Effect of Spray Mist Size on the Properties of Granules Prepared by Agitation Fluidized Bed Coating

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In this contribution, an organic solvent-based enteric coating was made using an agitation fluidized bed. Core spherical particles containing an aqueous pigment were coated with an enteric methacrylate–methyl methacrylate copolymer dissolved in an ethanol solution using an agitation fluidized bed under various spray mist sizes. Physical properties of coated granules such as the drug release properties, the specific surface area and the coating efficiency were investigated. The effect of spray mist size on the properties of coated granules was investigated and the film forming mechanism in agitation fluidized bed coating was discussed. The optimum operating conditions were also determined.

Key words enteric coating; agitation fluidized bed; spray mist size; drug release property; film forming mechanism

Conventional film coating processes for oral drugs have generally been conducted with an organic solvent-based system because of its favorable drying efficiency. It is used to control the drug release rate, to mask bitter taste and to add some effective functions to granules.

Recently, these operations have frequently been carried out using a fluidized bed,[1,2] because it has many advantageous points in effective heat and mass transfer, high contact efficiency and good mixing characteristics. Masuda[3] proposed a new coating method using a fluidized bed, and stated that effective coating could be done using the side spray method. Ohkuma *et al.*[4-6] applied a centrifugal fluidized bed to the coating method using highly concentrated coating solution, and concluded that the combination of the coating apparatus and the optimum operating conditions realized the effective coating. Some studies also suggested that film coating should be done using spray mist of small size. However, quantitative analyses regarding the effect of spray mist size on the properties of coated granules and the coating efficiency have not been well conducted. Also, the effect of spray mist size on the properties of granules in a fluidized bed coating with agitation function has not been sufficiently investigated.

In this study, an organic solvent-based enteric coating was done using an agitation fluidized bed. The effect of spray mist size on the properties of granules was analyzed quantitatively, and the film forming mechanism in the agitation fluidized bed coating was discussed. The optimum operating conditions for the enteric coating were determined.

Experimental

Materials As core particles, spherical granules made of crystalline cellulose (Celphere CP507, Asahi Chemical Industry Co., Ltd.) with a mean particle diameter of 600 μm and a true density of 1070 kg/m^3 were used. Before experiments, the core granules were sieved to have their sizes between 500 and 850 μm.

An organic solvent based enteric methacrylate–methyl methacrylate copolymer (Eudragit L-100, Rohm Pharma) was adopted as the coating material. The organic-based spray liquid in this study contained 10% of the copolymer, 1.0% of polyethyleneglycol (PEG 6000) as a plasticizer, and 3.1% of talc as a dispersant (Table 1).

Equipment Figure 1 shows the experimental setup used. An agitation fluidized bed[7] (NQ-160, Fuji Paudal Co., Ltd.), equipped with an agitator blade at the bottom was used for the coating operation. An air distributor composed of three circular plates was installed under the blade, and heated air was blown through the plate to fluidize particles. The particles in this bed were also agitated while fluidizing, thus, the film during coating received favorable tumbling and compacting effects from the agitator rotation.

The operational variables were continuously measured, and the main operational variables of agitator rotational speed, air flow rate and inlet air temperature were feedback controlled to maintain stable operation. The operating conditions are listed in Table 2.

Method The coating experiment was conducted as follows: Core

Table 1. Component of Spray Liquid

Component	Mixing ratio (%)	Mixing weight (kg)
Eudragit L100	10.0	0.210
PEG 6000	1.0	0.021
Talc	3.1	0.065
Ethanol	67.7	1.421
Purified water	18.2	0.380
(Total)	100.0	2.100

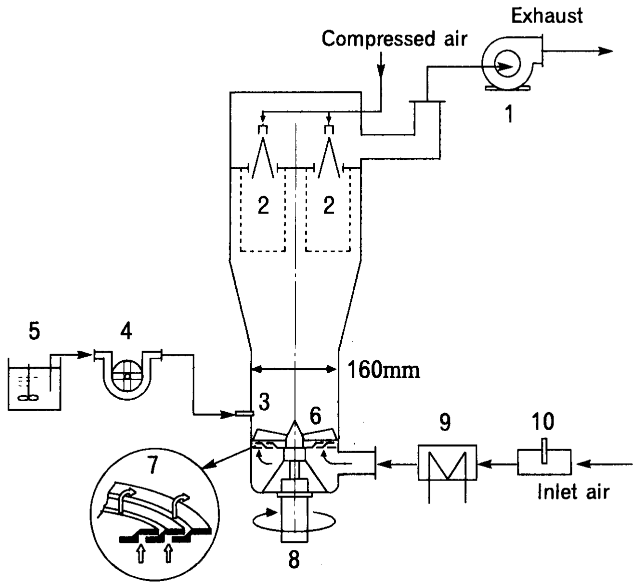

Fig. 1. Schematic Diagram of Experimental Setup

1, blower; 2, bag filter; 3, spray nozzle; 4, feed pump; 5, coating liquid; 6, agitator blade; 7, slit plate; 8, motor; 9, heater; 10, anemometer.

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Table 2. Operating Conditions

Fluidizing air velocity	1.0	m/s
Agitator rotational speed	300	rpm
Liquid flow rate	6—36	g/min
Fluidizing air temperature	313	K
Spray air pressure	0.8×10^5—1.5×10^5	Pa
Nozzle insert (i.d.)	0.7	mm

particles of 0.7 kg were first undercoated with a water solution of pigment (Blue No. 1, Toushoku Pigment Co., Ltd.) selected as a model drug. Once the particles in the coater were dry, 2.1 kg of the spray liquid (coating level was 30%), was sprayed while a constant feed speed was maintained. After having sprayed the liquid, the coated particles were dried in the coater. A side spraying method[3] was used in this study.

Evaluation of the Coated Particles Size of the spray mist was measured using the He–Ne laser scattering method (LDSA-1300A Meiwashoji Co., Ltd.) at various liquid flow rates and air pressures under room temperature and humidity.

Agglomeration tendency of the coated granules was defined as a mass fraction larger than 850 μm based on a preliminary experiment.[8]

Dissolution tests of the coated particles were performed in 900 ml of JP 1st and 2nd fluids using a paddle method (dissolution tests, JP XII, 100 rpm and 37 °C). The release of drug (pigment blue No. 1) was analyzed spectrophotometrically and continuously at 630 nm.

Specific surface area of the coated granules was observed 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.

Coating efficiency was calculated as mass ratio of the polymer attached to the granules to the amount of polymer sprayed throughout the coating operation. The mass of the polymer actually attached to the granules was measured by dissolving the film in an alkali solution.

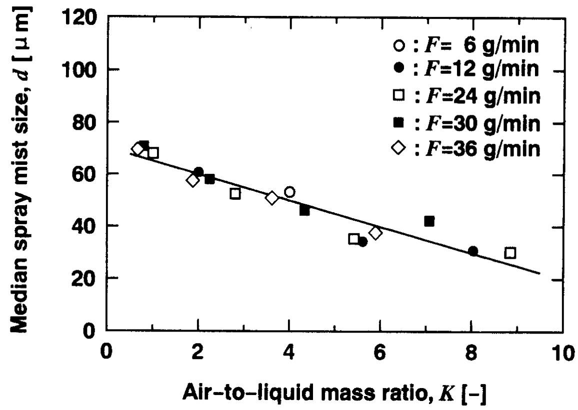

Fig. 2. Effect of Air-to-Liquid Mass Ratio on Median Spray Mist Size

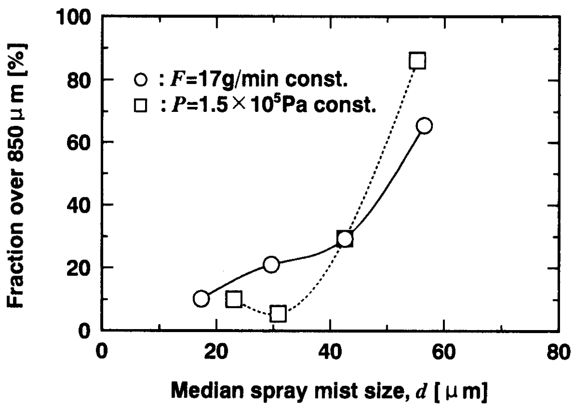

Fig. 3. Effect of Median Spray Mist Size on Agglomeration Tendency

Results and Discussion

Measurement of Spray Mist Size Figure 2 shows the relationship between spray air-to-liquid mass ratio[9] and spray mist size at various liquid flow rates, F, using 10% solution of Eudragit L-100.

As seen, an increase in the air-to-liquid mass ratio resulted in a smaller spray mist size, due to the more intense contact between the liquid and the pneumatic air. Also, a linear relationship was found between spray mist size and the air-to-liquid mass ratio at various liquid flow rates. Since the same relationship was obtained if the spray air pressure varied, the spray mist size could presumably be estimated only by the air-to-liquid mass ratio.

Effect of Spray Mist Size on the Properties of Coated Granules Figure 3 indicates the relationship between agglomeration tendency and spray mist size. Here, circles show the data under constant liquid flow rate ($F=17$ g/min) at various spray air pressures, P, ($0.8\times10^5 \leqq P \leqq 2.0\times10^5$ Pa), and squares show the data under constant spray air pressure ($P=1.5\times10^5$ Pa) at various liquid flow rates ($6\leqq F\leqq 36$ g/min). In these experiments, spray air pressure or liquid flow rate was changed properly to maintain a constant spray mist size.

As can be seen from Fig. 3, the agglomeration tendency increased with an increase in spray mist size, regardless of liquid flow rate and spray air pressure. This phenomenon can be explained as follows: when the mist was sprayed onto the granule surface, the organic solvent was evaporated simultaneously and the dissolved polymer was made into smooth film. In this case, however, there was a good possibility of colliding with other granules, and at this time, the spray mist effectively acted as a binder to adhere to both granules. Since the large spray mist could formulate a large liquid bridge between granules,[10] the possibility to formulate agglomerate increased. Therefore, an increase in the spray mist size resulted in a promotion of agglomeration tendency. This tendency was more influenced by the liquid flow rate increase rather than the air pressure increase. Although the same sized spray mist would make the same sized liquid bridge between the granules, the adhesion force by the liquid bridge was assumed to be the same. However, an increase in the liquid flow rate caused an increase in the number of spray mist particles adhering to granules in a unit of time. The agglomeration tendency increased remarkably as the liquid flow rate increased, while the spray mist size was kept constant. The phenomenon that the agglomeration tendency increased again when the spray mist size was small under constant spray air pressure was due to static electricity in a rather dry condition.

Figure 4 shows the effect of spray mist size on R_{2h}, which was defined as the amount of drug release after a 2 h dissolution test in the JP 1st fluid. Figure 5 expresses the effect of spray mist size on t_{75}, which was defined as the time required to release 75% of the total amount of the drug in the JP 2nd fluid. Here, the control value of R_{2h} and t_{75} of the granules without coating were 100% and 0.3 min, respectively. An increase in spray mist size resulted in the progress of acid-proof and sustained-release properties under various liquid flow rates and spray air pressures. These results were thought to be contrary to

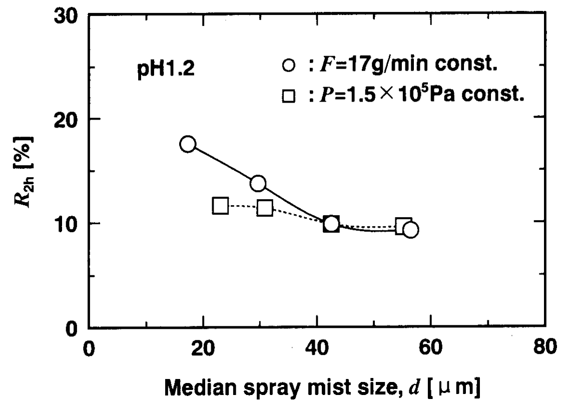

Fig. 4. Effect of Median Spray Mist Size on R_{2h}

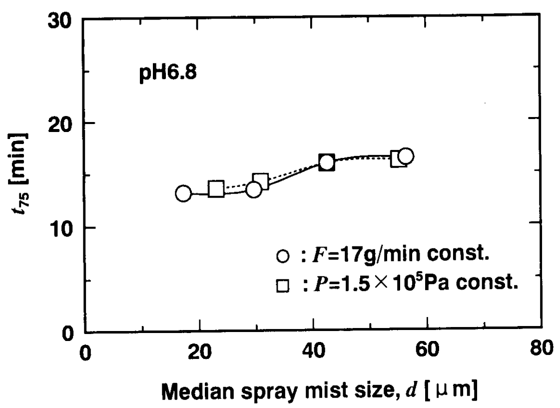

Fig. 5. Effect of Median Spray Mist Size on t_{75}

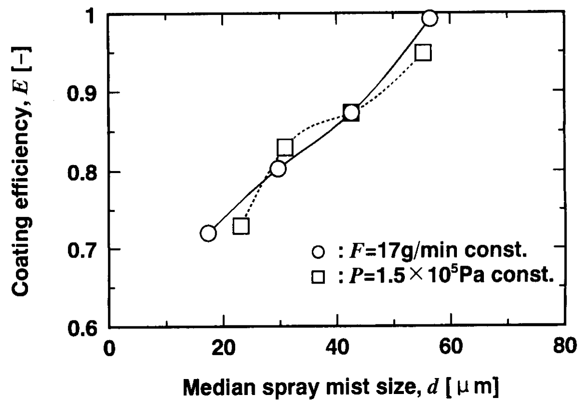

Fig. 6. Effect of Median Spray Mist Size on Coating Efficiency

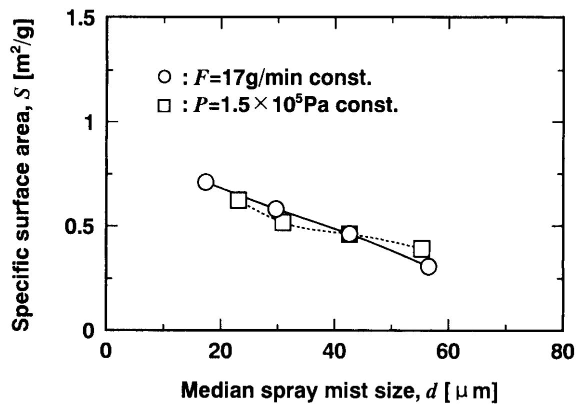

Fig. 7. Effect of Median Spray Mist Size on Specific Surface Area

those obtained by the typical fluidized bed coating method.[1,2] In the following, the film forming mechanism in agitation fluidized bed coating is discussed.

Figures 6 and 7 indicate effect of spray mist size on the coating efficiency and the specific surface area of granules, respectively. As seen in Fig. 6, an increase in the spray mist size resulted in greater coating efficiency and a decrease in the specific surface area. If the spray mist size decreased, the interfacial surface area of the mist increased remarkably, and spray drying, in which the mist was dried before adhering to the particles, occurred. This caused lower coating efficiency.

As can be seen from Fig. 7, an increase in the spray mist size resulted in a decrease in the specific surface area. Although this N_2 absorption method for the measurement of specific surface area had a possibility to measure inside voidage, the coated granules had smooth surfaces and well compacted film layer when the spray mist size was large. This was because the large spray mist required a longer time to dry, thus an adequate tumbling effect was achieved by the agitator rotation and the film was spread favorably. These results were the same as the experimental data shown by Ohkuma *et al.*[4-6] who also used a fluidized bed equipped with a rotating disk.

By contrast, in the typical fluidized bed coating, since the granules experienced no effect of tumbling, the rough and low density film was supposed to be produced when the spray mist size was large. In this case, the mist should be small to make smooth film.

Considering again the agglomeration tendency and the drug release properties, the acid-proof and sustained-release properties progressed with an increase in spray mist size, however, the agglomeration tendency increased. To produce coated granules with favorable drug release properties without agglomeration, the agitation fluidized bed coating should be done using spray mist around 40 μm.

Also, since a close agreement was obtained between drug release data under constant liquid flow rate and those under constant spray air pressure, the drug release properties can also be estimated by the spray mist size.

Conclusions

An organic solvent-based enteric coating was made using an agitation fluidized bed. The effects of spray mist size on the properties of granules such as agglomeration tendency, drug release properties (1st and 2nd fluids), specific surface area and coating efficiency were investigated and analyzed quantitatively. When the spray mist size was large, agglomeration tendency increased because the adhesion force of the mist increased remarkably. However, the acid-proof and sustained-release properties strengthened because the spray drying was prevented due to the small interfacial area of the mist, and also the film received a favorable tumbling and compacting effect by the agitator rotation due to a longer drying dry. These mechanisms were confirmed quantitatively by the coating efficiency and the granule specific surface area. It was concluded that the agitation fluidized bed coating should be done using spray mist of 40 μm to produce coated granules with favorable drug release properties without agglomeration. It was also found that the results of coating could be estimated by the spray mist size under various spray liquid flow rates and air pressures.

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