Preparation of Core Particles for Aqueous Film Coating Using Agitation Fluidized Bed

Satoru WATANO,*[,a] Kengo ANDO,[a] Kei MIYANAMI,[a] Yoshinori II,[b] and Seiei SASATANI[b]

Department of Chemical Engineering, Osaka Prefecture University,[a] 1–1 Gakuen-cho, Sakai, Osaka, 593 Japan, and Ono Pharmaceutical Co., Ltd.,[b] 3–1–1 Sakurai, Shimamoto-cho, Mishima-gun, Osaka 618, Japan.
Received April 30, 1997; accepted July 31, 1997

Core particles used for aqueous film coating were prepared by agitation fluidized bed granulation, and effect of the damping speed on the granule properties of mass median diameter, geometric standard deviation, apparent density, yield, friability and specific surface area were investigated. Film coating by an aqueous acrylic copolymer (Eudragit NE-30D) was carried out using the core particles granulated under three levels of damping speeds, and the drug release properties of each coated product were identified. Relationship between properties of core particles and the drug release properties were clarified and the optimal granulation conditions to make optimal core particles for film coating were determined.

Key words core particle; granulation; agitation fluidized bed; damping speed; film coating; drug release property

Conventional film coating processes for oral drugs have generally been conducted using spherical core particles. It is well known that properties of the particles greatly influence the characteristics of the coated products, however, there have been few reports describing the relationship between properties of core particles and those of the coated products.

An agitation fluidized bed[1–3] developed for multi-purpose usage has frequently been used especially in the pharmaceutical and food industries for the following reasons: i) It has many advantageous points of effective heat and mass transfer, high contact efficiency and good mixing characteristics; ii) it can perform mixing, granulation, coating and drying processes in a single unit, saving processing time, space and costs; iii) contamination by dust can also be eliminated. If we are able to establish a continuous system of mixing, granulation, coating and drying in a single agitation fluidized bed, excellent production efficiency can be expected.

In this study core particles were granulated and an aqueous film coating was applied to the particles using an agitation fluidized bed to learn the effects of core particle properties on the properties of coated granules. With agitation fluidized bed granulation conducted at various damping speeds, the effect of each speed on the properties of granulated particles was determined. After sieving the granulated particles, an aqueous film coating was carried out using an aqueous acrylic copolymer, and effects of the core particle properties on the drug release of the coated products were identified. Optimal granulation conditions were elucidated for the aqueous film coating, and the possibility of continuous operation from mixing, granulation, coating to drying was also evaluated.

Experimental

Materials Table 1 lists powder samples used for granulation. Water-soluble thiamin hydrochloride was used as a model drug. A mixture of manitol, cornstarch, and crystalline cellulose (the mixing ratio was 7:2:1) was used as an excipient. Hydroxypropylcellulose as a binder was added to the powder samples before granulation. Purified water was adopted as a binder liquid, which was sprayed through a binary nozzle located 100 mm above the bed bottom. Using the powder samples listed in Table 1, granulation was conducted to produce core particles before film coating. The core particles produced were sieved into the range from 180 to 850 μm, which was used for the coating experiments.

Table 2 shows materials used for the spraying liquid. Aqueous dispersion of a methyl meta-acrylate·ethyl acrylate copolymer (Eudragit NE-30D, Rohm Pharma), with a dissolution property was irrelevant to pH, was adopted as the coating material. The spraying liquid also contained 0.5% of triethyl citrate as a plasticizer and 2.5% of talc as a dispersant. Minimum film forming temperature (MFT) and glass transition temperature of the copolymer were both less than 273 K.

Equipment An agitation fluidized bed[3,4] (NQ-125, Fuji Paudal Co., Ltd.), equipped with an agitator blade at the bottom, was used for granulation and coating. An air distributor composed of three circular plates was installed under the blade, and heated air was blown through the plate to fluidized particles. The particles in this bed were also agitated as they were fluidized, thus granules during granulation were made spherical, and film during coating received favorable tumbling and compacting effects from the agitator rotation.

The operational variables were continuously measured, and the main variables of agitator rotational speed, air flow rate and inlet air temperature were automatically controlled to maintain stable operation. The main operating conditions are listed in Table 3; these were optimized previously.[3]

Method The granulation experiment was conducted as follows: Starting materials listed in Table 1 were fed into the agitation fluidized bed, then mixed by agitating and fluidizing for 180 s. After the mixing

Table 1. Starting Materials for Granulation

Thiamine Hydrochloride[a]	9.0 g
Mannitol[b]	203.7 g
Cornstarch (ST-C)[c]	58.2 g
Crystalline cellulose (PH-101)[d]	29.1 g
Hydroxypropylcellulose (HPC-L)[e]	15.0 g
(Total)	315.0 g

a) Katayama Chemical Industrial Co., Ltd. *b*) Towa Chemical Industrial Co., Ltd. *c*) Nichiden Chemical Co., Ltd. *d*) Asahi Chemical Industrial Co., Ltd. *e*) Nippon Soda Co., Ltd.

Table 2. Component of Spray Water

Eudragit NE30D	66.7%
Triethyl citrate	0.5%
Talc	2.5%
Purified water	30.5%
(Total)	100.0%

* To whom correspondence should be addressed.

Table 3. Operating Conditions

	Granulation	Coating
Fluidizing air velocity	1.0 m/s	1.0 m/s
Fluidizing air temperature	313 K	303 K
Agitator rotational speed	450 rpm	300 rpm
Spary air pressure	8×10^4 Pa	8×10^4 Pa
Spray method	Top spray	Side spray
Operating moisture content	21%	9%

was over, a binary nozzle began to spray water. When the operational moisture content measured by an IR moisture sensor (Fuji Paudal Co., Ltd.)[4,5] reached 21%, spraying was stopped and a drying process started. After the drying, granules obtained were evaluated and several physical properties were examined. The granules were then sieved to sizes ranging from 180 to 850 μm to produce core particles used for the next coating experiments.

In the coating experiments, the core particles were first dampened with water to 9%, then the coating liquid listed in Table 2 was sprayed on them while moisture content was maintained at 9%. Thereafter the coated products were dried in a vessel.

Evaluation of the Coated Particles Mass median diameter, geometric standard deviation, and yield of granules were calculated by sieve analysis with a row-tap shaker. The mass of granules on each sieve was weighed, then mass based particle size distribution was computed using a log-normal distribution. The yield used here was defined as the mass fraction within the particle size d_p of $180\,\mu m \leqq d_p < 850\,\mu m$.

Apparent density of granules was measured using a powder tester (Hosokawa Micron Co., Ltd.).

Friability of the granules was evaluated as follows: 25 g of the granulated products which had already been sieved to sizes ranging from 180 to 850 μm were fed into a friabilator (4G18, Kayagaki Industrial Co. Ltd.) with 25 g of glass beads (diameter was 7 mm), and rotated at 25 rpm for 20 min. The weight percent of the fraction that would then go through 200 mesh was measured.

Specific surface area of the coated granules was measured by an automatic surface area analyzer (Model 4200, Nikkisou) based on the principle that the number of nitrogen molecules attached to the surface was indicative of the area.

Dissolution tests of the coated particles were performed in 900 ml of purified water using a paddle method (dissolution tests, J.P. XII, 100 rpm and 37 °C). The release of drug (thiamine hydrochroride) was analyzed spectrophotometrically and continuously at 246 nm.

Results and Discussion

Preparation of Core Granules by Agitation Fluidized Bed Granulation Figure 1 shows the temporal change in moisture content during granulation.

Variation of the damping speed during granulation was done using 3 levels of water flow rate (F=10,12 and 15 g/min).

Figures 2, 3 and 4 illustrate mass median diameter, geometric standard deviation, yield, apparent density, friability and specific surface area of granules as a function of water flow rate. With a decrease in the liquid flow rate, granule mass median diameter, yield and apparent density increased, while geometric standard deviation, friability and specific surface area of granules decreased. The decrease in the water flow rate resulted in an increase of granulation time (damping process) as shown in Fig. 1, and this time increase was assumed to greatly affect granule properties.

When the granulation time increased, frequency of adhesion increased, and granule adhesion and growth were promoted. Mass median diameter and yield of granules thus increased with time.[6,7] Also, ungranuated fine particles were easily consumed due to adhesion, thus

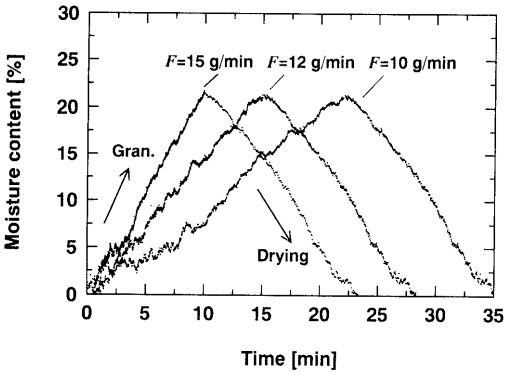

Fig. 1. Temporal Change in Moisture Content during Granulation

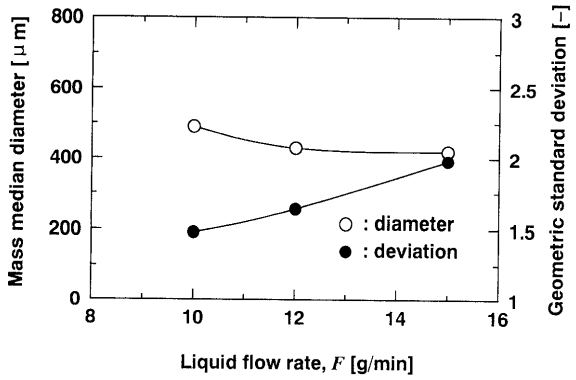

Fig. 2. Mass Median Diameter and Geometric Standard Deviation as a Function of Water Flow Rate

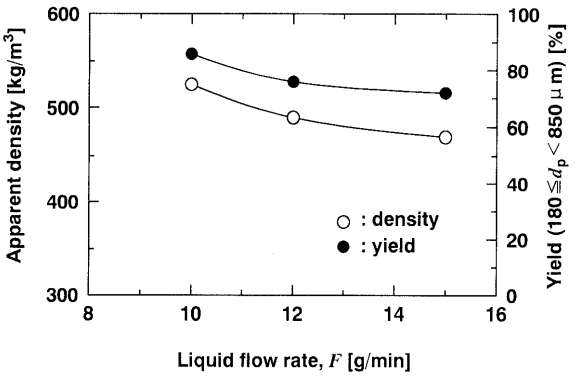

Fig. 3. Apparent Density and Yield of Granules as a Function of Water Flow Rate

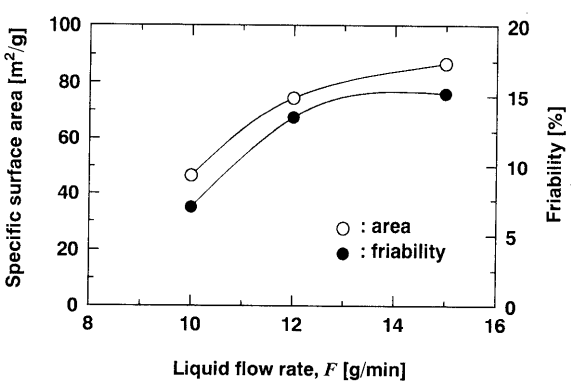

Fig. 4. Specific Surface Area and Friability of Granules as a Function of Water Flow Rate

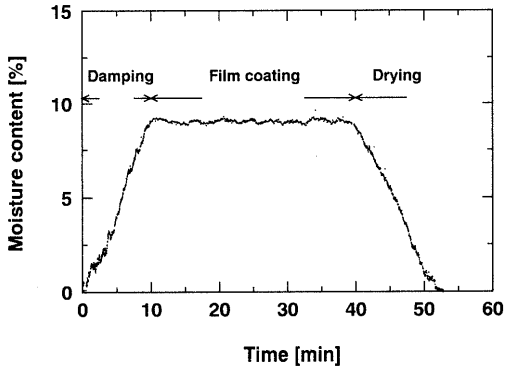

Fig. 5. Temporal Change in Moisture Content during Coating Process

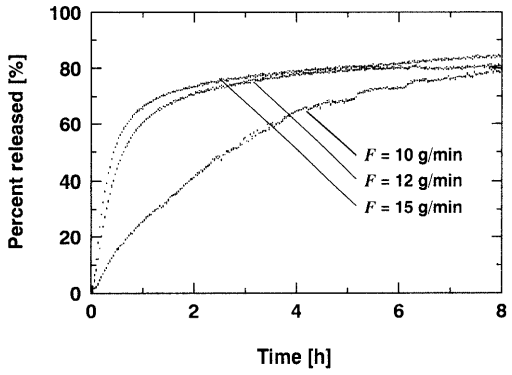

Fig. 7. Drug Release Properties at Various Water Flow Rates (Coating Level = 30%)

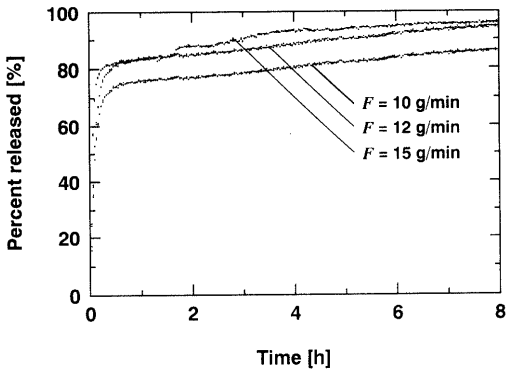

Fig. 6. Drug Release Properties at Various Water Flow Rates (Coating Level = 10%)

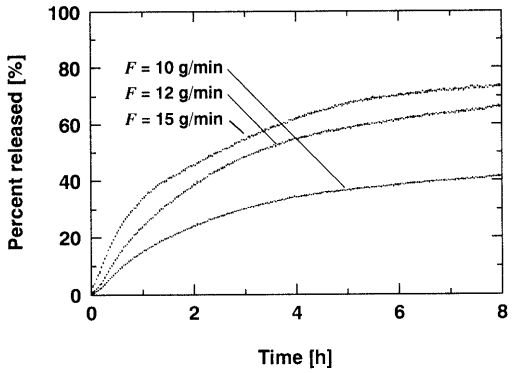

Fig. 8. Drug Release Properties at Various Water Flow Rates (Coating Level = 50%)

particle size distribution narrowed, and the geometric standard deviation of granules became small.[6,7]

Time increase also caused a rise in the number of collisions between granules and the agitator blade, making the granules well compacted and spherical.[8] The apparent density thus increased, while friability and specific surface area decreased.

Scanning Electron Microscope (SEM) observation showed that granules having a specific surface area larger than $60\,m^2/g$ were rather porous and their shape was far from spherical. However, the surface of those having a surface area nearly $40\,m^2/g$, was smooth and granules could be used for core particles in the film coating.

Effects of Granule Properties on Drug Dissolution Properties Our aim in this study was to produce the following coated granules: (i) Those with a dissolution rate of under 50% in 4 h and almost 100% at 8 h; this target was based on the absorption rate of the drug and dosage regimen: (ii) We also sought to reduce the amount of polymer in order to decrease cost. These factors were determined to create an optimal condition.

Figure 5 illustrates the temporal change in moisture content during the film coating process. As described earlier, moisture content during coating was maintained at 9%. This level has been previously determined based on results showing maximum coating efficiency and relatively small agglomeration tendency.

Figures 6, 7 and 8 show the drug dissolution characteristics under various liquid flow rates of granulation, F, and coating levels. It can be seen that drug dissolution was more suppressed when the liquid flow rate during granulation was minimal (longer granulation time), regardless of coating levels. This was due to the properties of granules: when the liquid flow rate was low, friability and specific surface area of granules were both small. Small friability prevented crushing of the granule surface, and prevented crushed any fine granules from adhering again to the film during coating. Small specific surface area could make a thick film. Both advantages served to suppress the release of drug from the film. Comparison of the results of Figs. 6, 7 and 8, shows that the coating should be done to a 30% level with minimal liquid flow rate during granulation to achieve the above mentioned drug dissolution characteristics.

Excellent reproducibility of drug release properties was obtained when we applied the moisture control method to the granulation and coating processes.

The agglomeration tendency was rarely observed if the coating level was increased. However, this tendency lessened with the slowing of water flow rate (longer granulation time). As mentioned, granule growth progressed and the amount of ungranulated fine granules decreased with the decrease in water flow rate. Therefore, spraying of the coating liquid prevented the agglomeration.

Core particles used for film coating thus should be well compacted and their specific surface area and friability small, to produce coated products with good drug dissolution characteristics. Granulation should be done with a low liquid flow rate to produce optimum core particles for film coating.

Conclusion

Core particles were granulated and aqueous film was coated onto the particles using an agitation fluidized bed. Agitation fluidized bed granulation on granule properties conducted at a low liquid flow rate (long granulation time) resulted in large granule size and density, while size distribution, friability and specific surface area were small. This also resulted in strong suppression of drug release from the coated granules. The quality of the coated particles was therefore greatly dependent on the granulation procedure.

References

1) Masuda Y., *Powder Sci. Eng.*, **28**, 61—69 (1996).
2) Hirayama M., Ohkuma M., Abstract of Papers, Fluidized Bed Processing for Functional Powder Materials, Osaka, November 1994, p. 15.
3) Watano S., Yoshikawa K., Miyanami K., *Chem. Pharm. Bull.*, **42**, 663—667 (1994).
4) Watano S., Miyanami K., *Powder Technol.*, **83**, 55—60 (1995).
5) Watano S., Takashima H., Yasutomo T., Miyanami K., *Chem. Pharm. Bull.*, **44**, 1267—1269 (1996).
6) Watano S., Morikawa T., Miyanami K., *Chem. Pharm. Bull.*, **43**, 1764—1771 (1995).
7) Watano S., Morikawa T., Miyanami K., *Chem. Pharm. Bull.*, **44**, 409—415 (1996).
8) Watano S., Morikawa T., Miyanami K., J. *Chem. Eng. Jpn.*, **28**, 171—178 (1995).