

## Preparation and Evaluation of Taste Masked Orally Disintegrating Tablets with Granules Made by the Wet Granulation Method

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Using furosemide (FU) as a model drug, we examined the wet granulation method as a way to improve the taste masking and physical characteristics of orally disintegrating tablets (ODTs). In the wet granulation method, yogurt powder (YO) was used as a corrective and maltitol (MA) was used as a binding agent. The taste masked FU tablets were prepared using the direct compression method. Microcrystalline cellulose (Avicel® PH-302) and mannitol were added as excipients at a mixing ratio of 1/1 by weight. Based on the results of sensory test on taste, the prepared granules markedly improved the taste of FU, and a sufficient masking effect was obtained at the YO/FU ratio of 1 or more. Furthermore, it was found that the masking effect achieved by YO granules made with the wet granulation method was similar to or better than that produced by the granules made with dry granulation method. All types of tablets displayed sufficient hardness (over  $3.5 \times 10^{-2}$  kN), and rapidly disintegrating tablets were obtained with YO granules produced at a mixing ratio of FU/YO=1/1, which disintegrated within 20 s. Disintegration time lengthened as the mixing ratio of YO to FU increased. In the mixing ratio of FU/YO=1/1, the hardness of tablets with granules made by the wet granulation method exceeded that of tablets with granules made by the dry granulation method, with minimal differences in disintegration time. The hardness and disintegration time of the tablets with granules made by the wet granulation method could be controlled by varying the compression force. In conclusion, YO was found to be a useful additive for masking unpleasant tastes. FU ODTs with improved taste, rapid disintegration and greater hardness could be prepared with YO-containing granules made by the wet granulation method using MA as a binding agent.

**Key words**—orally disintegrating tablet; wet granulation method; maltitol; yogurt powder; taste masking

### INTRODUCTION

As the practice of medicine advances, the apparent needs of patients change. In drug therapy, for example, it has become essential to improve patients' quality of life (QOL) and rates of treatment compliance. Although various dosage forms are used in drug therapy, oral dosage forms such as tablets, capsules, powders, granules and liquids are in wide use. In particular, tablets may be the most convenient dosage form for patients over a broad age range,<sup>1)</sup> because they can be easily handled and transported, and remain stable for a prolonged period.<sup>2)</sup> Oral dosage forms are not ideal for all patients, however, since many elderly patients often have difficulty swallowing tablets as well as capsules.

Therefore, it is desirable to develop a dosage form that can be easily used by elderly patients. Starting in

the late 1980s, orally disintegrating tablets (ODTs) were developed as an easily ingestible dosage form for patients with swallowing disorders, including elderly persons. ODTs are now widely used in clinical practice. Since ODTs rapidly disintegrate in saliva or in a small volume of water, elderly, infantile, and dialysis patients with restricted water intake can easily ingest them. They have been produced by various methods, including drying after filling the pockets of a blister package with a drug dispersion,<sup>3,4)</sup> drying after low-pressure compression of wet powder and/or granules,<sup>5-7)</sup> compression of dry powder and/or granules,<sup>8-10)</sup> and shaping by direct compression after mixing excipients with the drug.<sup>11)</sup> One problem with ODTs is that, unlike conventional tablets, they allow patients to taste the drug. Because an unpleasant or bitter taste of the drug often leads to patients' non-compliance and reduction of QOL, taste masking is necessary in designing ODTs.

Several taste-masking options are available, includ-

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ing sensory masking by adding correctives, chemical masking by means of chemical modifications such as the preparation of prodrugs and inclusion compounds of drugs, masking by coating the drug surface, and physical masking using a matrix or by inhibiting oral drug dissolution through adsorption to additives.<sup>12)</sup> The sensory masking method, being simple and inexpensive, is usually the first choice. Sweeteners and other flavors used for sensory masking include sugars and sugar alcohols such as sucrose, xylitol, maltose, sorbitol and mannitol, as well as aromatic substances such as cocoa, green tea, coffee, vanilla, apple and strawberry.<sup>13,14)</sup>

We focused on the development of taste masked ODTs by sensory masking because that is a simple method. In a previous study,<sup>15)</sup> we attempted to prepare the masked taste granules by the dry granulation method using furosemide (FU) as a model drug and maltitol (MA) and yogurt powder (YO) as correctives. As the results, it was suggested that YO with sourness is more useful than MA with sweetness in masking the taste of FU and that the taste masked ODTs can be prepared with the YO-containing granules.<sup>15)</sup> However, further improvement was necessary for taste masking and hardness of tablets. In this study, we prepared and evaluated the ODTs using YO-containing granules made by the wet granulation method.

## MATERIALS AND METHODS

**Materials** Furosemide (FU; Sigma Co., Ltd., South Croydon, Australia) was used as a model drug. For granule preparation, yogurt powder (YO; T. Hasegawa Co., Ltd., Tokyo, Japan) was used as a corrective. Maltitol (MA; Towa Chemical Industry Co., Ltd., Osaka, Japan) was used as a binding agent. Microcrystalline cellulose (Avicel® PH302, Asahi Chemical Co., Ltd., Tokyo, Japan) and mannitol (Towa Chemical Industry Co., Ltd., Osaka,

Japan) were used as fillers for tablet preparation. Magnesium stearate (Mg-St; Kozakai Pharmaceutical Co., Ltd., Tokyo, Japan) was used as a lubricant. All other reagents used were of analytical grade.

**Preparation of Granules** According to the formulation shown in Tables 1 and 2, YO was mixed with FU to mask its taste at ratios of 1/1, 2/1 and 3/1 by weight, and granules were prepared by means of the wet granulation method using 10–30% (w/v) MA aqueous solution as a binder. The aqueous binder solution amounts were 5% (v/w) of granules. The granules were dried at 60°C for 24 h, and the granules that passed through a 20-mesh sieve but remained on a 22-mesh sieve were used in this study. The obtained granules were checked for their apparent density, calculated as the ratio of weight to the apparent volume (Table 1).

**Sensory Test on Taste** A sensory test on taste of all granule preparations was performed using 6 healthy adult volunteers (5 males and 1 female, with a mean age of 33.3 years). This test was done according to the Declaration of Helsinki. Namely, prior to the tasting, the volunteers were informed precisely about

Table 1. Formulation and Apparent Density of YO-containing Granules Prepared by Means of the Wet Granulation Using MA as a Binding Agent

Granules	Mixing ratio	MA aqueous solution conc. (%)	App. density (g/ml)
Y1-10M	FU/YO (1/1)	10	0.385
Y1-20M		20	0.333
Y1-30M		30	0.281
Y2-10M	FU/YO (1/2)	10	0.417
Y2-20M		20	0.455
Y2-30M		30	0.453
Y3-10M	FU/YO (1/3)	10	0.524
Y3-20M		20	0.389
Y3-30M		30	0.468

Table 2. Formulation of Tablets Prepared from YO-containing Granules

Formulation	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8	Y9
	Y1-10M	Y1-20M	Y1-30M	Y2-10M	Y2-20M	Y2-30M	Y3-10M	Y3-20M	Y3-30M
Granules : FU/YO (mg)	20/20	20/20	20/20	20/40	20/40	20/40	20/60	20/60	20/60
Mannitol (mg)	80	80	80	70	70	70	60	60	60
Microcrystalline cellulose (mg)	80	80	80	70	70	70	60	60	60
Total (mg)	200								

the purpose of the tasting and the pharmacological characteristics and possible adverse effects of FU. They rinsed their mouths sufficiently before and after the tasting. FU powder and each sample were kept in the volunteer's mouth for 30 s and then spat out. FU powder tasted unpleasant for all the volunteers, and its taste was recognized as the score 1. When the unpleasant taste by FU was lost completely and only the taste of FU was felt, the score was set to 5. The taste score was set to the range of 1–5 based on the degree of FU unpleasant taste in the manner as reported previously.<sup>15,16</sup> Namely, the scores were set as follows: 1 (distasteful, equivalent to FU powder taste), 2 (slightly taste, FU taste remaining fairly), 3 (mean, FU taste remaining to some extent), 4 (slightly tasty, FU taste slightly remaining), 5 (tasty, FU taste is completely lost and only YO taste). The scores were analyzed using the Kruskal-Wallis test, in which a higher score was considered to indicate a higher masking effect, and  $p < 0.05$  was regarded as significant.

**Preparation of Tablets** An SSP-10A manual press (Shimadzu Corp., Kyoto, Japan) was used to produce tablets. Flat tablets with a diameter of 10 mm (200 mg/tablet) were prepared. These tablets contained the granules along with mannitol and microcrystalline cellulose at a mixing ratio of mannitol to microcrystalline cellulose = 1/1, according to the compositions shown in Table 2. A small amount of Mg-St was added as a lubricant.

**Physical Characteristics of Tablets** Hardness was measured in the diametral direction using a Monsanto hardness tester (Creve Coeur, MO, USA). This measurement was performed on 6 tablets of each type and the mean hardness for each type was calculated.

Tablet disintegration time was measured at 37°C using the JP 15th disintegration test apparatus (Toyama Sangyo Co., Ltd., Osaka, Japan), and defined as the time taken for each tablet to completely disintegrate and disappear from the basket. Purified water was used as the test medium. This measurement was performed on 6 tablets of each type and the mean disintegration time for each type was calculated.

Water absorption time of tablets was measured using methylene blue aqueous solution to find the disintegration mechanism of the tablets. Absorbent cotton soaked with a 0.04% aqueous solution of methylene blue was placed in a dish. A tablet was placed flat on the cotton, and the time required to change the color

of the whole tablet to blue was measured as water absorption time. This measurement was performed on 6 tablets of each type and the mean water absorption time for each type was calculated.

**RESULTS**

**The Taste-masking Effect of Granules** The results of the granule sensory test on taste are shown in Table 3. In this test, the median score for granules with YO ranged from 4–5. YO-containing granules were given high scores regardless of the FU/YO mixing ratio and the concentration of MA solution. It was found that high taste-masking effects could be achieved by adding a quantity of YO equal to or more than that of FU.

**Physical Characteristics of the Tablets**

**Hardness of Tablets** Initially, all tablets were pressed from granules prepared at a compression pressure of 1 kN for 30 s. The hardness values of these tablets are shown in Fig. 1. The hardness of each tablet was  $3.5 \times 10^{-2}$  kN or greater, and was not affected by the FU/YO mixing ratio.

In addition, we prepared Y1 tablet under varying levels of compression force to investigate the in-

Table 3. Sensory Test (Taste) of Granules

Granules	Y1-10M	Y1-20M	Y1-30M	Y2-10M	Y2-20M	Y2-30M	Y3-10M	Y3-20M	Y3-30M
Median	4	4.5	4.5	5	5	4.5	5	4.75	5
Minimum–Maximum	3–5	3–5	3–5	3–5	3–5	4–5	2–5	4–5	3–5

No significant among granules ( $p > 0.05$ ).

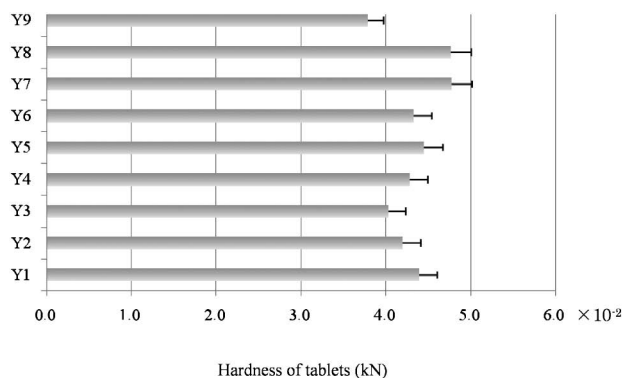


Fig. 1. Hardness of Tablets Prepared from YO-containing Granules  
 Compression force: 1 kN. The length of each bar indicates the mean  $\pm$  S.D. ( $n=6$ ).

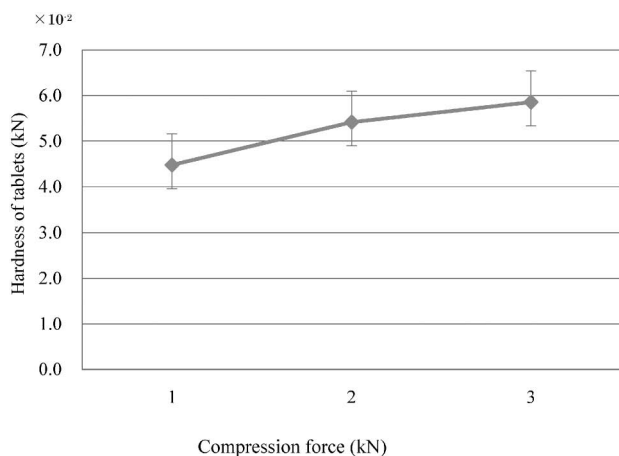


Fig. 2. Effect of Compression Force on Hardness of Tablets Prepared from Y1-10M Granules  
Each point represents the mean ±S.D. (n=6).

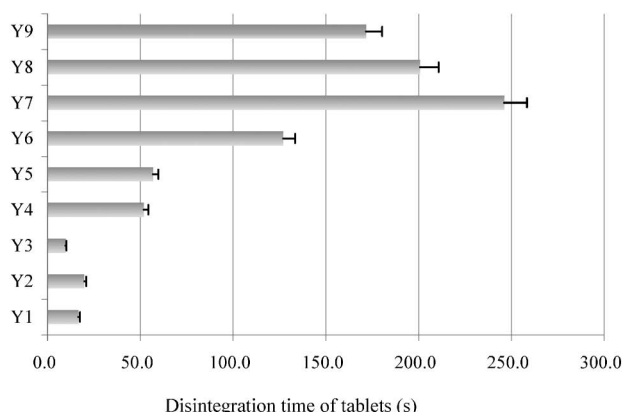


Fig. 3. Disintegration Time of Tablets Prepared from YO-containing Granules  
Compression force: 1 kN. The length of each bar indicates the mean ±S.D. (n=6).

fluence of compression force on tablet hardness (Fig. 2). The hardness of Y1 tablet increased as the compression force rose.

**Disintegration Time of Tablets** The disintegration times of the tablets prepared at a compression force of 1 kN for 30 s are shown in Fig. 3. Y1, Y2 and Y3 tablets prepared using the granules made at a FU/YO mixing ratio of 1/1 disintegrated much more rapidly, within 20 s. The disintegration time lengthened as the mixing ratio of YO to FU increased. From these findings, it was concluded that the tablets obtained using Y1 granules showed very short disintegration time (less than 20 s) and sufficient hardness (greater than  $3.5 \times 10^{-2}$  kN). Moreover, the influence of compression force on the disintegration time of Y1 tablets was also investigated (Fig. 4). The disintegrated

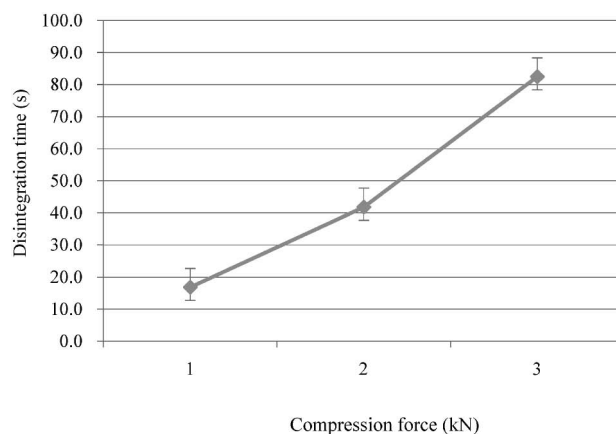


Fig. 4. Effect of Compression Force on Disintegration Time of Tablets Prepared from Y1-10M Granules  
Each point represents the mean ±S.D. (n=6).

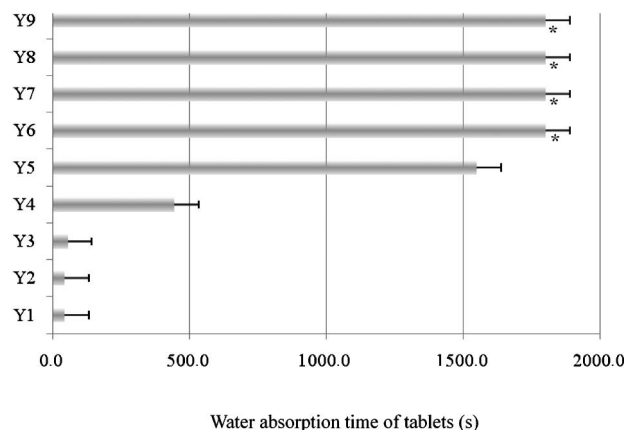


Fig. 5. Water Absorption Time of Tablets Prepared from YO-containing Granules  
Compression force: 1 kN. The length of each bar indicates the mean ±S.D. (n=6). \*Over 1800 sec.

tion times of Y1 tablets lengthened as compression force increased.

**Water Absorption Time of Tablets** The water absorption time of the prepared tablets was measured to study the difference in disintegration time among all the tablets. The water absorption times of the tablets prepared using granules at a compression force of 1 kN for 30 s are shown in Fig. 5. The tablets prepared from granules composed of FU and YO at a mixing ratio of 1/1 showed the fastest water absorption. The water absorption time lengthened as the YO content increased.

In addition, we also investigated the influence of compression force on water absorption time in Y1 tablet. It was found that absorption time lengthened as compression force rose (Fig. 6).

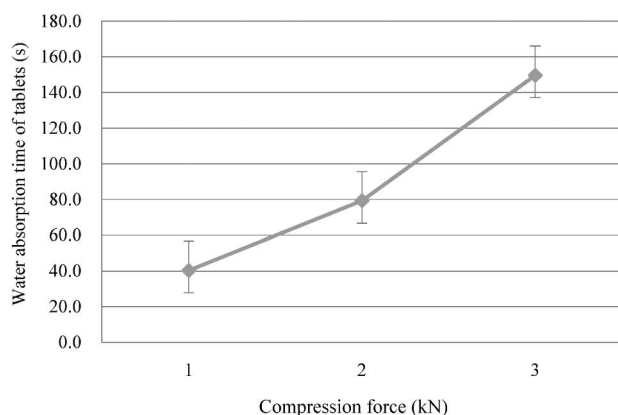


Fig. 6. Effect of Compression Force on Water Absorption Time of Tablets Prepared from Y1-10M Granules  
Each point represents the mean  $\pm$ S.D. ( $n=6$ ).

## DISCUSSION

FU has an unpleasant taste, and we attempted to prepare ODTs using a sensory taste-masking technique. The taste masked granules were first prepared by the wet granulation method using YO and MA, and then tablets were produced using these granules. In order to produce taste-masked granules, YO was added to FU at various mixing ratios, and an MA solution was used as a binder. As a result of the sensory test on taste, the median score for YO-containing granules made by wet granulation method ranged from 4–5 (Table 3). In our previous study, the median score of the mixture of FU and corn starch (1 : 1, w/w) was 1, and that of YO-containing granules made by dry granulation method ranged from 3–3.5.<sup>15,16)</sup> Therefore, it was indicated that the wet granulation method was similar or better than to the dry granulation method for taste masking. The improvement may be because MA was used as binder in this study. Further, the increase of amount of YO did not affect taste score. It was found that a sufficient masking effect could be achieved by the addition of a quantity of YO equal to that of FU.

The hardness of tablets prepared using taste masked granules was not affected by the ratio of FU to YO. All types of tablets exhibited hardness of more than  $3.5 \times 10^{-2}$  kN. The disintegration time lengthened with the increase in the concentration of YO. The tablets prepared using granules at a FU/YO mixing ratio of 1/1, which showed a sufficient masking effect, could withstand a force over  $3.5 \times 10^{-2}$  kN, and disintegrated rapidly (within 20 s). As reported

previously,<sup>15)</sup> the hardness and disintegration time of tablets prepared using granules made by the dry granulation method were approximately  $3.43 \times 10^{-2}$  kN and 18.5 s, respectively. Based on those findings, the tablets by wet granulation appeared to show good hardness and rapid disintegration ability, similar to or better than the previously reported tablets by dry granulation. The influence of compression force on the physical characteristics of the tablets in this study was similar to that found for the dry granulation method, namely, the hardness and disintegration time of tablets could be controlled by altering the compression force.

From the water absorption properties of the tablets, it was suggested that water absorption rate should be importantly related to the disintegration rate of the tablets produced by the wet granulation method as in the case of the tablets produced by the dry granulation method. When FU and YO were mixed in equal amounts, the disintegration time was correlated with water absorption time. Increase in the concentration of YO lengthened water absorption time of the tablets. It seems that the different solubility and binding abilities of YO affect the water absorption times of the resulting tablets. Also, addition of microcrystalline cellulose and mannitol at a higher ratio might be one of the reasons for rapid water absorption in the tablets prepared using the Y1 granules. Greater compression force raised hardness and water absorption time probably due to the promotion of the contact of components and lower porosity of the tablets, which are general phenomena.

## CONCLUSION

Using FU, which has an unpleasant taste, as a model drug, we produced and characterized taste masked ODTs using the granules prepared by the wet granulation method to find the adequate condition to obtain better taste masked ODTs. The YO-containing granules were clearly useful for masking the unpleasant taste of the FU. The taste masking was completed well for all the formulations, and the effect was not so different among these formulations. When the tablets were produced by compression using microcrystalline cellulose and mannitol as excipients, the tablets made with the granules prepared at a FU/YO mixing ratio of 1/1 exhibited excellent hardness and the most rapid disintegration, though the hardness and disintegration time depended on the compression

force.

The moderate sourness based on YO appeared to act effectively for the masking of FU tastes. In addition, it was indicated that the addition ratio of YO to FU did not have to be high for masking of the FU tastes.

In summary, we have found that the wet granulation method using YO as a corrective and MA as a binding agent is useful for masking unpleasant tastes of FU, and that good taste masked ODTs with rapid disintegration time and excellent hardness could be prepared with the granules of the mixing ratio of FU/YO=1/1.

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