Formulation Design of Taste-Masked Particles, Including Famotidine, for an Oral Fast-Disintegrating Dosage Form

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In this study, the taste-masking of famotidine, which could apply to any fast-disintegrating tablet, was investigated using the spray-dry method. The target characteristics of taste-masked particles were set as follows: the dissolution rate is not to be more than 30% at 1 min and not less than 85% at 15 min, and the particle size is not to be more than 150 μm in diameter to avoid a gritty feeling in the mouth. The target dissolution profiles of spray-dried particles consisting of Aquacoat ECD30 and Eudragit NE30D or triacetin was accomplished by the screening of formulas and the appropriate lab-scale manufacturing conditions. Lab-scale testing produced taste-masked particles that met the formulation targets. On the pilot scale, spray-dried particles with attributes, such as dissolution rate and particle size, of the same quality were produced, and reproducibility was also confirmed. This confirmed that the spray-dry method produced the most appropriate taste-masked particles for fast-disintegrating dosage forms.

Key words fast-disintegrating; famotidine; taste-masking; spray-dry; particle

Many elderly patients often have difficulty swallowing some of the dosage forms (tablets, capsules, and powders) currently used. For this reason, the development of an appropriate dosage form for elderly patients is most desirable. Since the late 1980s, many companies have developed fast-disintegrating dosage forms that disintegrate easily in the mouth and can be taken without water. Cardinal Health marketed a fast-disintegrating, freeze-dried porous wafer known as Zydis[1,2] and CIMA also marketed an effervescent tablet known as OraSolve.[3] Eisai developed the EMP tablet,[4] and Ethypharm developed Flashtab.[5] A new fast-disintegrating tablet consisting of high- and low-compressibility saccharides was reported in a previous study.[6] Although famotidine was used as a model drug for the new fast-disintegrating tablet, it had an unpleasant taste. In fact, most of the fast-disintegrating technologies described above were not applied to bitter-tasting drugs. Consequently, in this study, attempts have been made to produce a taste-masked, fast-disintegrating tablet using famotidine as a model drug.

Various taste-masking technologies, such as the addition of sweeteners and flavors, coating with water insoluble materials,[7] creating a wax matrix by spray congealing,[8] adsorption to ion-exchange resin,[9,10] and complexing with cyclodextrins[11] had been investigated. Water insoluble polymer coating technology was widely employed to control the initial dissolution rate and to suppress the bitter taste. Famotidine bulk powder was coated in a fluidized-bed granulator in an attempt to suppress the bitter taste, but this was not successful. Because the reproducibility of coating operation was not achieved due to the poor flowability of famotidine powder. Therefore, the spray-drying method was selected as an alternative to the powder coating method.

The objectives of this study were to determine the optimum formula and manufacturing conditions for producing taste-masked particles using the spray-drying method that could be applied to a fast-disintegrating tablet. If successful, this would result in a novel, taste-masked, fast-disintegrating tablet.

Experimental

Materials The D-mannitol (Mitsubishi Shoji Foodtech, brand name: Mannit P), maltose (Hayashibara, brand name: Sanmalt), Aquacoat ECD30 (Ethylcellulose Aqueous Dispersion, FMC Corporation), Eudragit NE30D (Ethyl Acrylate Methyl Methacrylate Copolymer Dispersion, Röhm GmbH & Co., KG), triacetin (Yuki Gosei Kogyo), and calcium stearate (Nippon Oil & Fats) were used in this study. Famotidine (Astellas Pharma Inc., JP standard) was used as the model drug.

Determination of Bitterness Threshold After mixing famotidine bulk powder and placebo granules consisting of mannitol granulated with 5% maltose in a fluidized-bed granulator, a tablet was prepared by compressing in an hydraulic press (weight of tablet: 170 mg, diameter of tablet: 8.5 mm). The concentrations of famotidine used were 0.5, 1, 2, and 5 mg per tablet. Sensory testing was conducted as follows: each volunteer washed his/her mouth well with tap water, and then allowed a tablet to disintegrate in his/her mouth. The tablet was evaluated for bitterness immediately after disintegration and tasting, after which it was spat out. Tablets were tested in order of increasing famotidine concentration (0.5, 1, 2, 5 mg).

Selection of Ingredients for Taste-Masking After mixing each ingredient (Table 2) with placebo granules (mannitol granulated with 5% maltose) at the rate of 20 to 80%, respectively, tablets were formed in the hydraulic press (weight of tablet: 120 mg, diameter of tablet: 7.0 mm). The testing procedure was almost the same as that for the sensory testing described above. Each volunteer washed his/her mouth well with tap water, and then allowed a tablet to disintegrate in his/her mouth. The time required for disintegration without chewing was measured, after which the tablet was immediately spat out.

Pulverization of Famotidine Bulk Powder Famotidine bulk powder was pulverized using sample mill (Hosokawa micron, AP-S) with 2 mm screen in diameter.

Powder X-Ray Diffraction Measurement The powder X-ray diffraction patterns were measured using an X-ray diffractometer (RINT-TTR III, Rigaku) with Cu anode material. The diffraction pattern was measured with a voltage of 50 kV and a current of 300 mA in the area of $5<2\theta<40°$ at an angular speed of 10°/min. The sample was prepared by grinding spray-dried particle using mortar.

Preparation of Spray-Dried Particles Spray dryer model CL-8 (Ohkawara kakohki) was used for the lab-scale production of spray-dried particles, and model OD-22M (Ohkawara kakohki) was used for pilot-scale production. Famotidine powder was suspended in Aquacoat ECD30 and Eudragit NE30D or triacetin in several ratios using the propeller mixer. This suspension was sprayed using the rotary atomizer method. The spray-dried particle was cured at 90 °C for 30—60 min in a thermostatic chamber.

Dissolution Testing The dissolution test of the spray-dried particles containing 20 mg of famotidine was performed using the paddle method at 100 rpm in pH 6.8 buffer containing 0.1% Tween 80. The detection of famo-

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tidine was performed using the UV method at 265 nm.

Evaluation of Particle Surface Using Scanning Electron Micrographs The surface morphology of the spray-dried particle was observed using scanning electron microscopy (JEOL, JSM-5510LV).

Determination of Particle Size Distribution The particle size distribution of famotidine bulk powder was measured using a Laser-Scattering Particle Distribution Analyzer (LA-910, Horiba). A robot sifter (RPS-85, Seishin Enterprise) was used for spray dried particles.

Results and Discussion

Setting the Target Dissolution Profile of Taste-Masked Particles In order to set the target dissolution profile, the bitterness threshold of famotidine had to be examined first *via* a sensory test using tablets containing famotidine in various concentrations. The results of the sensory test are shown in Table 1. In the 1 mg tablet, some volunteers sensed a change in taste, but no bitterness. In the 2 mg tablet, 3 of 6 volunteers sensed the bitterness, and in the 5 mg tablet, all the volunteers did. Therefore, the bitterness threshold for famotidine was around 2 mg.

In the dissolution profile of the taste-masked particles, the following two points have to be taken into consideration: (1) the dissolution rate must be controlled during the initial period in order to suppress the bitterness, and (2) the tablets must dissolve rapidly in the stomach to have the same bioavailability as the conventional famotidine product. Therefore, the dissolution rate was measured at 1 min (D1 min) for the early phase, and then also at 15 min (D15 min).

The target dissolution rate for the early phase was set to be 30% or less at 1 min, based on the bitterness threshold and the disintegration time of tablets in the mouth (within 20 s). The bitterness of famotidine was sensed in the mouth at 2 mg, which is 10% of a 20 mg Tablet. Since the target disintegration time of the tablets is within 20 s, it is necessary to keep the dissolution rate at 20 s to within 10%, that is if the disintegrated tablet is swallowed immediately after disintegration. However, it is difficult to get reproducible dissolution rate results at 20 s. Therefore, the sampling time during the early phase was set at 1 min, and the target dissolution rate was set at 30%, three times higher than 10%. For the dissolution rate at 15 min, the reference products showed a rate of not less than 85%. Therefore, D15 min was set to be not less than 85%, with reference to the "Guideline for bioequivalence studies of generic products."

The particle size of taste-masked particles must also be taken into account because it affects not only the dissolution rate, but also grittiness. So, setting of the particle size was important so that the most desirable characteristics of a fast-disintegrating tablet could be met. The target particle size was set at 150 μm or less, which was based on reference material.[12]

Consequently, the target characteristics of taste-masked particles are as follows:

1) Dissolution rate: not more than 30% at D1 min and not less than 85% at D15 min
2) Particle size: not more than 150 μm.

Screening of Ingredients for Taste-Masking In order to select an ingredient for bitter taste-masking that does not prolong oral disintegration time, the oral disintegration times of placebo tablets were measured. These tablets were prepared by mixing placebo granules consisting of mannitol and maltose together with various ingredients in a ratio of 80 : 20, respectively. The results showed that there was almost no prolongation of disintegration time for the tablets compounded with ethylcellulose, polyvinyl alcohol or stearic acid (shown in Table 2). However, the tablets compounded with stearic acid had a gritty texture and the hygroscopicity of polyvinyl alcohol was presumed to make its dissolution control difficult. Therefore, ethylcellulose was selected as the main ingredient for the taste-masking film and Aquacoat ECD30, an ethylcellulose aqueous dispersion was used for further study. Eudragit NE30D and triacetin were used as plasticizers for Aquacoat ECD30.

Effect of Pulverization of Famotidine Bulk Powder Famotidine bulk powder exists as needle-like crystals, and the mean particle size is around 30 μm even before pulverization. Therefore, the effect of pulverization of famotidine bulk powder on the characteristics of the spray-dried particles was examined, when the ratio of Aquacoat ECD30 to triacetin was 8 : 2, and the famotidine was coated in 40% under 6000 rpm of an atomizer rotation speed. When non-pulverized famotidine was used for spray drying, many spherical particles with spikes could be seen in the spray-dried particles when observed under the microscope (Fig. 1a). The presence of a large number of big crystals more than 100 μm in diameter was considered to be the major cause of these spiky particles. Since the surfaces of these spike-like crystals were not completely coated with ethylcellulose, the taste of the famotidine bulk powder might not be masked sufficiently. Therefore, pulverization was deemed necessary for the manufacture of taste-masked particles. The particle sizes of famotidine bulk powder before and after pulverization by a sample mill are shown in Table 3. After pulverization, the volumetric mean particle size in all 3 lots was almost the same, 15 to 16 μm. The maximum particle size also decreased from about 300 to about 100 μm, and there were almost no crystals with diameters over 100 μm. When the pulverized famotidine powder was used for spray drying, the surface was coated smoothly with ethylcellulose, and no

Table 1. Result of Sensory Evaluation Using Famotidine Tablets

Famotidine (mg/tablet)	Volunteer					
	A	B	C	D	E	F
0.5	−	−	−	−	−	−
1	±	±	−	±	−	−
2	+	+	−	+	±	±
5	++	++	+	++	+	+

−: not notified taste change, ±: notified taste change, +: slightly bitter taste, ++: strong bitter taste.

Table 2. Oral Disintegration Time of Tablets Using Different Ingredients

Ingredients	Oral disintegration time (s)
Ethylcellulose	13, 15, 18
Pullulan	72, 85, 90
Polyvinyl alcohol	18, 20, 25
Gelatin	18, 25, 30
Carnauba wax	35, 123, 200
Castor wax	100, 150, 155
Stearic acid	18, 20, 21

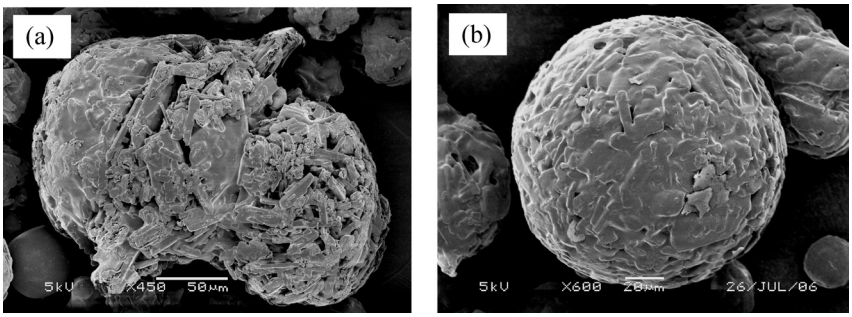

Fig. 1. Scanning Electron Micrographs of Spray-Dried Particles Using (a) Non-pulverized Famotidine Bulk Powder (×450) and (b) Pulverized Famotidine Powder (×600)

Table 3. Particle Sizes of Famotidine Bulk Powder before and after Pulverization

Lot number	Particle size[a)]	
	Before pulverizing	After pulverizing
YA023	37.0 μm (344—3.4)	15.8 μm (88—2.6)
YA035	37.7 μm (300—3.4)	15.8 μm (101—2.6)
YB010	28.5 μm (344—3.4)	15.0 μm (52—2.3)

a) Mean particle size (maximum—minimum).

famotidine crystals could be observed (Fig. 1b). Furthermore, the crystallinity of famotidine in spray-dried particles was examined not to affect on stability or dissolution property. Figure 2 shows the X-ray diffraction patterns of spray-dried particles and famotidine in spray-dried particles was confirmed to be present in a crystalline state. Consequently, famotidine powder pulverized by the sample mill was used for the remainder of the study.

Evaluation of Spray-Dried Particles Consisting of Aquacoat ECD30 and Eudragit NE30D At first, the combination of Aquacoat ECD30 as the main masking ingredient and Eudragit NE30D as the plasticizer was investigated. The effect of the atomizer rotation speed and the solid concentration in the spray suspension on the characteristics of the spray-dried particles was examined preliminarily (Table 4) when the ratio of Aquacoat ECD30 to Eudragit NE30D was 7 : 3, and the famotidine was coated in 20%. The solid content (%) showed the concentration of famotidine and polymers in water and was adjusted by amount of water. When the solid content was 30% (SD1), many fine particles not more than 63 μm in diameter were produced. The number of fine particles tended to increase with increase in the atomizer rotation speed. As a result, the dissolution rate at 1 min was not well-controlled, and did not meet the target dissolution profiles. Consequently, the low solid content was not suitable for taste-masking. The mean particle size decreased with the increase in the atomizer rotation speed. The effect of the rotation speed was greater when the concentration of solids was 50% rather than 30%. The dissolution rate tended to decrease as the mean particle size increased. At a 50% concentration of solids (SD2), a good relationship between mean particle size and dissolution at 1 min was observed (R^2= 0.999). From these results, it was judged that manufacturing conditions would be difficult to control at a solid concentration of 30%, compared to 50%. Therefore, the remainder of the study was performed mainly with a solid content of 50%.

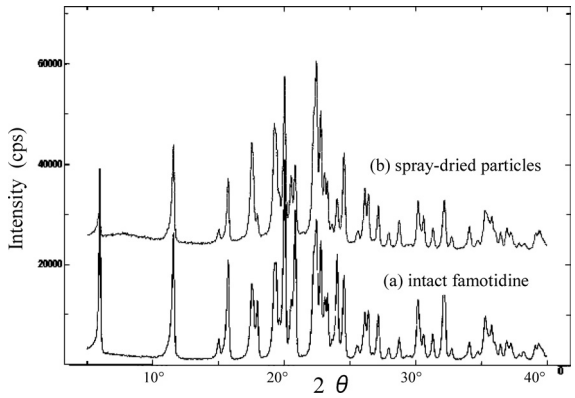

Fig. 2. X-Ray Diffraction Patterns: (a) Intact Famotidine and (b) Spray-Dried Particles

Next, the effect of the composition ratio of Aquacoat ECD30 and Eudragit NE30D on manufacturing and the dissolution rate was examined. The manufacturing conditions and the characteristics of the spray-dried particles obtained are shown in Table 4 (SD3). Spray drying was performed under the following conditions: the coating amounts to famotidine of 50%, a solid concentration of 50% in the spray suspension, and an atomizer rotation speed of 8000 rpm. When the ratio of Aquacoat ECD30 to Eudragit NE30D was 4 : 6 (SD3-1), spray-dried particles stuck on the bottom of the chamber of the spray dry equipment. This phenomenon was also observed with the 5 : 5 ratio (SD3-2), although it was slight. The chamber temperature was over 80 °C, and was higher than the softening temperature of the coating films when the ratio was 4 : 6 and 5 : 5, which suggests that this might be a cause of sticking.

In contrast, all batches almost met the target dissolution profiles, D1 min$<$30% and D15 min$>$85%. The dissolution rate of the spray-dried particles obtained decreased with the increase in the amount of Eudragit NE30D as well as with the increase in mean particle size. In addition, the bitterness became more alleviated and the masking property was improved. Taking the sticking in the chamber and the initial dissolution rate at 1 min into consideration, the 6 : 4 ratio of Aquacoat ECD30 to Eudragit NE30D was selected, and the other manufacturing conditions were further investigated.

The effect of the coating amount to famotidine and the solid content of the spray suspension on the characteristics of spray-dried particles was examined, and the results are shown in Table 5. For the 20% coating (SD4-1), the atomizer be-

Table 4. The Characteristics of Spray-Dried Particle in Aquacoat ECD30 and Eudragit NE30D Manufactured Using Lab-Scale Spray Dryer (CL-8)

Lot No.		SD1-1	SD1-2	SD1-3	SD2-1	SD2-2	SD2-3	SD3-1	SD3-2	SD3-3	SD3-4
Aquacoat ECD30 : Eudragit NE30D		7 : 3	7 : 3	7 : 3	7 : 3	7 : 3	7 : 3	4 : 6	5 : 5	6 : 4	7 : 3
Coating amounts (%)		20	20	20	20	20	20	50	50	50	50
Solid content (%)		30	30	30	50	50	50	50	50	50	50
Atomizer rotation speed (rpm)		6000	8000	12000	6000	8000	12000	8000	8000	8000	8000
Mean particle size (μm)		94	91	81	124	116	88	111	98	86	85
Distribution (%)	500 μm—	0.0	0.6	1.6	1.3	0.4	0.4	0.3	0.0	2.3	0.9
	350—500 μm	0.4	0.2	0.6	0.2	0.6	0.6	0.3	0.5	0.0	0.0
	250—350 μm	0.6	0.6	0.6	0.6	0.4	0.8	0.5	0.7	0.0	0.3
	180—250 μm	2.3	1.2	1.2	0.6	0.2	0.6	2.0	1.2	1.3	0.9
	150—180 μm	3.5	2.9	1.4	16.3	1.9	1.2	0.7	0.5	1.3	0.6
	106—150 μm	29.2	27.8	12.4	51.9	60.0	14.5	51.2	37.9	17.4	15.4
	75—106 μm	36.8	33.0	40.0	23.0	23.1	55.3	30.6	37.1	43.6	46.5
	63— 75 μm	17.2	20.1	22.5	4.0	8.0	15.6	11.5	18.1	28.5	27.3
	— 63 μm	10.0	13.7	19.7	2.1	5.4	11.1	2.8	4.0	5.6	8.1
% Dissolved	1 min	51.4	69.3	76.5	30.4	35.5	50.5	21.7	23.6	27.6	30.6
	3 min	86.2	95.8	99.2	54.9	68.8	86.6	40.6	47.2	49.8	54.0
	15 min	99.8	99.9	99.7	70.1	97.1	99.2	91.5	96.3	97.5	99.2

Table 5. The Characteristics of Spray-Dried Particle in Aquacoat ECD30 and Eudragit NE30D Manufactured Using Lab-Scale Spray Dryer (CL-8)

Lot No.		SD4-1	SD4-2	SD4-3	SD4-4	SD4-5	SD4-6	SD4-7
Aquacoat ECD30 : Eudragit NE30D		6 : 4	6 : 4	6 : 4	6 : 4	6 : 4	6 : 4	6 : 4
Coating amounts (%)		20	30	30	50	50	75	100
Solid content (%)		60.0	65.0	60.0	56.2	50.0	50.0	46.2
Atomizer rotation speed (rpm)		6000	6000	6000	6000	8000	8000	8000
Yield (%)		16	41	60	66	78	84	85
Mean particle size (μm)		—	141	134	116	86	82	75
Distribution (%)	500 μm—	—	0.0	0.2	0.4	2.3	2.9	3.6
	350—500 μm	—	0.0	0.0	0.0	0.0	0.0	0.0
	250—350 μm	—	0.2	0.2	0.7	0.0	0.2	0.0
	180—250 μm	—	3.1	4.6	1.1	1.3	1.0	1.1
	150—180 μm	—	38.1	27.8	1.9	1.3	1.0	1.7
	106—150 μm	—	42.2	48.3	58.1	17.4	13.8	11.1
	75—106 μm	—	13.3	13.6	29.3	43.6	40.5	30.6
	63— 75 μm	—	2.3	2.9	7.8	28.5	32.4	41.2
	— 63 μm	—	0.8	2.3	0.7	5.6	8.1	10.6
% Dissolved	1 min	16.5	13.8	20.3	16.4	27.6	26.2	27.0
	3 min	43.5	34.6	43.8	37.8	49.8	48.2	51.3
	15 min	93.9	88.1	96.4	90.1	97.5	94.4	95.4

came clogged during spraying. This was considered to be due to exceeding volume of famotidine in the spray suspension. The 30% coating (SD4-2, SD4-3) contained many particles that were 150 μm or more in diameter due to the high solid content, which did not meet the particle size criterion. For the 50% coating (SD4-4, SD4-5), the dissolution rate was lower in the lots with higher solid content since the mean particle size increased with the increase in solid content. It should be noted, though, that all lots with 50% coating almost met the dissolution profile criteria. For the lots of SD4-5, SD4-6, and SD4-7 with 50%, 75%, and 100% coating amounts, respectively, the dissolution rate was almost the same. This indicates that increases in the amount of coating had no effect on the dissolution rate. This is probably due to the large surface area of the particles which kept the diffusion of famotidine constant, though the amount of coating changed from 50 to 100%.

These results allowed the final composition and basic spraying conditions for Aquacoat ECD30 and Eudragit NE30D to be selected: the ratio of Aquacoat ECD30 to Eudragit NE30D: 6 : 4, the coating amounts: 50%, the solid content of the spray suspension: 50%. In contrast, the yield was calculated using particles weight recovered from only collection container and was not more than 90% in any of the lots. This was caused by the occurrence of sticking on the chamber wall, which was probably due to the small diameter of the chamber. This will be considered again in the scale-up study.

Evaluation of Spray-Dried Particles Consisting of Aquacoat ECD30 and Triacetin When triacetin was used as plasticizer instead of Eudragit NE30D, the effect of the ratio of Aquacoat ECD30 and triacetin on the dissolution rate was investigated by changing the ratio of Aquacoat ECD30 to triacetin so that it would fall in the range of 85 : 15 to 70 : 30. The manufacturing conditions and the characteristics of the spray-dried particles obtained are shown in Table 6. The study was performed under the following conditions: the coating amounts to famotidine: 40%, the solid concentration in the spray suspension: 56%, and the atomizer rotation speed: 6000 rpm. When the ratio of Aquacoat ECD30 to triacetin was 70 : 30 (SD5-1), the handling was difficult because of rapid coagulation caused by the high viscosity of the spray-dried particles, however, there was no sticking on the bottom of the chamber. The dissolution rate of the spray-

Table 6. The Characteristics of Spray-Dried Particles in Aquacoat ECD30 and Triacetin Manufactured Using Lab-Scale Spray Dryer (CL-8)

Lot No.	SD5-1	SD5-2	SD5-3	SD5-4	SD6-1	SD6-2	SD6-3	SD6-4
Aquacoat ECD30 : Triacetin	70 : 30	75 : 25	80 : 20	85 : 15	80 : 20	80 : 20	80 : 20	80 : 20
Coating amounts (%)	40	40	40	40	100	50	40	30
Solid content (%)	56	56	56	56	52	52	56	56
Atomizer rotation speed (rpm)	6000	6000	6000	6000	8000	7000	6000	6000
Yield (%)	55	33	54	39	—	49	51	35
Mean particle size (μm)	117	145	115	157	118	85	93	111
% Dissolved 1 min	14.4	13.7	15.4	18.9	9.2	15.2	16.3	17.2
3 min	32.4	33.2	33.0	38.7	18.2	29.2	33.5	36.1
15 min	84.1	74.9	83.4	82.0	47.1	75.2	86.5	90.4

dried particles was almost the same in the range of 80 : 20 to 70 : 30 (SD5-1, 2, 3). Based on these results, the 80 : 20 ratio of Aquacoat ECD30 to triacetin was selected as the appropriate ratio.

With reference to the results obtained with the Aquacoat ECD30 and Eudragit NE30D system, the spray dry conditions with the Aquacoat ECD30 and triacetin system were investigated. For the 100% and 50% coating amounts (SD6-1, SD6-2), the dissolution rate at 15 min was too low, and coating amounts of over 50% were not suitable for bioavailability. In contrast, the characteristics of taste-masked particles with 40% and 30% coating almost met the target dissolution profiles, therefore, the 40% coating amount was selected.

As with the Aquacoat ECD30 and Eudragit NE30D system, the yield did not reach the desired value. This issue should be addressed in the next scale-up study.

Scale-Up Study of the Spray Drying Process The scale-up study was performed using a pilot-scale spray dryer with 2.2 m chamber diameter. The formula, operating conditions, and properties of the spray-dried particles are shown in Table 7. The objectives of the first scale-up study (SD7) were to evaluate the yield and compare the dissolution rate with that of the lab-scale particles. The lab-scale yield was very low at 40 to 80%, because the spray-dried particles stuck to the chamber wall. It was considered that the chamber diameter in lab-scale spray dryer was too small to obtain the 100 μm spray-dried particles. Therefore, the yield was expected to improve if the chamber diameter was increased in the scale-up study.

As shown in Table 7, the yield was 93% and 92% for the Aquacoat ECD30–Eudragit NE30D and Aquacoat ECD30–triacetin formulas (SD7-1, SD7-2), respectively. As expected, the larger chamber diameter in the scale-up study prevented the material from sticking to the chamber wall, which improved the yield. However the dissolution rate of the pilot-scale particles tended to be slightly slower than that of the lab-scale particles, even though the same formula was used.

The second scale-up study (SD8) was performed to improve the low dissolution rate at 15 min observed in the first study. Focus was placed on the combination of Aquacoat ECD30 and triacetin, and, to improve the dissolution rate, the coating amounts were decreased to 40%, which was the optimum proportion determined in the lab-scale (SD6-3). The results indicated that the size of spray-dried particles in the pilot-scale (SD8-1) was around 100 μm, and the dissolution rate was almost equal to that of the lab-scale particles. It was confirmed that a coating amounts of 40% was the best formula for both pilot-scale and lab-scale production.

Table 7. Characteristics of Spray-Dried Particles in the Scale-Up Study Manufactured Using Pilot-Scale Spray Dryer (OD-22M)

Lot No.	SD7-1	SD7-2	SD8-1	SD8-2	SD8-3
Formula					
Famotidine	1.00	1.00	1.00	1.00	1.00
Aquacoat ECD30	0.30	0.40	0.32	0.32	0.32
Eudragit NE30D	0.20	—	—	—	—
Triacetin	—	0.10	0.08	0.08	0.08
Operating condition					
Batch size (kg)	5.0	4.5	4.2	47.8	6.3
Coating amounts (%)	50	50	40	40	40
Solid content (%)	56	52	56	56	56
Spraying rate (g/min)	360	420	310	350	700
Atomizer rotation speed (rpm)	5000	5000	8000	8000	10000
Inlet temperature (°C)	120	120	120	120	170
Outlet temperature (°C)	92	94	88	90	90
Particle characteristics					
Yield (%)	93	92	91	95	92
Mean particle size (μm)	127	121	101	102	120
% Dissolved 1 min	16.0	12.6	23.3	24.6	18.1
3 min	—	—	61.4	68.5	57.4
15 min	81.0	73.8	94.3	96.5	90.8

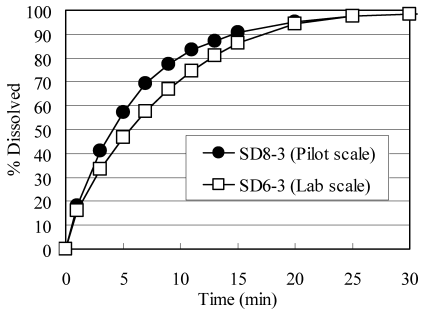

Fig. 3. Comparison of Dissolution Rate between Lab-Scale and Pilot-Scale Spray-Dried Particles

Test method: paddle method, 100 rpm in pH 6.8 buffer containing 0.1% tween 80.

The reproducibility of particle characteristics and yield on the pilot scale was investigated next. About 85 kg of spray suspension was used (SD8-2) for a 4-h continuous run test. The results showed that the dissolution rate and particle size of the spray-dried particles was almost the same as the previous short-run batch (SD8-1). This confirmed the reproducibility of particle characteristics after 4 h of continuous running. The feasibility of shortening the run time was investigated by increasing the spray rate through adjustment of inlet temperature and atomizer rotation speed (SD8-3). When the spray rate was doubled (350 g/min→700 g/min) by in-

creasing the inlet temperature to keep the same outlet temperature, spray-dried particles were manufactured without any problems, and the yield was more than 90%. The dissolution rate of the pilot-scale particles was within the target range, in fact, they were almost the same as those created on the lab-scale (Fig. 3), and the taste was acceptable.

These scale-up results indicated that the yield improved to more than 90% by increasing the chamber diameter. In addition, spray-dried particles were produced with the same dissolution rate and particle size quality as those created on the lab-scale. Reproducibility was confirmed, and it was possible to reduce the run time by doubling the spray rate through inlet temperature adjustment.

Conclusion

The taste-masking of famotidine for application to a fast-disintegrating tablet was investigated using the spray-dry method. The formulas and appropriate lab-sale manufacturing conditions were determined and the target dissolution profiles were completely accomplished. The size of the spray-dried particle was no more than 150 μm, which meant there would be no gritty feeling in patients' mouths. Spray-dried particles of the same dissolution rate and particle size quality as the lab-scale particles were produced on the pilot scale. The reproducibility of these particles was also confirmed. These results indicated that the spray-dry method produced the most appropriate taste-masked particles for fast-disintegrating dosage forms.

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