—Regular Articles—

Preparation of Orally Disintegrating Tablets with Taste-masking Function: Masking Effect in Granules Prepared with Correctives Using the Dry Granulation Method and Evaluation of Tablets Prepared Using the Taste-masked Granules

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We investigated several methods of taste masking in the preparation of orally disintegrating tablets (ODTs), using furosemide (FU) as a model drug. Four types of FU preparations were prepared: granules with maltitol (MA), granules with yogurt powder (YO), a physical mixture of FU and MA, and a physical mixture of FU and YO. All taste-masking granules were prepared using the dry granulation method. The taste of each type of preparation was evaluated. All four preparations markedly improved the taste of the FU tablets, but the mixing ratios of the correctives did not affect the masking effect. No difference in masking effect was found between MA and YO in the physical mixtures, but the masking effect in the granules with YO was superior to that of the granules with MA. Taste-masked FU tablets were prepared using the direct compression method; crystalline cellulose (Avicel PH-302) and mannitol were added as excipients at the mixing ratio of 1/1. All four types of tablets displayed sufficient hardness, but MA-containing tablets were harder than YO-containing tablets. The hardness of the tablets prepared from YO granules increased as the YO content increased. The most rapidly disintegrating tablets were those of YO granules prepared at a mixing ratio of FU/YO=1/1, which disintegrated within 20 s, followed by the tablets of MA granules prepared at a mixing ratio of FU/MA=1/1. The disintegration times of the tablets made from physical mixtures, in contrast, were longer than 200 s. Disintegration time lengthened as the mixing ratio of YO or MA increased. The hardness and disintegration time of these tablets could be controlled by varying the compression pressure. We found that YO is more useful than MA in masking unpleasant tastes and confirmed that orally disintegrating tablets with taste-masking function can be prepared using granules of YO prepared using the dry granulation method as a new corrective.

Key words——orally disintegrating tablet; dry granulation method; maltitol; yogurt powder; taste-masking

INTRODUCTION

With advances in medical care, the needs of patients have increased. In drug therapy, improved treatment compliance and patients' quality of life (QOL) have come to be regarded as essential. Various dosage forms are used in drug therapy, including oral and external preparations and injections; among these, oral dosage forms such as tablets, capsules, powders, granules, and liquids are widely used. Tablets may be the most convenient dosage form for patients over a broad age range,[1] because they can be easily handled, easily transported, and are stable for a prolonged period.[2] Patients with swallowing disorders often find it difficult to swallow tablets, however. When swallowing tablets is not possible, the dosage form may be switched to powders or liquids, or tablets may be ground or dissolved, but grinding and dissolution are not applicable for many medications due to their stability, enteric coating, unpleasant taste, or irritation. Therefore the development of new preparations is expected to solve this problem.[3]

Recently, orally disintegrating tablets (ODTs) have been developed as an easily ingestible dosage form for patients with swallowing disorders including elderly persons,[4–11] and they are now widely administered clinically. Since ODTs rapidly disintegrate in saliva or in a small volume of water, elderly, pediatric, and hemodialysis patients with restricted water intake can easily ingest this dosage form. ODTs with sufficient disintegration ability and strength may be prepared using the liquid-drying method, wet compression method, or dry compression method. One problem with ODTs is that, unlike conventional tablets, they allow patients to taste the medication. Unpleasant or bitter tastes of drugs can result in patient noncompli-

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ance and reduction of QOL, and thus taste masking is necessary in designing ODTs.

Several taste-masking options are available, including sensory masking by adding correctives, chemical masking by chemical modification such as the preparation of prodrugs and inclusion compounds of drugs, masking by coating the particle surfaces, masking using a matrix, and physical masking by physically inhibiting drug dissolution in the mouth through adsorption to additives.[12] The sensory-masking method, which is simple and low cost, 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; aromatic substances, such as cocoa, green tea, coffee, vanilla, apple, and strawberry, are applicable as correctives.[13,14]

In this study, to solve the problem of the unpleasant taste of ODTs, we prepared ODTs containing furosemide (FU), which has an unpleasant taste and is commonly administered to dialysis patients. We chose maltitol (MA) and yogurt powder (YO) as correctives because MA as a masking agent, has a sweet taste, and is a flavoring and taste-improving agent and YO is used as a food additive. ODTs of FU were prepared using several sensory-masking preparation methods including taste-masked granules and physical mixtures with MA and YO.

MATERIALS AND METHODS

Materials FU (Sigma Co., Ltd., South Croydon, Australia) was used as a model drug. For granule preparation, MA (Towa Chemical Industry Co., Ltd., Osaka, Japan), YO (T. Hasegawa Co., Ltd., Tokyo, Japan), and cornstarch (CS, Kozakai Pharmaceutical Co., Ltd., Tokyo, Japan) were used as correctives. Crystalline cellulose (Avicel PH302, Asahi Chemical Co., Ltd., Tokyo, Japan) and mannitol (Towa Chemical Industry) were used as excipients for tablet preparation. Magnesium stearate (Mg-St, Kozakai Pharmaceutical Co., Ltd.) was employed as a lubricant. All other reagents used were of analytical grade.

Preparation of Granules and Physical Mixtures According to the formulation shown in Table 1, correctives were mixed with FU at various ratios, and granules were prepared using the dry granulation method. Once it was sufficiently mixed, each mixture was compressed with an SSP-10A manual press (Shimadzu Corp., Kyoto, Japan) at 1 kN, and the compaction products were then ground into granules. The granules that passed through a 20-mesh sieve and remained on a 22-mesh sieve were used in this study. As shown in Table 1, the physical mixtures were designated as CS, CM1, CM2, CM3, CY1, CY2 and CY3, and the granules were designated as CSG, M1, M2, M3, Y1, Y2 and Y3, respectively.

Table 1. Formulation of Samples

Sample (Granules/Physical mixtures)	Mixing ratio (in parts)			
	FU	CS	MA	YO
CSG/CS	1	1		
M1/CM1	1		1	
M2/CM2	1		2	
M3/CM3	1		3	
Y1/CY1	1			1
Y2/CY2	1			2
Y3/CY3	1			3

Taste Test A taste test of all four types of granules and physical mixtures was performed by 6 healthy adult volunteers (3 males and 3 females, with a mean age of 25.7 years), from whom informed consent was first obtained. Prior to the tasting, the volunteers were informed precisely about the purpose of the tasting and the possible adverse effects of FU. They rinsed their mouths thoroughly before and after the tasting. Each sample was held in the volunteers' mouths for 30 s and then expectorated, and the taste was evaluated and assigned a numerical value according to the following scale: 1, distasteful; 2, slightly distasteful; 3, fair; 4, slightly tasty; 5, tasty. The scores were analyzed using the Kruskal-Wallis test, and a higher score indicated a greater masking effect. A p value of <0.05 was regarded as significant. The difference between the tastes of physical mixtures and granules was analyzed using the Wilcoxon rank sum test, and a p value of <0.05 was regarded as significant.

Preparation of Tablets For tableting, an SSP-10A manual press (Shimadzu) was used. Flat tablets 10 mm in diameter (200 mg/tablet) were prepared using the granules or physical mixtures along with mannitol and crystalline cellulose as excipients at mixing ratios of mannitol/crystalline=1/1, according to the compositions shown in Table 2. A small amount of Mg-St was applied to the punch and die for lubrication.

Table 2. Formulation of Tablets Prepared from Granules or Physical Mixtures

Materials	M1-T	M2-T	M3-T	Y1-T	Y2-T	Y3-T
Granules FU/MA/YO (mg)	20/20/0	20/40/0	20/60/0	20/0/20	20/0/40	20/0/60
Physical mixture FU/MA/YO (mg)	20/20/0	20/40/0	20/60/0	20/0/20	20/0/40	20/0/60
Mannitol (mg)	80	70	60	80	70	60
Crystalline cellulose (PH302) (mg)	80	70	60	80	70	60
Total weight (mg)	200					

All tablets had a total weight of 200 mg.

Physical Characteristics of Tablets Hardness was measured in the diameter direction using a Monsanto (Creve Coeur, MO, USA) hardness tester. 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 15 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.

The water absorption time of tablets was measured using methylene blue aqueous solution. 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 for the entire tablet to become blue was defined as the 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 AND DISCUSSION

Masking Effects of Granules and Physical Mixtures The results of the taste test of granules and physical mixtures are shown in Fig. 1. The median taste scores for the granules and the physical mixtures were both 1 when CS was used as an additive. For physical mixtures, the median score was 3 in mixtures with MA, and ranged from 2.75–4 in mixtures with YO. For granules, the median score ranged from 2–3 in those with MA, and from 3–3.5 in those with YO. Preparations made with MA and YO were significantly more tasty than those made with CS, demonstrating the masking effects of MA and YO ($p<0.05$ in the Kruskal-Wallis test). Increases in the mixing ratios of MA and YO did not influence the masking effect, however. Also, no marked difference in masking effect was noted between MA and YO in the physical mixtures, but in granules, YO showed a greter masking effect than MA. Our data shows that YO addition effectively masked the taste of FU, and that YO was superior to MA as a masking agent to overcome the unpleasant taste of the drug. Further, the YO-containing granules prepared using the dry granulation method tended to display a greater masking effect; a sufficient effect could be obtained by adding a quantity of YO equal to that of FU.

Hardness of Tablets Initially, all tablets were prepared at a compression pressure of 2 kN for 30 s. The values of hardness of these tablets are shown in Fig. 2. In any formulation, the MA-containing tablets were harder than the YO-containing tablets, with hardness measuring 4 kg or greater. Among MA-containing tablets, the hardness of those prepared with physical mixtures was equivalently high (6 kg or higher) regardless of the amount of MA. In contrast, the hardness of tablets made up of granules decreased as the MA content increased, although the hardness of M1-T, which contained the smallest amount of MA, was greater than 6 kg. Among YO-containing tablets, the hardness of those prepared with a physical mixture was sufficient when a small quantity of YO was used (Y1-T, approximately 3.5 kg), but decreased as the YO content increased until the hardness of Y3-T, which contained the largest amount of YO, was less than 2 kg. The hardness of all tablets prepared with granules were greater than 4 kg and increased as the YO content increased.

These differences in tablet hardness may have been caused by the marked difference in binding ability between MA and YO. MA has high formability, which

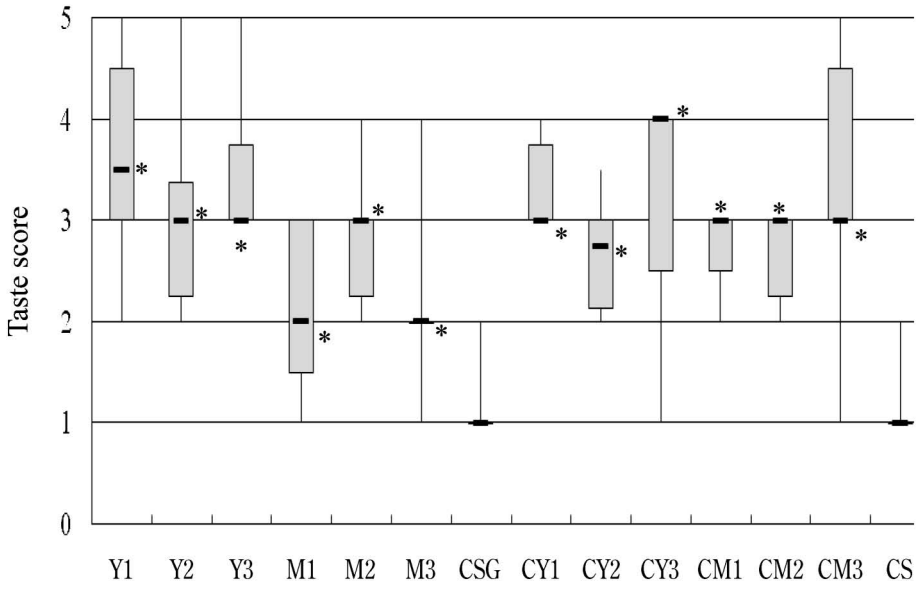

Fig. 1. Taste Scores of Granules and Physical Mixtures

Each black bar represents the median score ($n=6$). Each error bar represents the maximum and minimum score and columns represent 25% or 75% of the minimum score. $p<0.05$ in the Kruskal-Wallis test. *$p<0.05$ *vs.* CS and CSG.

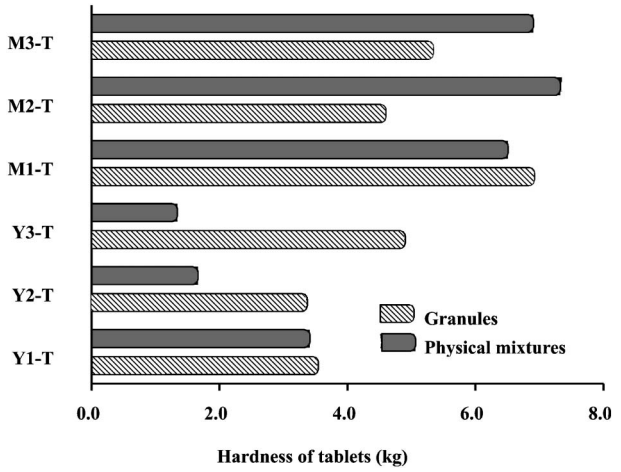

Fig. 2. Hardness of Tablets Prepared from Granules and Physical Mixtures

Compression force: 2 kN. The length of each bar represents the mean hardness ($n=6$).

may have led to the increased hardness of MA-containing tablets. Moreover, the binding ability of MA appears to have had a greater effect in the tablets prepared with physical mixtures, while its effect was reduced in the tablets prepared with granules. The process of granulation, together with the reduced excipient content in the tablets prepared with granules, may have decreased tablet hardness. In contrast, the low binding ability of YO may explain why an increase in YO content and a decrease in excipient content in the physical mixtures reduced the hardness of tablets produced by this method, while granulation may have resulted in plastic deformation and thereby increased the hardness.

According to the results of the taste test, granule tablets including YO or MA in a quantity equal to that of FU are suitable for applications. Accordingly, we prepared M1-T and Y1-T tablets under varying levels of compression force to investigate the influence on tablet hardness (Fig. 3). The hardness of M1-T and Y1-T tablets increased as the compression force rose, demonstrating that the hardness of tablets can be controlled by altering the compression force.

Disintegration Time of Tablets The disintegration time of the tablets prepared at a compression force of 2 kN for 30 s are shown in Fig. 4. The disintegration time of Y1-T tablets prepared from granules was the shortest (18.5 s), followed by that of M1-T tablets prepared from granules. In all types of tablet, including those prepared from physical mixtures and those prepared from granules, disintegration time increased as the mixing ratios of MA and YO increased. The disintegration time tended to be shorter in tablets prepared from granules than in those prepared from physical mixtures. When MA was used as the corrective, tablets prepared from granules appeared to disintegrate more rapidly. When YO was used as the corrective, tablets prepared from Y1 granules disintegrated rapidly, but the disintegration times of Y2-T and Y3-T were similar, and both were greater than

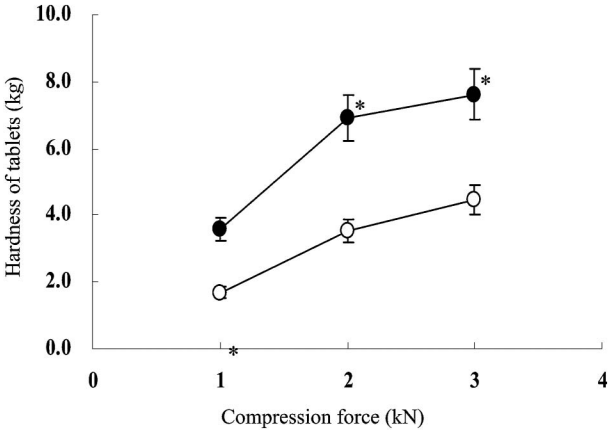

Fig. 3. Effect of Compression Force on Hardness of Tablets Prepared from Granules

●, M1-T; ○, Y1-T. Each point represents the mean±S.D. hardness (n=6). *p<0.05 in the t-test.

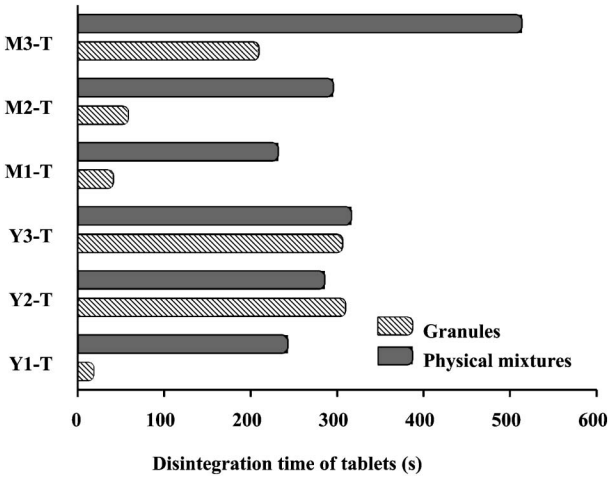

Fig. 4. Disintegration Time of Tablets Prepared from Granules and Physical Mixtures

Compression force: 2 kN. The length of each bar represents the mean disintegration time (n=6).

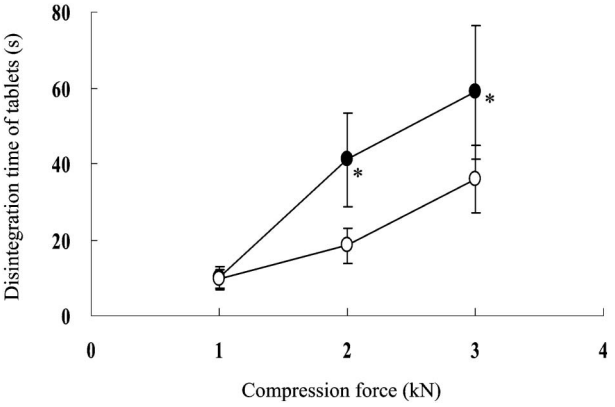

Fig. 5. Effect of Compression Force on Disintegration Time of Tablets Prepared from Granules

●, M1-T; ○, Y1-T. Each point represents the mean±S.D. disintegration time (n=6). *p<0.05 in the t-test.

Table 3. Water Absorption Time of Tablets Prepared from Granules

Sample	Water absorption time (s)
M1-T	30.0±1.7
M2-T	122.0±3.5
M3-T	445.0±52.2
Y1-T	39.0±1.0
Y2-T	136.0±10.4
Y3-T	2,606.0±341.3

Each time represents the mean±S.D. (n=3). Compression force: 2 kN.

300 s. Based on these findings, rapidly disintegrating tablets can be prepared using granules, and, as we showed above, M1-T and Y1-T tablets have sufficient hardness (greater than 3 kg; *see* Fig. 2).

The influence of compression force on the disintegration time of M1-T and Y1-T tablets prepared from granules was also investigated (Fig. 5). The disintegration times of M1-T and Y1-T tablets were same at 1 kN; they lengthened as compression pressure increased. However, the disintegration time of M1-T tablets lengthened more rapidly than that of Y1-T tablets.

Water Absorption Time of Tablets The water absorption time of the prepared tablets was measured to confirm the observed differences in disintegration time. The water absorption time of the tablets prepared from granules at a compression force of 2 kN for 30 s are shown in Table 3. The water absorption time lengthened as the MA or YO content increased at a faster rate in YO than in MA. This corresponds to our observation that the disintegration time lengthened as MA or YO content increased and at a faster rate in YO than in MA (*see* Fig. 4). These findings indicate that changes in water absorption time affect disintegration time. Further, because MA-and YO-containing tablets exhibited different absorption times, it seems that the solubility and binding abilities of MA and YO affect absorption time. Both MA and YO are highly soluble, which would seem to indicate that both correctives promote water absorption, but solutions of these may actually inhibit water absorption as their content increases. This phenomenon may have been marked in the tablets containing YO.

We investigated the influence of compression force

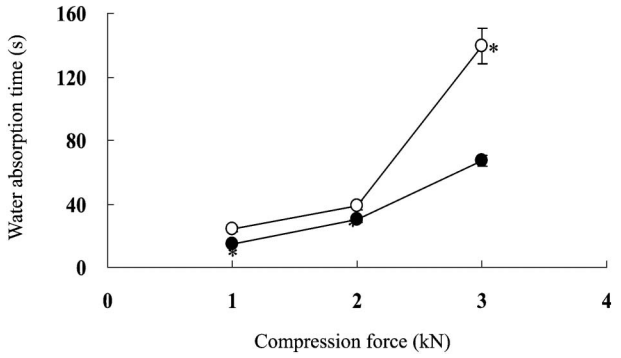

Fig. 6. Water Absorption Time of Tablets Prepared from Granules

●, M1-T; ○, Y1-T. Each point represents the mean±S.D. water absorption time ($n=6$). $^{*}p<0.05$ in the t-test.

on water absorption time in M1-T and Y1-T tablets prepared from granules and found that absorption time increased as compression force rose. At any compression force, the water absorption time was slower in Y1-T than in M1-T tablets; in addition, changes in compression pressure had a greater effect on the water absorption time of Y1-T tablets than on that of M1-T tablets (Fig. 6). Changes in water absorption time resulting from changes in compression pressure were related to changes in tablet porosity. Despite their slow water absorption rate, Y1-T tablets disintegrated rapidly; this may have been due to the low binding ability of YO, which may have caused the binding network to disintegrate when YO dissolved.

CONCLUSION

Using insoluble FU with an unpleasant taste as a model drug, we investigated the preparation of ODTs using different methods of taste masking to improve the taste of the tablets. MA and YO were added as taste-masking correctives, and granules prepared using the dry granulation method and physical mixtures were examined. MA is useful as the masking agent as it has a sweet taste and is used as a flavoring and taste-improving agent. The most favorable masking effect was obtained with granules using YO as a corrective; in these preparations, the masking effect did not change even when the mixing ratio of YO to FU ranged from 1/1 to 1/3. It was confirmed that YO addition effectively masked the taste of FU, and that YO was superior to MA as a masking agent to overcome the unpleasant taste of the drug. It was also suggested that a sufficient effect could be obtained by adding a quantity of YO equal to that of FU. When crystalline cellulose and mannitol were added as excipients for tableting, the tablets prepared from granules of FU/YO at a mixing ratio of 1/1 exhibited the most rapid disintegration and sufficient hardness. Hardness and the disintegration time of the tablets can be controlled by varying the compression force. In summary, we found that YO is a more useful additive than MA for masking unpleasant tastes and that ODTs using YO as a corrective to mask an unpleasant taste can be prepared with granules produced using the dry granulation method.

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