Evaluation of Aqueous Enteric Coated Granules Prepared by Moisture Control Method in Tumbling Fluidized Bed Process

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Based on the moisture control system developed previously, we have already reported that the operational moisture content during aqueous polymeric coating by a type of fluidized bed should be controlled for a better coating efficiency.

In this paper, effects of operational moisture content and agitator rotational speed on the properties of granules prepared by the aqueous polymeric coating were investigated experimentally, and optimization of this process was conducted. Core granules (mean diameter 600 μm) containing a model drug, pigment Blue No. 1, were coated with the aqueous dispersion of enteric polymer (Eudragit L30D) by the tumbling fluidized bed with controlling the operational moisture content. The coated granules were evaluated by dissolution tests in JP 1st (pH 1.2) and 2nd fluid (pH 6.8) and by agglomeration tendency. Film thickness and specific surface area of the granules were examined to discuss the film forming process. Based on the evaluation, effects of the operational variables on the drug release rate and agglomeration tendency were investigated. It was found that the drug release rate was suppressed with increase in moisture content at any rotational speed in the JP 1st and 2nd fluid, and the agglomeration tendency was prevented with increase in moisture content and agitator rotational speed. It was concluded from the results that the aqueous coating with the enteric polymer by the tumbling fluidized bed process should be carried out under a condition of moisture content between 12 and 14% with agitation below 5 rps.

Keywords enteric coating; aqueous polymer; tumbling fluidized bed; moisture control; drug release rate; agglomeration tendency

Film coating processes for oral drugs were originally conducted with organic solvent-based systems. This was because that these systems had low heat for vaporization efficiency and were preferable for water sensitive materials. In the early 1970's, a remarkable shift was made from organic solvent-based systems to aqueous-based systems because of the latter's environmental and economic advantages. Aqueous film coating technology has advanced to a level of practical use, however, problems such as low operational efficiency due to the high heat required for vaporization and the adhesion of particles have not yet been settled.

Factory automation in the manufacturing process has also been discussed recently. In the coating process, establishment of a self control system has been recognized for its high reproducibility of product quality, improved operational safety, saving of labor and the like.

In the previous paper,[1] we suggested that, in an aqueous coating process by a tumbling fluidized bed,[2] it was necessary to control the operational moisture content with reference to the establishment of factory automation and the manufacturing of particles with desirable sustained release properties.

The purpose of this paper is to evaluate the granules coated with aqueous enteric polymer by a tumbling fluidized bed using the moisture control system in order to investigate the effects of operational variables on the physical properties of the coated particles. Optimization of this process was also conducted to clear up the operational guidance required to produce coated granules with superior enteric properties and low agglomeration tendency.

Experimental

Powder Samples As core particles for aqueous film coatings, spherical granules made of crystalline cellulose (mean particle diameter 600 μm, true density 1070 kg/m^3, Selphere CP507, Asahi Chemical Industry Co., Ltd.) were used. Dispersion of enteric acrylic polymer (Eudragit L30D-55, Rohm Pharma) which was resistant to gastric juice but soluble in intestinal juice with a solubility around pH 5.5 or above was adopted as the coating material. Dispersion of Eudragit L30D in this study was diluted with water to contain 15% of a dry lacquer substance, and 2.25% triethylcitrate was added as a plasticizer before application.

Evaluation of the Coated Particle The particle size distribution of the coated particle was determined by a sieve analysis with a row-tap shaker.

Dissolution tests were performed in accordance with JP XII[3] paddle method at 100 rpm and 37 °C. The JP XII disintegration 1st (pH = 1.2) and 2nd fluids (pH = 6.8) were used as dissolution media and as well as 0.5 g of coated granules with diameters ranging from 600 to 710 μm without agglomerated particles.

A cross section of the coated particle was observed by a scanning electron microscope (SEM) to determine film thickness.

Specific surface area 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.

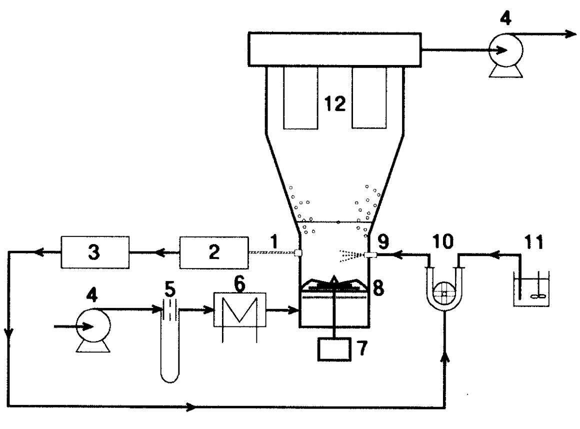

Fig. 1. Experimental Set Up

1, optical fiber; 2, IR moisture sensor; 3, controller; 4, blower; 5, orifice; 6, heater; 7, motor; 8, agitator; 9, spray gun; 10, pump; 11, coating suspension; 12, bag filter.

TABLE I. Operating Conditions for Enteric Polymeric Coating by Tumbling Fluidized Bed

Inlet air velocity	1.0 m/s
Inlet air temperature	35 °C
Spray air pressure	1.5×10^5 Pa
Nozzle insert	1.0 mm (i.d.)
Agitator rotation	2.5—15.0 rps
Moisture content	8.0—14.0%

Equipment Figure 1 shows the experimental set up of the coating system used. A tumbling fluidized bed[2] (NQ-LABO, Fuji Paudal Co., Ltd.) was used for the coating operation, and moisture content during the operation was continuously measured by an IR moisture sensor[4] (WET-EYE, Fuji Paudal Co., Ltd.). The operational variables were measured continuously and the main operational factors such as agitator rotational speed, air flow rate, bed inside pressure and inlet air temperature were feedback controlled (PID control) to maintain stable operation. Details of the equipment and principle of the measurement of the IR moisture sensor were described in the previous report.[1]

Coating Method The operating conditions for the coating experiment are shown in Table 1. The coating experiment was conducted as follows. Core particles of 300 g were first under coated with a water solution of pigment (Blue No. 1, Toushoku Pigment Co., Ltd.) selected as a model drug. After drying the particles in the coater, the dispersion of Eudragit L30D-55 was sprayed while moisture content was controlled. After having sprayed 300 g of the dispersion, the coated particles were dried in the coater until the moisture content was reduced to less than 1.0%. These operations were conducted automatically using the IR moisture control system developed previously.[1]

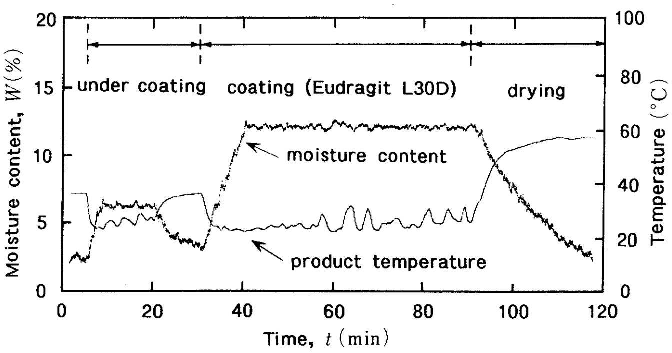

Fig. 2. Example of Moisture Control in the Coating Process

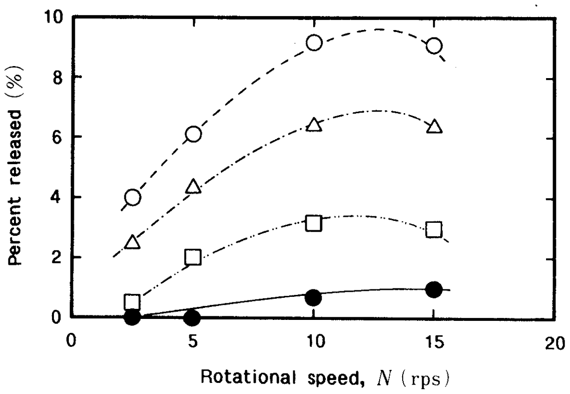

Fig. 3. Drug Release after 2 h Dissolution Test Using JP 1st Fluid
○, moisture content $W=8\%$; △, $W=10\%$; □, $W=12\%$; ●, $W=14\%$.

Results and Discussion

Moisture Control Figure 2 illustrates an example of moisture control in the coating process. In this system, each unit (under coating, film coating and drying) was automatically operated.

The phase $5\leqq t\leqq 30$ min shows the under coating of the pigment and its drying. To avoid unevenness in the amount of the pigment sprayed in each experiment, the moisture content during the under coating process was controlled to 6%, as determined by preliminary experiments.

The phase $30\leqq t\leqq 90$ min indicates the main coating process. Before spraying of the aqueous polymer, purified water was sprayed until the moisture content increased to a predetermined value. Eudragit L30D-55 was then sprayed under fixed command control of the moisture content. Overshoot of the moisture content was rare in any of the processes because of the stable control achieved by optimum PID control. After having been sprayed 300 g of the dispersion, the coated particles were dried ($90\text{ min}\leqq t$) in the coating chamber at 60 °C until the moisture content decreased to under 1.0%.

Effects of Operational Variables on the Dissolution Using JP 1st Fluid When the enteric coating is carried out, suppression of the drug release in the JP 1st fluid (pH = 1.2) is the first indication of whether the coated granules have adequate enteric release properties.

Figure 3 illustrates the drug release after a 2 h dissolution test using JP 1st fluid with various operational moisture contents and agitator rotational speeds. The percent of the pigment released in the JP 1st fluid after 2 h dissolution had a tendency to increase with increase in the agitator rotation, but decreased with an increase in operational moisture content. In other words, the drug release was suppressed in the acid media when the coating was conducted under high operational moisture content with low agitation. The enteric film layered on the granule is, however, not solved in the JP 1st fluid; the drug must diffuse through the film to release in the media. Therefore, diffusion coefficient and diffusion distance must affect drug release. Taking account of the fact that the amount of polymer sprayed was theoretically constant in every experiment, the film thickness (diffusion distance) must be determined by the coating efficiency. If the coating was conducted in the high moisture content range, the proportion of spray drying was decreased, which led to an increase in film thickness. In addition, the polymer particles sprayed on the surface of the core particles were able to move freely, which resulted in the formation of continuous and well packed film.

In any discussion about the effects of agitation on the properties of film formed, the movement of the particles must be analyzed. Observation by high speed video camera of the motion of a tracer particle gave us the following information; when the agitation was low, the speed of revolution around the center axis was slow, but favorable spinning was observed. On the contrary, with high agitation, translation rather than spinning was observed in spite of the high revolution. The results suggested that the particles during coating experienced a favorable tumbling motion by the spinning at low agitation, which contributed to spreading of the film. In addition, the micro cracks and scoring which were often found by SEM observation with excess agitation was also prevented in this low agitation. These effects resulted in the reduction

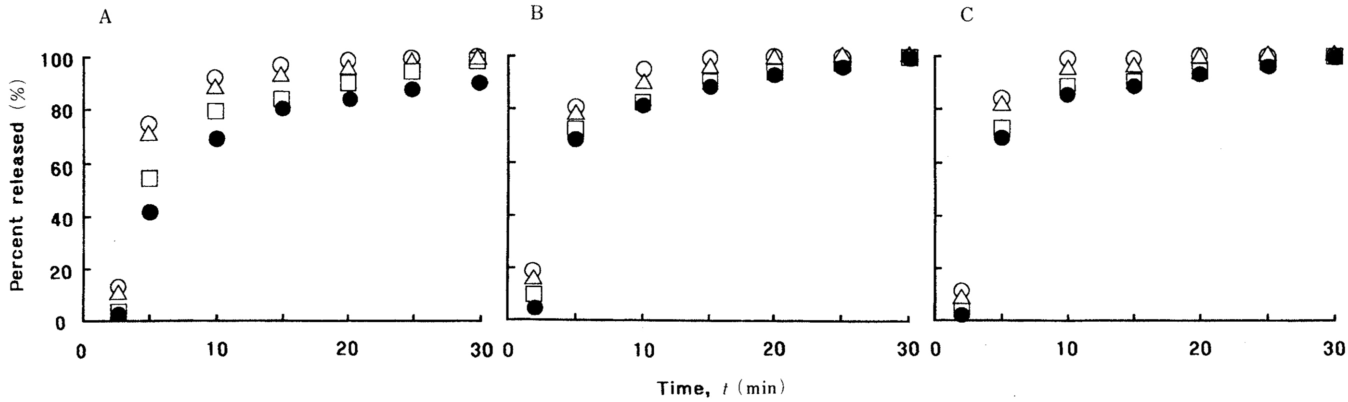

Fig. 4. Drug Release Profiles with Various Moisture Contents (JP 2nd Fluid)

A, agitator rotational speed, $N=5$ rps; B, $N=10$ rps; C, $N=15$ rps. ○, moisture content $W=8\%$; △, $W=10\%$; □, $W=12\%$; ●, $W=14\%$.

of the drug diffusion through the film.

Suppression of the drug release in JP 1st fluid thus progressed if the coating was conducted under conditions of high moisture with low agitation because of the good coating efficiency and the favorable film quality, well-spread and well packed, resulting from the tumbling effects in a large amount of free water.

Effects of Operational Variables on the Dissolution Using JP 2nd Fluid Figure 4 shows the results of the dissolution tests conducted using the JP 2nd fluid. At any rotational speed, the dissolution rates decreased with the increased in operational moisture content, which was the same tendency as illustrated in Fig. 3. Furthermore, the difference of each release profile obtained by changing the moisture content decreased with the increase in rotational speed.

To determine the reason for these tendencies, film thickness and specific surface area of the coated particles were investigated. In the dissolution tests using the JP 1st fluid, the drug release depends mainly on the diffusion phenomenon because the enteric film is not dissolved in the acid solvent. According to Fick's first law of diffusion under steady state assumption, the release rate of the drug is determined by the diffusion distance equivalent to the film thickness and by the diffusion coefficient characterized by the quality of the film.

In the dissolution tests using the JP 2nd fluid, on the contrary, Fick's first law of diffusion is not applied because the enteric film is easy to dissolve in the basic solvent. In the course of the dissolution, however, it can be expected that the dissolution behavior of the film may be largely influenced by the surface area, quality of the film and the film thickness. Therefore, we measured the film thickness and simultaneously determined the specific surface area to evaluate the film quality, under the assumption that the film formed would be continuous and well compacted if it had a smooth surface.

Figure 5 illustrates the plots of film thickness and specific surface area as a function of the operational moisture content. Here, the data of the specific surface area was measured only for the film, not including the pores inside the core particle, which was confirmed from the fact that the data of the specific surface area was almost the same when coated onto glass beads of the same diameter under the same operational conditions.

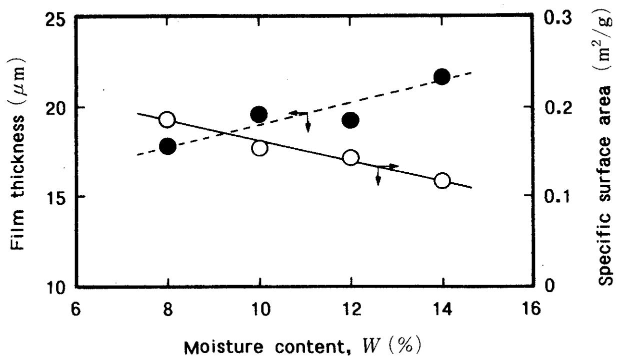

Fig. 5. Plots of Film Thickness and Specific Surface Area as a Function of Moisture Content

●, film thickness; ○, specific surface area.

As shown in Fig. 5, film thickness increased linearly with the increase in the moisture content. Since the humidity inside the chamber was closely connected with the operational moisture content, the drying efficiency decreased with increase of the moisture content. Therefore, spray drying, in which the spray mist dried before adhering to the particles was suppressed as the moisture content increased.

The specific surface area, on the contrary, decreased linearly with the increase in moisture content, which showed that continuous smooth film of high quality was formed. When the polymer particles were deformed by surface tension and capillary forces during the film forming process,[5] the deformation rate of the polymer particles exceeded the dehydration speed when the moisture content was high. In this case, the polymer particles were deformed because of having such a sufficient quantity of free water, drying time and thermal energy that their packing condition was improved. On the contrary, when the operational moisture content was low, dehydration speed exceeded the deformation rate of the polymer particles and an imperfect film was produced.

Figure 6 synthesizes these results by T_{75}, which was defined as the time required to release 75% of the total amount of the drug in the JP 2nd fluid.

In Fig. 6, the coating operation when the moisture content was 14% and the rotational speed was 2.5 rps was

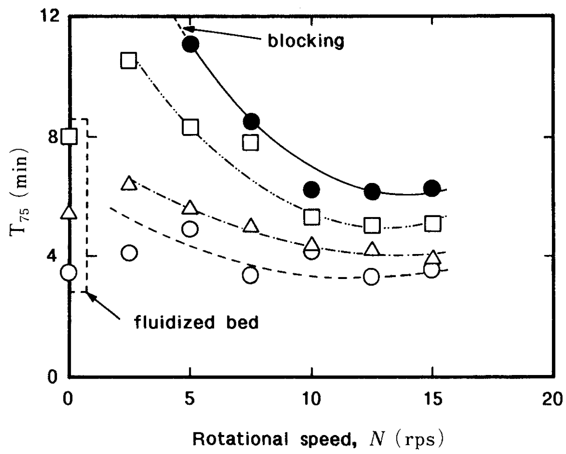

Fig. 6. Time Required to Release 75% of the Total Amount of the Coated Drug

○, W=8%; △, W=10%; □, W=12%; ●, W=14%.

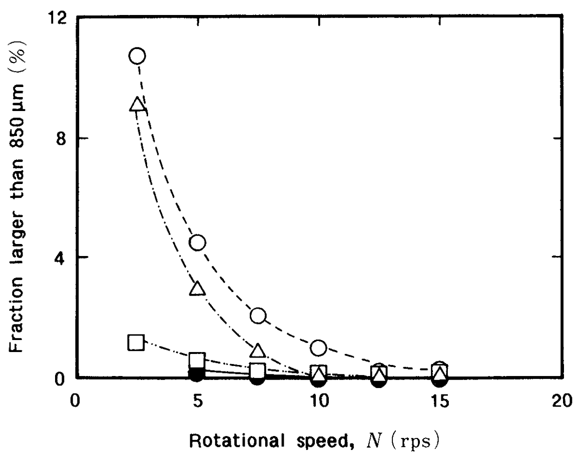

Fig. 7. Fraction Larger than 850 μm as a Function of Agitator Rotational Speed and Moisture Content

○, moisture content W=8%; △, W=10%; □, W=12%; ●, W=14%.

impossible due to the blocking. Simultaneously, the T_{75} obtained by a fluidized bed without agitation (agitator blade removed and equipped with a perforated distributor disk) is plotted in Fig. 6 for comparison. The fact that the T_{75} of the fluidized bed without agitation showed a small value implied that the tumbling motion of the agitator blade was very effective for the progress of the sustained release properties.

Generally, Fig. 6 shows a tendency for the T_{75} to increase with decrease of the agitation and increase of the moisture content. Judging from the effects of moisture content and agitator rotational speed on the T_{75}, the same tendency as illustrated in Fig. 3 was found in this case. As mentioned above, in the course of deformation of the polymer particle, a large bulk of free water on the surface contributed to form a continuous and well packed film and to increase the coating efficiency. Slow agitation generated particle spinning and promoted spread of the film. Too much agitation, on the contrary, negatively affected film quality by causing surface cracking or scoring. It was therefore concluded that slow agitation in the tumbling fluidized bed with high moisture content was the best way to realize excellent sustained release properties.

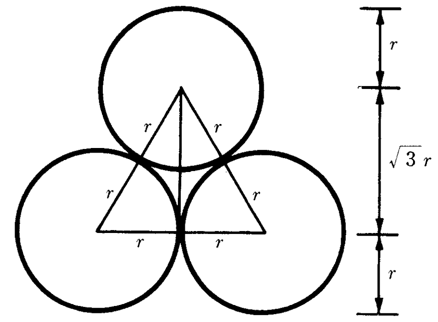

Fig. 8. Agglomerated Particles Forming a Triangular Conformation

Effects of Operational Variables on the Agglomeration Tendency Figure 7 illustrates the fraction larger than 850 μm as a function of agitator rotational speed and moisture content. In this example, although the core particles had already been sieved to assume particle size of 500 to 710 μm (22 mesh on, 32 mesh under) and the average film thickness was estimated by SEM to be 20 μm, the particle coated by 20 μm continuously without agglomeration might have a theoretical diameter ranging from 540 to 750 μm. Let three particles of the same diameter be agglomerated to form a triangular conformation, each having two contact points to the other two,[6] as illustrated in Fig. 8, the smallest diameter of the agglomerated particles would become;

$$d_p = (2+\sqrt{3}) \times r$$
$$= (2+\sqrt{3})/2 \times d$$
$$= 1.87d$$

where d_p is the smallest diameter of the agglomerated particle, r the radius and d the diameter of the core particle theoretically coated. If the three smallest particles of 540 μm were agglomerated to form a triangular conformation like this, the smallest diameter of the agglomerated particle would become 1009 μm. Therefore, it was clear that the fraction larger than 850 μm (20 mesh) contained agglomerates. From this point of view, we defined the agglomeration tendency as a fraction larger than 850 μm.

Plots of the fraction over 850 μm against rotational speed suggested that at any moisture content, the agglomeration tendency decreased with an increase in agitator rotational speed. The particles during the film forming process by the tumbling fluidized bed experienced such an intensive shear force by the high agitation that the agglomeration tendency was reduced. The fraction over 850 μm also decreased with increase in moisture content. If particles of low moisture content collided with each other, one particle easily reached the deforming polymer layer of another particle because of the lack of free water. Since the deforming polymer particles easily adhered to each other on contact, the possibility of constructing agglomerates grew large. On the contary, with high moisture content, free water located over the deforming polymer layer could become the buffer in a collision. Since the droplet of water on the polymer layer was thought to have such small viscosity that it would adhere to each particle, the adhesion of particles to each

TABLE II. Agglomeration Tendency of the Product Prepared by Tumbling Fluidized Bed and Typical Fluidized Bed

Moisture content (%)	Fraction larger than 850 μm (%)		
	Tumbling fluidized bed		Fluidized bed without agitation
	$N=5$ rps	$N=10$ rps	
8	4.5	1.0	7.4
10	3.0	0	18.4
12	0.5	0	39.9
14	0.1	0	Blocking

other occurred rarely.

Table II gives the fraction larger than 850 μm obtained by the fluidized bed without agitation. The data from the tumbling fluidized bed coating at typical rotational speed are listed for comparison. The fraction larger than 850 μm obtained by the typical fluidized bed without agitation showed a large value, with a tendency to increase with increase in moisture content, while the data by the tumbling fluidized bed tended to decrease. Since the typical fluidized bed has no agitation motion, the shearing force between particles was so small that it could not prevent agglomeration and spread the film. In addition, fluidization became worse as the coating progressed. The tumbling fluidized bed, in contrast, had the agitation motion, the particles were given sufficient shearing force by the agitation and worsening of the fluidization was also prevented.

Considering both that the agglomeration tendency was suppressed at any rotational speed at a moisture content above 12%, and that the enteric properties were advanced at a high moisture content with low agitation, the aqueous coating with the enteric polymer in the tumbling fluidized bed process should be carried out under a condition of moisture content between 12 and 14% and agitation below 5 rps.

Conclusions

Aqueous polymeric coating was conducted using the moisture control system in the tumbling fluidized bed process. Granules coated with the aqueous enteric polymer were evaluated, the effects of operational variables on the properties of the coated particles were determined and the following conclusions made; 1) The drug release rate was restrained with increase in moisture content at any rotational speed in the JP 1st and 2nd fluids. Facts suggested that the film thickness increased and the specific surface area decreased with increase in moisture content, and that spray drying was suppressed and the packing condition was advanced. Tumbling motion of the slow agitation also contributed to the spreading of the polymer film, which resulted in the development of the sustained release properties. 2) The agglomeration tendency was restrained with increase in agitator rotational speed and moisture content. Intensive agitation played an important role in separating the particles, and a large bulk of free water on the surface of the film layer acted to decrease their probability to adhere to each other. 3) The operational guidance necessary for manufacturing particles with better enteric characteristics has thus been confirmed. The coating operation should clearly be carried out under conditions of 12 to 14% moisture content and agitation below 5 rps.

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