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

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A fast-disintegrating dosage form has been developed as a user-friendly formulation that disintegrates in the mouth immediately. Patients can take it without water like a liquid formulation. In this study famotidine taste-masking technology was applied to the new fast-disintegrating tablet in an attempt to produce a novel, taste-masked, fast-disintegrating tablet. Partial granulation was found to be an effective and practical way to address content uniformity, however, oral disintegration time tended to become longer as content uniformity improved. The disintegration time was improved considerably by controlling ambient humidity during the compression process (>50% RH). Furthermore, since the new fast-disintegrating technology made it possible to use low compression force, there was no change in the structure or dissolution rate of the taste-masked particles after compression. Therefore, this system can produce a taste-masked fast-disintegrating tablet with satisfactory attributes.

Key words fast-disintegrating; famotidine; taste-masking; ambient humidity; oral disintegration time

Since the ability to swallow deteriorates with age, many elderly patients find it difficult to swallow the solid dosage forms currently available, such as tablets and capsules. In a survey conducted by Honda and Nakano,[1] half of the patients experienced difficulty taking medication. To address this problem, a fast-disintegrating, user-friendly dosage form has been developed.[2,3] This formulation disintegrates immediately in the mouth so that patients can take it without water, like a liquid formulation. This will be convenient for the patients and enhance compliance, especially for those who have difficulty swallowing solid dosage forms, or do not have ready access to water. Many companies have developed various types of fast-disintegrating dosage forms. A freeze-dried porous wafer known as Zydis,[4,5] a molding tablet known as EMP,[6] an effervescent tablet known as OraSolve,[7] and a disintegrant addition[8,9] have all been developed. In addition, a new fast-disintegrating tablet consisting of high- and low-compressibility saccharides was reported in a previous study.[10]

Most of these fast-disintegrating technologies have not been applied to bitter-tasting drugs. The objective of this study was to merge technologies to produce a taste-masked, fast-disintegrating tablet. The method for producing taste-masked particles using famotidine as a model drug by the spray-drying has been previously reported.[11] In this study, famotidine taste-masked particles were applied to the new fast-disintegrating tablet in an attempt to produce a novel, taste-masked, fast-disintegrating tablet.

Experimental

Materials D-Mannitol (Mitsubishi Shoji Foodtech, brand name: Mannit P), maltose (Hayashibara, brand name: Sanmalt), Aquacoat ECD30 (Ethylcellulose Aqueous Dispersion, FMC Corporation), 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.

Preparation of Taste-Masked Particles Spray dryer model CL-8 (Ohkawara kakohki) was used for the production of taste-masked particles. Famotidine powder was suspended in Aquacoat and triacetin (famotidine : Aquacoat ECD30 : triacetin = 20 : 6.4 : 1.6) using a propeller mixer. This suspension was sprayed using the rotary atomizer method. The spray dry conditions were as follows: a spray rate of 20—40 g/min, a disk rotation speed of 6000—8000 rpm, and an inlet temperature of 100—120 °C.

Preparation of Fast-Disintegrating Tablets 1) Physical Mixture: Formula is shown in Table 1, formulation A. Mannitol was granulated with 5% (w/w) maltose solution in a fluidized-bed granulator (Uni-glatt, Okawara Mfg.) and fast-disintegrating placebo granules was produced in batch size of 500 g. The granulation conditions were as follows: a spray rate of 10 g/min, a spray pressure of 1.5 kg/cm^2, and a bed temperature of 28—35 °C. After mixing the placebo granules with 16% (w/w) taste-masked particles containing 20 mg famotidine and 0.8% (w/w) calcium stearate, the mixture was compressed using a rotary tableting machine (Hata Seisakusho) at a compression speed of 20 rpm to yield a tablet weight and diameter of 175 mg and 8.5 mm, respectively.

2) Partial Granulation: Formulas are shown in Table 1, formulations B—D. A part of mannitol and 16% (w/w) taste-masked particles in a predetermined ratio were granulated with 5% (w/w) maltose solution in the same manner as described above. The rest of mannitol was also granulated with 5% (w/w) maltose solution to make placebo granules. These two granule types in a predetermined ratio were mixed together with 0.8% (w/w) calcium stearate, and then compressed in tablet weight of 175 mg with a tablet diameter of 8.5 mm.

3) Normal Granulation: Formulas are shown in Table 1, formulations E, F. Mannitol and 16%(w/w) taste-masked particles were granulated with 4—5% (w/w) maltose solution in a fluidized-bed granulator in batch size of 500 g. After mixing the granules with 0.8% (w/w) calcium stearate, and then compressed in tablet weight of 175 mg with a tablet diameter of 8.5 mm.

As conditioning process, the tablets were kept in a thermostatic chamber set at 25 °C and 70% RH for 24 h (Tabaiespec Co., Ltd., PR-35C), followed by another period of 3 h at 30 °C and 40% RH in the same equipment.

Control of Ambient Humidity during the Compression Process The tableting equipment was covered with a clear plastic sheet, and its interior humidity was adjusted *via* controlling steam and dried air as a balance. The compression study began after the target humidity had been maintained for at least 20 min.

Recovering the Taste-Masked Particles from the Tablet The tablets were lightly crushed, and 5 ml of purified water was added. After shaking for 30 s, the suspension was filtered with a 0.45 μm filter. The water-insoluble substances were recovered from the filter paper and dried at 40 °C overnight.

Tablet Characteristics Measurement of oral disintegration time was performed using 3—4 volunteers. 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.

Hardness (n=5) was measured using a hardness tester (Schleuniger, model 6D), and the thickness (n=3) of the tablet was measured using a dial thickness gauge (Teclock). Tablet weight was indicated as the mean weight

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Table 1. Formulas of Tablets with Various Granulation Methods

	Formulation A Physical mixture	Formulation B Partial granulation (1 : 1)[a)]	Formulation C Partial granulation (1 : 2)[a)]	Formulation D Partial granulation (1 : 4)[a)]	Formulation E Normal granulation	Formulation F Normal granulation
Taste-masked particles	28	28	28	28	28	28
Mannitol	—	54.4	81.9	103.9	136.85	138.6
Maltose	—	4.38	5.8	7	8.75	7
Placebo granules						
Mannitol	136.85	82.45	55	33	—	—
Maltose	8.75	4.38	2.9	1.7	—	—
Calcium stearate	1.4	1.4	1.4	1.4	1.4	1.4
Total (mg)	175	175	175	175	175	175

a) Ratio of placebo granules to partial granules.

of 10 tablets, and friability was calculated by weight loss after 100 revolutions at 25 rpm (Pharmatest, PTFR-A). Moisture content of tablet was measured by Karl–Fischer method using 5 tablets.

Adsorption Isotherm An automatic vapor adsorption apparatus (VTI, SGA-100) was used to measure the adsorption profiles for about 10 mg of granules containing amorphous maltose. The sample was prepared by grinding granules or tablet using mortar. The adsorption profile was measured at predetermined relative humidity after drying the sample for at least 2 h at 60 °C.

Dissolution Testing Dissolution testing of tablets containing taste-masked particles of famotidine (20 mg) was performed using the paddle method at 50 rpm in water. For taste-masked particles, pH 6.8 buffer containing 0.1% Tween 80 was used because of a low wettability of particle. Famotidine was detected using the UV method (265 nm).

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

Determination of Particle Size Distribution The size distribution of taste-masked particles was measured using a robot sifter (RPS-85, Seishin Enterprise).

Results and Discussion

Determination of the Amount of Maltose as a Granulation Binder To achieve objectives, the criteria for tablet characteristics were summarized in Table 2. The hardness was more than 30 N, and the friability was less than 1% after 100 revolutions to assure adequate durability during handling. The oral disintegration time was 20—30 s or less for a fast-disintegrating tablet. The dissolution rate was less than 30% at 1 min (to suppress the bitter taste of famotidine), but more than 85% at 15 min (to obtain a good bioavailability).[11)]

To determine the amount of maltose that should be used as binder in the formulation, tablets containing 2, 3, and 5% (w/w) maltose were all manufactured to compare their characteristics. During compression, the relative humidity was controlled at two levels, about 40% RH and about 50% RH, and the compression force was adjusted so that about 15 N of initial hardness could be obtained. Table 3 shows the properties of tablets granulated with different amounts of maltose and compressed at different ambient humidity levels.

Oral disintegration time was shorter for the tablets manufactured at 50% RH than those at 40% RH and showed statistically significant difference at 3 and 5% (w/w) maltose ($p<0.05$). Sebhatu *et al.*[12)] reported an increased moisture content gave an increased tablet tensile strength. Consequently, it was presumed that the humidity helped increase of compressibility, thereby allowing the target initial hardness, 15 N, to be obtained at a lower compression force. As a result, tablet thickness and porosity increased, which led to a shorter oral disintegration time. Thus, controlling ambient humidity is an effective and practical way to improve oral disintegration time. Furthermore tablet hardness increased about 30 N *via* a conditioning process which changed amorphous maltose to crystal state and achieved the target hardness.

Table 2. Criteria for Tablet Characteristics

Tablet characteristics	Criteria
Hardness	>30 N
Friability at 100 revolutions	<1 %
Oral disintegration time	<20—30 s
Dissolution rate at 1 min	<30%
Dissolution rate at 15 min	>85%

When 2% (w/w) maltose was used as a binder, the disintegration time was prolonged, even at 50% RH, because of high compression force and decreased thickness that led to the low porosity of tablet. In contrast, there was no difference in the tablet properties when 3% (w/w) and 5% (w/w) maltose were used, and both 3% (w/w) and 5% (w/w) maltose tablets manufactured at 50% RH met the target disintegration time within 20 s. Since 3% (w/w) maltose was not considered to be enough binder amounts for forming the target granules, 4—5% (w/w) was selected as the amount of maltose. However, the friability needed to be improved in further investigation, since that of 5% (w/w) maltose tablets did not meet the criteria (less than 1%, based on USP).

Improvement of Content Uniformity Since physical mixture is a simple and low cost process, the physical mixing of taste-masked particles and fast-disintegrating placebo granules which was granulated mannitol with 5% (w/w) maltose was attempted. The physical mixture of taste-masked particles and fast-disintegrating placebo granules was compressed after 30 min of mixing. The tablet taken at each sampling time and whole tablets were then assayed and tested for content uniformity (Tables 1 and 4, formulation A). Although the CV% for the content uniformity at each sampling time were less than 2%, that of the whole tablets was more than 3%, which was unacceptable. The reason for high CV%, found in the whole tablets, was that the flowability between taste-masked particles and fast-disintegrating placebo granules was quite difference. Therefore, the physical mixture method was deemed inappropriate.

In an attempt to improve content uniformity, the partial

Table 3. Properties of Tablets Granulated with Different Amounts of Maltose and Compressed at Different Ambient Humidity Levels

Ambient humidity	2% (w/w) maltose		3% (w/w) maltose		5% (w/w) maltose	
	24 °C 43% RH	25 °C 52% RH	24 °C 43% RH	26 °C 51% RH	24 °C 42% RH	25 °C 52% RH
Compression force (kN)	1.7	1.5	1.7	1.0	1.5	0.8
Tablet weight (mg)	176.1	175.2	177.5	174.8	176.9	174.5
Thickness (mm)	3.67±0.01	3.67±0.01	3.74±0.01	3.81±0.01	3.8±0.01	3.96±0.01
Initial hardness (N)	14±0.9	13±0.5	16±0.5	14±1.9	15±0.5	14±0.7
Treated hardness (N)	27±1.9	27±0.7	36±1.3	27±0.8	41±1.5	32±0.7
Friability (100 revolutions, %)	1.33	1.30	0.91	1.65	0.80	1.20
Oral disintegration time (s)	25±0.7	24±2.5	20±0.7	15±2.1*	22±1.4	14±1.4*

Mean±S.D. * t-test, $p< 0.05$.

Table 4. Effect of Granulation Method on the Content Uniformity of the Tablet

Tableting time	Formulation A Physical mixture		Formulation B Partial granulation (1 : 1)[b]		Formulation C Partial granulation (1 : 2)[b]		Formulation D Partial granulation (1 : 4)[b]		Formulation E Normal granulation	
	Assay (%)	CV%[a]	Assay (%)	CV%[a]	Assay (%)	CV%[a]	Assay (%)	CV%[a]	Assay (%)	CV%[a]
Start	92	1.17	97	1.59	106	1.71	101	0.89	101	1.15
20 min	—	—	—	—	109	1.76	—	—	—	—
40 min	98	1.53	102	1.02	111	1.31	100	1.68	103	0.91
60 min	—	—	—	—	110	1.33	—	—	—	—
80 min	100	1.08	102	0.94	—	—	101	1.35	105	1.81
Whole tablet	96	3.67	100	2.47	109	2.32	101	1.36	103	1.84
Oral disintegration time (s)[c]	13±2.5		16±1.0		17±2.5		24±4.5		26±3.5	

a) Coefficient of variation. *b*) Ratio of placebo granules to partial granules. *c*) Mean±S.D.

granulation method was tried (Tables 1 and 4, formulations B—D). A part of mannitol and taste-masked particles were granulated with 5% (w/w) maltose, and this granule was mixed with placebo granule at predetermined ratios (placebo granule : partial granule = 1 : 1 to 1 : 4). As with the physical mixture, the CV% at each sampling time were within the target value in all lots. Furthermore, the CV% for whole tablets improved with the increase in the ratio of partial granulation, with formulation D (1 : 4) showing a good CV% of less than 2%. The reason was that the high flowability of taste-masked particles by partial granulation with mannitol was closely related to that of fast-disintegrating placebo granules. However, the oral disintegration time was longer as the ratio of partial granulation increased (more than 20 s for formulation D). Furthermore, the normal granulation (Tables 1 and 4, formulation E), which was granulated the mixture of taste-masked particles and all of the mannitol with 5% (w/w) maltose, showed a good CV% for content uniformity, but disintegration time was prolonged. In conclusion, the granulation of mannitol and taste-masked particles improved content uniformity, but prolonged oral disintegration time.

Improvement of Oral Disintegration Time It would be possible to improve oral disintegration time by controlling moisture content as shown in Table 3. Since moisture content in granules was easy to control by drying condition in granulation process, the control of granule moisture content was investigated in an attempt to improve the oral disintegration time. However, the granules containing amorphous maltose absorbed moisture readily as referred to hereinafter (Fig. 1), and it was predicted granule moisture content was easily changed by ambient humidity over the course of compression. Therefore, considering commercial production, the control of granule moisture content was not a valid approach for improving oral disintegration time.

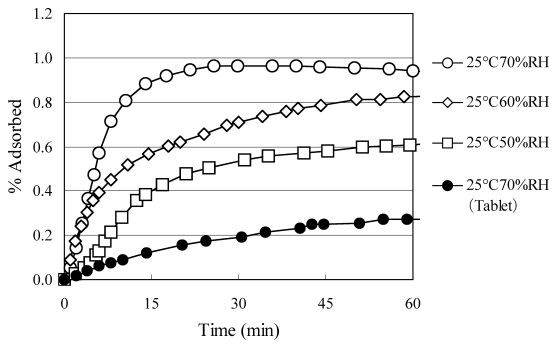

Fig. 1. Adsorption Profiles of Granules and Tablet under Different Relative Humidity

The effect of ambient humidity during the compression process on tablet characteristics was examined in detail in an attempt to enhance oral disintegration time. The mixture of taste-masked particles and mannitol was granulated with 4% (w/w) maltose (normal granulation) and mixed with 0.8% (w/w) calcium stearate (Table 1, formulation F). When these granules were stored at 50, 60, and 70% RH, the granule adsorbed moisture rapidly as shown in Fig. 1. The reason for this rapid adsorption was that the maltose used as the binder was present in an amorphous state that absorbed moisture readily as described previously.[10] As a consequence, compression was started after the granules had been allowed to sit in the tablet equipment under controlled ambient humidity

Table 5. Effect of Ambient Humidity during Compression on Tablet Characteristics

Ambient humidity during compression	23 °C 30% RH	23 °C 40% RH	24 °C 50% RH	23 °C 57% RH	24 °C 65% RH
Compression force (kN)	1.8	1.8	1.6	1.4	0.99
Tablet weight (mg)	175.4	175.2	175.1	175.4	175.2
Thickness (mm)	3.76±0.01	3.74±0.01	3.74±0.01	3.82±0.01	3.85±0.01
Moisture content of initial tablet (%)	—	0.54	0.59	0.62	0.82
Initial hardness (N)	15±1.3	16±0.9	15±0.9	16±1.1	15±1.6
Treated hardness (N)	41±1.3	38±4.4	37±2.3	35±2.6	34±1.9
Friability (100 revolutions, %)	0.22	0.30	0.32	0.29	0.17
Oral disintegration time (s)	25±3.0	23±1.5	19±1.5*	17±2.6*	14±2.4*

Each values represent the mean±S.D. * *t*-test, $p<0.05$ compared with value of 23 °C 30% RH.

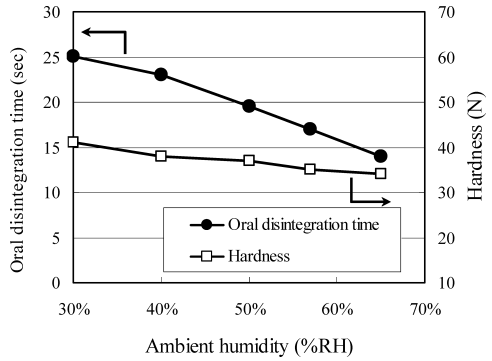

Fig. 2. Relationship between Ambient Humidity during Compression and Oral Disintegration Time and Hardness

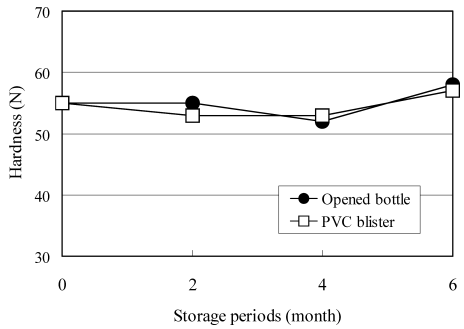

Fig. 3. Stability of Tablet Hardness under 25 °C 75% RH Storage Conditions

(30—65% RH) for more than 20 min to equilibrate to the target humidity.

When the initial hardness was set at 15 N, the compression force decreased with the increase in ambient humidity and with the increase of moisture content of tablets as shown in Table 5. Figure 2 shows the relationship between ambient humidity during the compression process and oral disintegration time or hardness. The hardness kept more than 30 N which was a sufficient strength level for handling, even though ambient humidity increased. In contrast, oral disintegration time was shorter as ambient humidity increased, and reached the target value (less than 20 s) at RH levels of more than 50%. Oral disintegration time at more than 50% RH showed statistically significant difference from that of 30% RH ($p<0.05$). It was presumed that humidity would play a peripheral role in the enhancement of compressibility. Consequently, it was confirmed that controlling ambient humidity during the compression process at more than 50% RH was a promising way to achieve quick disintegration.

The friability was also improved to less than 1% as shown in Table 5, since the adequate strength was achieved by appropriate selection of granulation and compression conditions. Furthermore, since amorphous maltose was intentionally changed into the crystalline state *via* a conditioning process, the tablet hardly adsorbed any moisture, even at 25 °C 70% RH (Fig. 1). Under these conditions, tablet characteristics like hardness was expected to be stable during storage. Figure 3 shows the stability of tablet hardness under 25 °C 75% RH storage conditions in opened bottle and PVC blister packaging forms and both hardness were stable for 6 months as expected.

Influence of Compression Force on the Characteristics of Taste-Masked Particles In general, when a tablet contained dissolution-controlled particles, the dissolution-control attribute was generally damaged by compression force and its dissolution rate was accelerated. However, the new fast-disintegrating technology[10] applied in this study would be produced with low compression pressure and enable to avoid damage to the dissolution-control attribute. The new fast-disintegrating formulation included high- and low-compressibility saccharides. The high-compressibility saccharide used as a binder solution was present in an amorphous state after the granulation process. The change from the amorphous to crystalline state was induced intentionally *via* a post-compression conditioning process that strengthened adhesion between particles in the tablet, thereby enhancing hardness. Therefore, the application of this new fast-disintegrating technology was not expected to damage the dissolution-control attribute because the tablets were compressed with low force, while still maintaining sufficient hardness.

Figure 4 shows scanning electron micrographs of (a) intact taste-masked particles and (b) particles recovered from tablets (Table 1, formulation F). The surface of the intact taste-masked particle was coated smoothly with no observable famotidine crystals. In contrast, the surface of the recovered particle was a little bit rough due to being recovered *via* water washing, but its spherical structure remained intact. Therefore, it could be concluded that the structure of taste-masked particles was not damaged by compression pressure, and the taste-masked attribute was maintained. Furthermore, the distributions of taste-masked particles recovered from tablets (Table 1, formulation F) compressed under different pressures were evaluated and compared to that of the intact taste-masked particles (Table 6). For all tablets, the mean size of the particles was almost the same as that of intact particles. The particle distributions were also identical. These re-

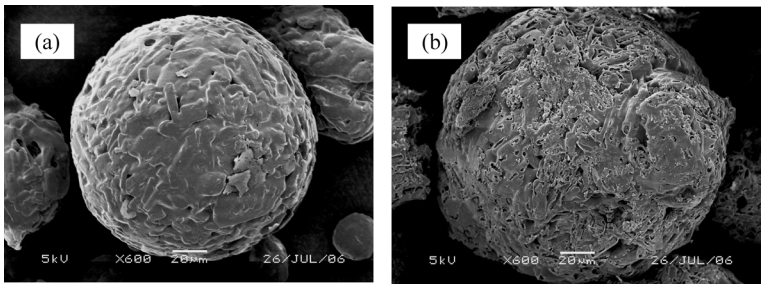

Fig. 4. Scanning Electron Micrographs of (a) Intact Taste-Masked Particles and (b) Particles Recovered from Tablets

Table 6. Particle Distribution of Intact Taste-Masked Particles and Particles Recovered from Tablets

	Intact taste-masked particles	Particles recovered from tablets compressed at 2 kN	Particles recovered from tablets compressed at 4 kN	Particles recovered from tablets compressed at 6 kN
Mean particle size (mm)	79.3	72.8	82.3	78.6
Particle distribution (%)				
150 μm—	6.0	4.2	9.0	6.4
106—150 mm	23.0	22.3	23.9	23.9
45—106 μm	57.3	57.5	57.9	57.9
45 μm or less	13.1	16.0	11.8	11.8

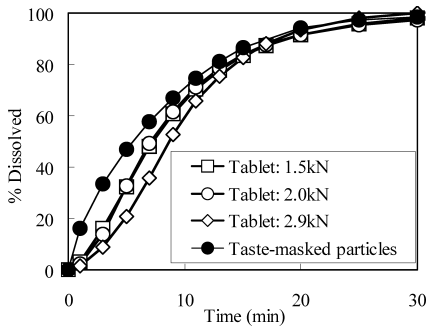

Fig. 5. Dissolution Profiles for Famotidine from Tablets Compressed at Various Pressures and Taste-Masked Particles by Paddle Method at 50 rpm in Water for Tablet and in pH 6.8 Containing 0.1% Tween80 for Taste-Masked Particles

sults suggested that taste-masked particles were not crushed during compression. Figure 5 shows the dissolution rates of tablets (Table 1, formulation F) compressed at various pressures and taste-masked particles as reference. Dissolution rates of all tablets showed the almost the same as taste-masked particles, although dissolution medium for taste-masked particles was pH 6.8 buffer containing 0.1% Tween 80 because of a low wettability of particle. Namely dissolution rates of tablets were not affected by compression pressure. It was confirmed that compression did not affect the taste-masking attribute and those tablets conformed to the target dissolution rates, D1 min$<$30% and D15 min$>$85%, and showed no bitter taste of famotidine.

In conclusion, partial granulation was an effective way to solve the content uniformity problem, even for tablets containing taste-masked particles. Unfortunately, oral disintegration time tended to be longer as content uniformity improved. However, when ambient humidity was maintained at 50% RH, or more during compression, a quick disintegration time was achieved. In addition, since the new fast-disintegrating technology made it possible to compress at a low compression force, no changes in the structure or dissolution rate of the taste-masked particles occurred after compression. Therefore, the system described in this report successfully produced a taste-masked, fast-disintegrating tablet with satisfactory attributes.

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