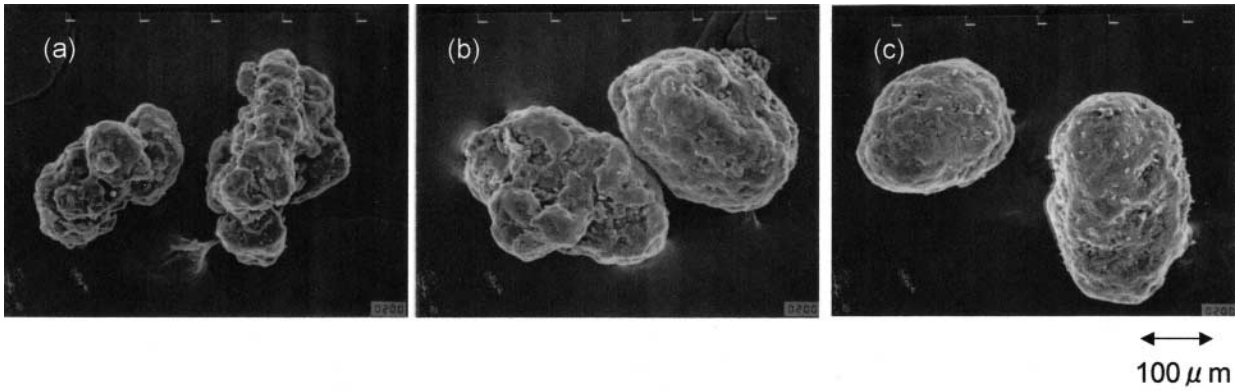

Figure 4. Effects of atomizing flow volume on the resulting particle appearance (airflow rate $= 5.56 \times 10^{-3}\,m^3/s$). (a) Atomizing flow volume $= 5.0 \times 10^{-4}\,m^3/s$. (b) Atomizing flow volume $= 6.7 \times 10^{-4}\,m^3/s$. (c) Atomizing flow volume $= 8.3 \times 10^{-4}\,m^3/s$.

Solid preparations containing aspirin are mainly tablets, so the compressive properties of the resulting aspirin particles were evaluated by using the Kawakita equation as shown in formula (2). The constants a and $1/b$ represent the definitive compressibility and the pressure necessary to reduce the porosity by half, respectively, in another words, a and $1/b$ represent the compression degree of particles in the process of compression. Generally, the higher a is and the lower $1/b$ is, the easier it is to compress the particles. At different airflow rates and different atomizing air volumes, the changes in a and $1/b$ with the compression force are illustrated in Figs. 5 and 6. Figure 5 shows that there were only a few differences in a at various compression forces with the changes in air flow rate, but it increases obviously with the decrease in atomizing air volume. Furthermore, in Fig. 6, the same as shown in Fig. 5, $1/b$ shows little difference at different compression forces with the changes in airflow rate. However, with the increase in atomizing air volume, $1/b$ also shows an increasing tendency, especially at the higher compression force. Based on the analysis of a and $1/b$, it was found that the particles prepared with the tower atomizing air volume were easier to compress. The results also coincide well with that of the particles strength above.

To assess the effects of the resulting particles under different airflow rates and atomizing air volumes on the tablets, the resulting particles were compressed into tablets without any excipient and the tensile strength was investigated, as shown in Figs. 7(a) and (b). As is shown in Fig. 7, there was not so much difference in the tensile strength between the tablets compressed from the particles prepared with different airflow rates, but at the same airflow

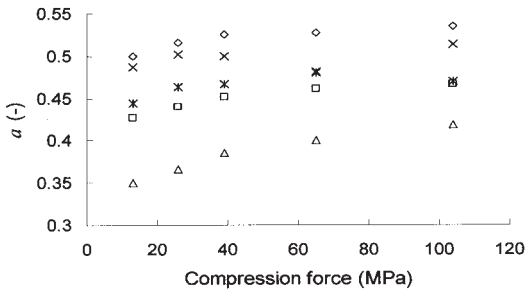

Figure 5. Effects of compression force on a. ◇ Airflow rate $= 5.56 \times 10^{-3}\,m^3/s$, atomizing flow volume $= 5.0 \times 10^{-4} m^3/s$; × Air flow rate $= 8.33 \times 10^{-3}\,m^3/s$, atomizing flow volume $= 5.0 \times 10^{-4}\,m^3/s$; ∗ Airflow rate $= 11.1 \times 10^{-3}\,m^3/s$ atomizing flow volume $= 5.0 \times 10^{-4}\,m^3/s$; □ Airflow rate $= 5.56 \times 10^{-3}\,m^3/s$, atomizing flow volume $= 6.7 \times 10^{-4}\,m^3/s$; △ Airflow rate $= 5.56 \times 10^{-3}\,m^3/s$, atomizing flow volume $= 8.3 \times 10^{-4}\,m^3/s$.

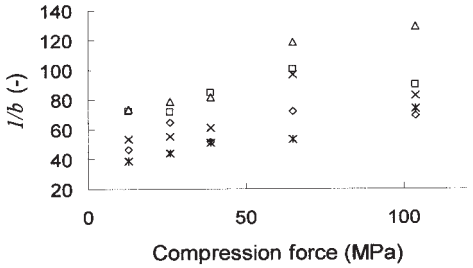

Figure 6. Effects of compression force on $1/b$. ◇ Airflow rate $= 5.56 \times 10^{-3}\,m^3/s$. ◇, Atomizing flow volume $= 5.0 \times 10^{-4}\,m^3/s$. ×, Airflow rate $= 8.33 \times 10^{-3}\,m^3/s$, atomizing flow volume $= 5.0 \times 10^{-4}\,m^3/s$. ∗, Airflow rate $= 11.1 \times 10^{-3}\,m^3/s$, atomizing flow volume $= 5.0 \times 10^{-4}\,m^3/s$. □, Airflow rate $= 5.56 \times 10^{-3}\,m^3/s$, atomizing flow volume $= 6.7 \times 10^{-4}\,m^3/s$. △, Airflow rate $= 5.56 \times 10^{-3}\,m^3/s$, atomizing flow volume $= 8.3 \times 10^{-4}\,m^3/s$.

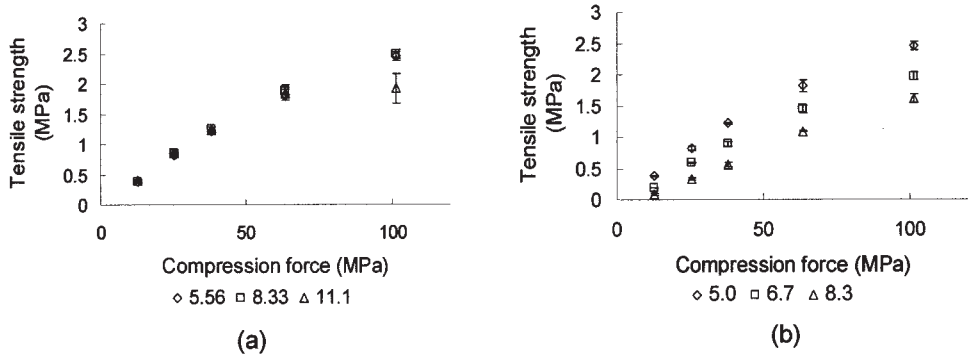

Figure 7. Effects of airflow rate and atomizing flow volume on the resulting particle compressibility. (a) Effect of airflow rate (atomizing flow volume $= 5.0 \times 10^{-4}\,m^3/s$). (b) Effect of atomizing flow volume (airflow rate $= 5.56 \times 10^{-3}\,m^3/s$).

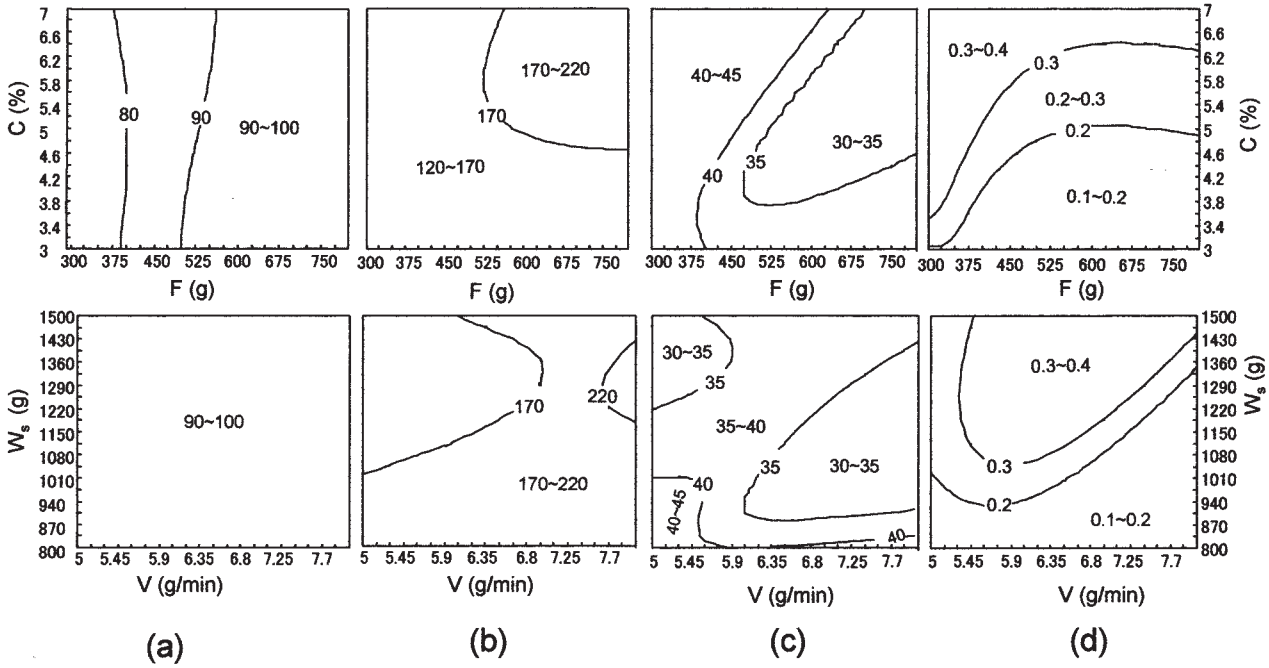

Figure 8. Relationship between controlling factors and response variables. (a) Effect of controlling factors on yield (%). (b) Effect of controlling factors on granule diameter (μm). (c) Effect of controlling factors on angle of repose (°). (d) Effect of controlling factors on aspirin degradation (%).

rate, the particles prepared with the lower atomizing flow volume made the tablets show higher tensile strength.

In this study, from the point of view for the preparation of tablets, particles with a high yield, suitable size, and good compressibility are desired, so the airflow rate was decided at $5.56 \times 10^{-3}\,m^3/s$. and the atomizing flow volume was fixed at $5.0 \times 10^{-4}\,m^3/s$.

On the basis of the fixed conditions of airflow rate and atomizing flow volume, the relationship between the resulting particle properties and the other operation conditions such as the binder concentration and the amount of binder supplied were analyzed by the ANN method. The operation conditions are shown in Table 2. The relationships between the selected controlling factors and the response variables are analyzed through contour figures, which are shown in Fig. 8. From this figure, it can be seen that there was a good correlation between the amount of powder supplied and the yield. The more the amount of supplied powder was, the higher the yield. The median diameter of particles increased with increasing spray liquid concentration and the spray rate.

However, because of the low hydrophilic property, aspirin particles showed a low growth in the whole process of granulation. The flowability of aspirin granules showed complex changes and mainly depended on the spray liquid concentration and the amount of spray liquid used. With advancing granulation, the amount of fine powder was decreased, and the particle surface became smooth, resulting in an improvement in flowability. However, an increase in the spray liquid used was not advantageous to the stability of aspirin because aspirin could be easily hydrolyzed under conditions of high temperature and high moisture content. Based on these analyses, the optimum operation conditions were determined by superimposing the contour figures, as shown in Figs. 9 (a) and (b). From Fig. 9, an optimum operation condition was selected as 650 g of supplied powder, 5% of HPMC solution, 7.5 g/min of spray rate, and 1000 g of binder used. A comparison between the optimized granules prepared with this condition and original powder is shown in Table 3, and from these results, it was clear that the optimized granules had better physical properties than those of the original powder. The SEM photographs of aspirin before and after granulation are shown in Fig. 10.

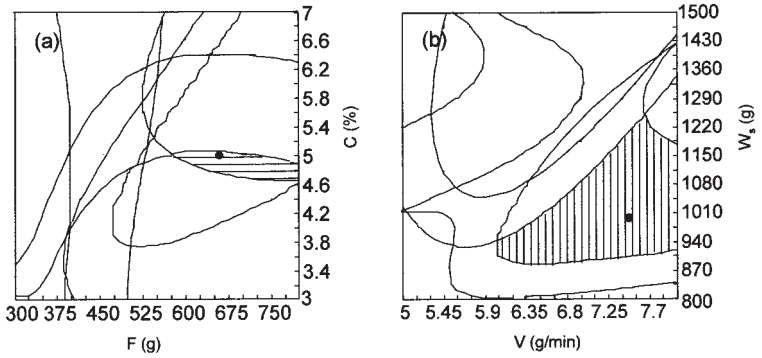

Figure 9. Optimum region of d_{50}(170∼220 μm), Y(90∼100%), θ(30∼35°), $D(s(g)$ ●: V, 7.5 g/min; W_s, 1000 g.

Table 3. Properties of aspirin before and after granulation.

	d_{50} (μm)	Angle of repose (°)	Loose density (g/cm^3)	Tapping density (g/cm^3)	Compressibility (%)	Degradation (%)
Before	123.5	50	0.639	0.835	23.5	< 0.01
After	180.2	34	0.624	0.726	14.0	< 0.1

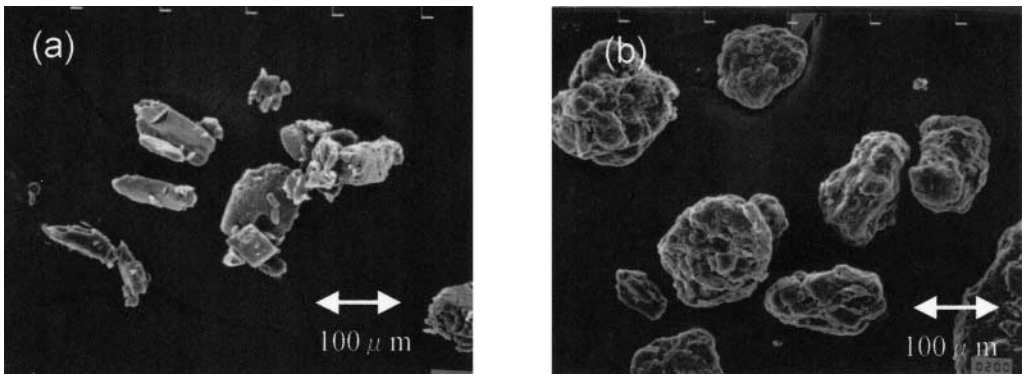

Figure 10. The SEM photos of original aspirin powder and granulation particles. (a) Original powder. (b) Particles after granulation.

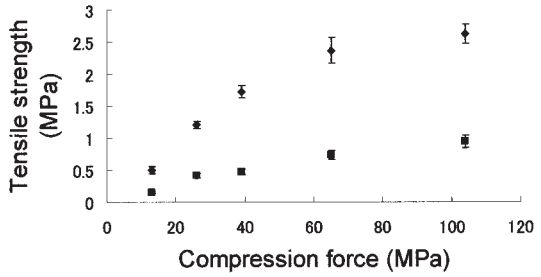

Figure 11. Comparison of compressibility between optimized particles and original powder. ◆, Tablets prepared from optimized aspirin particles. ◆, Tablets prepared from original aspirin powder.

Furthermore, the theoretical aspirin content was 92.3%, and the practical content was about 90.0%. When the particles are prepared into tablets, the good physical properties can decrease the amount of excipients required such as the fillers and lubricants. The good flowability and the high drug content also indicate that the optimized particles cannot only be compressed into tablets but also be coated with functional high molecular polymer as the core particles.

To evaluate the compressibility of the optimized particles, the relationship between the compression force and tensile strength of tablets compressed with the optimized particles was investigated, as shown in Fig. 11. Through comparing with the original powder, it was found that the tablets compressed with the optimized particles showed about twice the tensile strength of those prepared with the original powder. Furthermore, the tablets prepared with the optimized granules showed a higher tensile strength even if compressed at a relatively lower compression force such as 26 or 39 MPa.

A disintegration test of the tablets prepared from the optimized particles was conducted, but the tablets compressed at any compression force disintegrated over 900 sec. This indicated that some suitable disintegrant needs to be added when the particles are compressed into tablets.

CONCLUSIONS

With a Wurster fluidized bed, high drug content granules with desired properties can be prepared by adjusting the operation conditions. The resulting granules possess excellent flowability, suitable size, good compressibility, and high drug content, which will help to decrease the amount of excipient required to miniaturize solid dosage forms.

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REFERENCES

1. Tasaka, M.; Sunada, H.; Yonezawa, Y. Characterization of core particles for film coating with high active ingredient content. J. Pharm. Sci. Technol. Jpn. **1999**, *59*, 57–66.
2. Tsujimoto, H.; Nagata, K.; Yokoyama, T.; Kamata, T.; Terashita, K.; Miyanami, K. Preparation of core particles with high drug content from slurry materials using a direct granulation method with a fluidized bed granulator. J. Soc. Powder Technol. Japan. **2000**, *37*, 107–144.
3. Elwood, P.C. Aspirin: past, present, and future. Clin. Med. **2001**, *1*, 132–137.
4. Elwood, P.C. Reducing the risk: heart disease, stroke and aspirin. J. Med. Assoc. Thai. **2001**, *84*, 1164–1174.
5. Santoni, G.; Fabbri, L.; Grantteri, P.; Renzi, G.; Pinzauti, S. Simultaneous determination of aspirin, codeine phosphate, and propyphenazone in tablets by reversed-phase high-performance liquid chromatography. Int. J. Pharm. **1992**, *80*, 263–266.
6. Leslie, P.J.; Dyson, E.H.; Proudfoot, A.T. Opiate toxicity after self poisoning with aspirin and codeine. B. M. J. **1986**, *292*, 96.
7. Osako, Y.; Fukumori, Y. Effect of operation condition on the particle size distribution of granules in the wurster fluidized bed granulation. Pharm. Tech. Japan **1990**, *6*, 85–91.
8. Watano, S.; Takashima, H.; Miyanami, K. Scale-up of agitation fluidized bed granulation by neural network. Chem. Pharm. Bull. **1997**, *45*, 1193–1197.
9. Bi, Y.; Yonezawa, Y.; Sunada, H. Rapidly disintegrating tablet prepared by the wet compression method: mechanism and optimization. J. Pharm. Sci. **1999**, *88*, 1004–1010.
10. Adans, M.J.; Mullier, M.A.; Sevelle, P.K. Agglomerate strength measurement using a

uniaxial confined compression test. Powder Technol. **1994**, *78*, 5–13.

11. Shimada, Y.; Sunada, M.; Mizuno, M.; Yonezawa, Y.; Sunada, H.; Yokosuka, M.; Kimura, H.; Takebayashi, H. Measurement of the adhesive force of fine particles on tablet surface and method of their removal. Drug Dev. Ind. Pharm. **2000**, *26*, 149–158.
12. Takahara, J.; Takayama, K.; Isowa, K.; Nagai, T. Multi-objective simultaneous optimization based on artificial neural network in a ketoprofen hydrogel formula containing *O*-ethylmenthol as a percutaneous absorption enhancer. Int. J. Pharm. **1997**, *158*, 203–210.
13. Ejiofor, O.; Esezobo, S.; Pilpel, N. The plasto-elasticity and compressibility of coated powders and the tensile strengths of their tablets. J. Pharm. Pharmacol. **1985**, *38*, 1–7
14. Jones D. Air suspension coating for multi-particulates. Drug Demo. Ind. Pharm. **1994**, *20*, 3175–3206.