—Regular Articles—

Preparation of Orally Disintegrating Tablets with Masking of Unpleasant Taste: Comparison with Corrective-adding Methods

Yayoi KAWANO,*[,a] Akihiko ITO,[b] Masanaho SASATSU,[a] and Yoshiharu MACHIDA[a]

[a]*Department of Drug Delivery Research, Hoshi University, 2–4–41 Ebara, Shinagawa-ku, Tokyo 142–8501, Japan, and* [b]*Department of Medicinal Therapy Research, Meiji Pharmaceutical University, 2–522–1 Noshio, Kiyose, Tokyo 204–8588, Japan*

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Many orally disintegrating tablets have recently been developed to improve oral ingestion and usability and are widely administered clinically, resulting in improved quality of life for patients. Since orally disintegrating tablets rapidly disintegrate in the mouth, the masking of unpleasant taste is important. We investigated the masking of the taste of furosemide (FU) as a model drug with correctives and prepared orally disintegrating tablets. Using maltitol (MA) as a corrective, granules were prepared employing mixing, coating, and mixing/coating methods using a desktop granulator. Each preparation was subjected to tasting. The taste was masked well when granules were prepared by the mixing and mixing/coating methods. Tablets were prepared from these granules with mannitol and crystalline cellulose added as fillers. Tablets made from granules prepared by the mixing and mixing/coating methods showed appropriate strength and disintegrated rapidly. When the amount of MA was increased in the mixing method, the disintegration time was prolonged, and thus the amount should be determined considering both taste masking and disintegration property. The results showed that orally disintegrating tablets of insoluble drugs with an unpleasant taste such as FU should be prepared with the taste masked employing the methods used in this study.

Key words——orally disintegrating tablet; taste masking; maltitol; granule; corrective

INTRODUCTION

Various dosage forms, such as oral and external preparations and injections, are used in drug therapy. Currently, oral preparations account for a high proportion of drugs used in clinical practice. Oral dosage forms, such as tablets, capsules, powders, and liquids, are associatied with various problems in ingestion: capsules can adhere to the throat; powder causes a residual sensation due to an unpleasant taste and adheres to the throat; granules can cause pain by entering the space between dentures, and gums; and the measurement of syrup is inconvenient and the taste is unpleasant.[1] In dialysis patients, powders and granules are not suitable because water ingestion is limited to avoid excessive hydration during dialysis.[2] Based on the above reasons, tablets are preferred, but their ingestion may be difficult for elderly persons with reduced swallowing function as well as children. Moreover, long-term dialysis patients ingest many oral drugs with a large volume of water and some patients cannot comply with the water limitation.

For easy, safe ingestion, orally disintegrating tablets have been developed[3–13] and are widely used clinically. Since orally disintegrating tablets rapidly disintegrate in saliva or a small volume of water, the elderly, children, and dialysis patients can easily ingest in this dosage form. However, for the preparation of orally disintegrating tablets with an unpleasant taste, the masking of taste is a major task, along with maintaining the appropriate strength and rapid disintegration in the mouth. Sensory masking by adding correctives, chemical masking by chemical modification such as the preparation of prodrugs and inclusion drug compounds, masking by coating particle surfaces, masking using a matrix, and physical masking by physically inhibiting drug dissolution in the mouth through adsorption to additives are available,[14] and the method is selected to correspond to drug features. For reliable masking, the inhibition of drug dissolution using an insoluble membrane is effective, which prevents the elution of the drug even if the tablet disintegrates in the mouth. However, roughness is sensed after tablet disintegration, which is problematic with regard to the sensation on ingestion.

To solve the problem of the unpleasant taste of orally disintegrating tablets, we prepared orally disin-

*e-mail: y.kawano@pha.twmu.ac.jp

tegrating tablets of furosemide (FU), which has an unpleasant taste and is commonly administered to dialysis patients, using a simple, low-cost sensory masking method. We used maltitol (MA) as an additive masking agent because it has a sweet taste and is used as a flavoring and taste-improving agent.

METHODS

Samples FU (Sigma Chemical, St. Louis, MO, USA) was used as a model drug. For granule preparation, MA (Towa Kasei Co., Ltd.) and cornstarch (CS, Kozakai Pharmaceutical Co., Ltd.) were used as additives. For the binders, 1% aqueous solution of hydroxypropylcellulose (HPC-L, Nippon Soda Co., Ltd.) and 10% aqueous solution of MA were prepared. As fillers for tablet preparation, crystalline cellulose (Avicel PH302, Asahi Kasei Co.) and mannitol (Towa Kasei Co., Ltd.) were used. Magnesium stearate (Mg-St, Kozakai Pharmaceutical Co., Ltd.) was employed as a lubricant.

Preparation of Granules Using a desktop granulator (Shimadzu Corporation), granules were prepared using three methods, as shown in Fig. 1. In all methods, the aqueous binder solution comprised 10% (v/w) of the granules.

Mixing Method A mixture of FU with MA or CS was placed in the desktop granulator, and granules were prepared by spraying the aqueous binder solution on the rotating mixture.

Coating Method FU was placed in the desktop granulator, and granules were prepared by spraying the aqueous binder solution on the rotating FU. Then the additive was added during continuous rotation.

Mixing/Coating Method FU and a portion of MA were placed in the desktop granulator, and the primary granules were prepared by spraying the aqueous binder solution on the rotating mixture and the remaining MA was added during continuous rotation. The same amounts of MA were used in each step.

The compositions of the granules prepared using the three methods are shown in Table 1. The granules

Table 1. Formulation of Granules

Sample	Binder sol.	Preparation method	Mixing ratio		
			FU	CS	MA
MH	1%HPC	Mixing method	1		1
CH	1%HPC	Coating method	1		1
MM(C)	10%MA	Mixing method	1	1	
MM(M)	10%MA	Mixing method	1		1
MM1	10%MA	Mixing method	1		2
MM2	10%MA	Mixing method	2		1
CM	10%MA	Coating method	1		1
CM2	10%MA	Coating method	2		1
MCM	10%MA	Mixing/Coating method	1		2

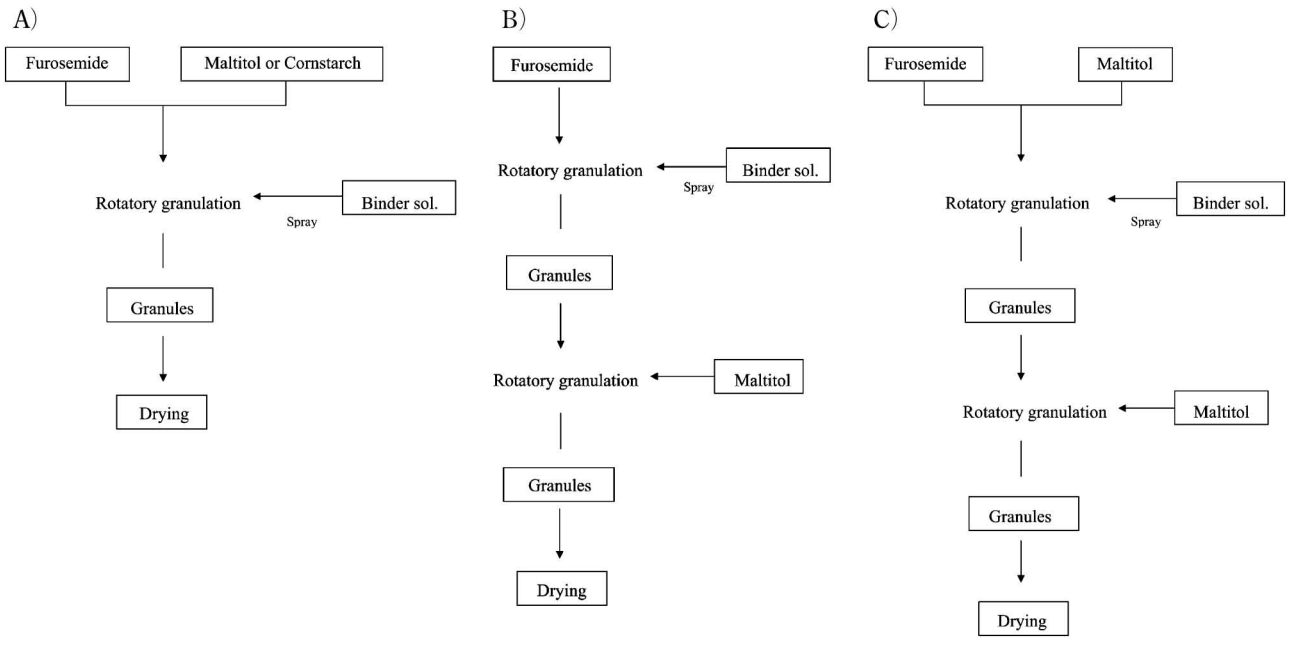

Fig. 1. Process of Granulation
A) Mixing Method; B) Coating Method; C) Mixing/Coating Method.

were designated as MH, CH, MM(C), MM(M), MM1, MM2, CM, CM2, and MCM, and the physical mixtures were designated as PM.

Measurement of the Physical Properties of Granules The bulk density and compressibility rate of the prepared granules were measured. The tap density was determined by placing 100 ml of granules in the same cylinder used to measure the bulk density. The compressibility rate (C) was calculated using Eq. (1) from the bulk densities with sparse (ρ) and bulk (ρt) filling.

$$C=(\rho t-\rho)/\rho\times 100 \quad (1)$$

Tasting of Granules Tasting was performed by 7 healthy adult volunteers (5 males and 2 females, with a mean age of 26.9 years). Prior to the tasting, the volunteers were informed of the purpose of the tasting and possible adverse effects of FU. All washed out their mouths immediately after the tasting.

The volunteers held the granules in their mouths, and the taste was given a numerical value graded as follows: 1, distasteful; 2, slightly distasteful; 3, slightly tasty; and 4, tasty. A higher value indicated a greater taste preference. Differences in the values were analyzed using the Kruskal-Wallis test ($p<0.05$).

The time required to sense an unpleasant taste was measured under actual ingestion conditions. The time until the volunteers sensed an unpleasant taste after holding the granules in the mouth was measured and graded, with a value of 1 representing the shortest time, for numerical presentation. The scores were analyzed using the Kruskal-Wallis test. A higher score thus represented a stronger masking effect, and a p value of 0.05 was considered significant.

Preparation of Tablets Flat tablets 10 mm in diameter (200 mg/tablet) were prepared from granules or a physical mixture of FU and MA with mannitol and crystalline cellulose added as fillers using a hydraulic press (Shimadzu Corporation) at compression force of 1, 2, and 3 kN. A small amount of Mg–St was applied to the punch and die for lubrication.

Measurement of Tablet Hardness Hardness was measured using a Monsanto hardness tester in the diameter dimension. The measurement was performed for 6 tablets in each batch, and the mean value was calculated.

Measurement of Tablet Disintegration Time Following the disintegration test method specified in the *Japanese Pharmacopoeia*, 15th edition, the time required for complete disintegration and disappearance of the tablets was regarded as the disintegration time. The mean of 6 tablets was calculated.

Measurement of Water Absorption Time of 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 for the color of the entire tablet to become blue was measured. The mean of 6 tablets was calculated.

RESULTS AND DISCUSSION

Taste The taste of granules containing FU and the additive at a ratio of 1 : 1 and their physical mixture were evaluated. The results are shown in Fig. 2. The median score for granules prepared by the mixing method using CS as the additive was 1, showing that its taste was perceived as unpleasant. When MA was used, the median score was 3 for all samples, showing a significantly higher masking effect. However, the score differed among the preparation methods, and variation in preference was less for granules prepared by the mixing method. There was no difference among the binders used in the perceived taste of granules prepared by the mixing method. In contrast, among granules prepared by the coating method, granules with 10% aqueous solution of MA as the binder tended to be scored higher.

These findings suggested that the addition of MA is useful for masking the taste of FU, and the effect is increased when it is mixed with FU. In the physical mixture of FU and MA, the median score was 3, similar to that for granules, but no higher score was given by any volunteer, suggesting that granulation increases the masking effect.

Based on the evaluation of preference, granules

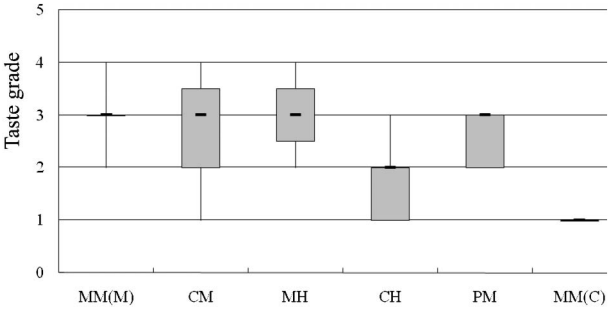

Fig. 2. Taste Grade of Granules

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.

were prepared using MA as a binder at different FU : MA ratios employing the mixing and mixing/coating methods, and the time required for an unpleasant taste to be perceived was evaluated under actual ingestion conditions (Fig. 3). The scores for granules prepared by the mixing method, MM(M) and MM1, were equivalent and the highest, followed by MCM prepared by the mixing/coating method, and the difference was significant. These findings suggest that the taste of FU can be masked through granulation by the mixing or mixing/coating method using MA as an additive and binder.

In MM2 and CM2 with a low MA content, the score was low regardless of the granulation method, showing that masking cannot be achieved when the amount of MA is insufficient. The score for CM was lower than that for MM(M), and the variation was large, as in the evaluation of preference.

These findings also suggest that the presence of MA in a mixture with FU is effective for masking the taste. The tastes of the two compounds may be simultaneously sensed when they are mixed, reducing the taste of FU. When MA is present around FU, as in samples prepared by the coating method, the taste of FU may not be sensed when the sweetness of MA is sensed, but the taste of FU may appear after MA disappears. The same mechanism may be present in granules prepared by the mixing/coating method, leading to the finding that the score was lower than that of MM(M) despite the addition of more MA.

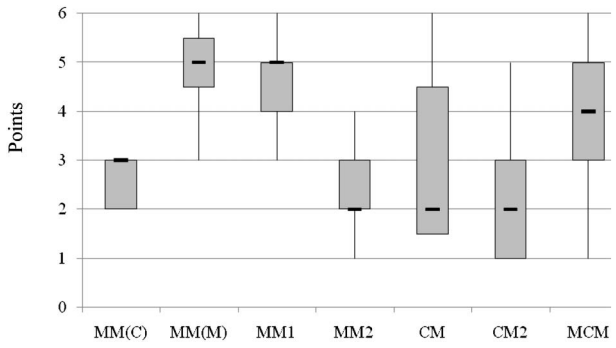

Fig. 3. Grading of Time Required for Sense of Unpleasant Taste

Each black bar epresents the mean median score ($n=6$). Each error bar represents the maximum and minimum score and columns represent 25% or 75% of the minimum score.

Preparation of Orally Disintegrating Tablets Based on the results of test tasting, tablets of MM(M), MM1, CM, MCM, and PM were prepared using mannitol and crystalline cellulose as fillers. The compositions of the tablets are shown in Table 2. The apparent densities and compressibility rate of the granules are shown in Table 3.

Hardness of Tablets Figure 4 shows the hardness of the tablets. The hardness increased as the compression pressure increased in all tablets prepared from the physical mixture and granules. At 3 kN, the hardness of all tablets was similar and sufficient, being greater than 3 kg. The hardness of CM-T changed slightly with the increase in compression pressure, and was close to 3 kg even at 1 kN. The hardness of MCM-T tended to be higher than those of the others. The compressibility ratio of CM and MCM were higher than those of MM(M) and MM1, as shown in Table 3, suggesting that plastic deformation was easily occurred with compression, while MA surrounding granules strengthened the binding, resulting in relatively marked hardness. The differences in the mannitol, crystalline cellulose, and MA contents did not affect the hardness.

Table 3. Properties of Granules

Sample	App. Density (g/ml)	Compressibility rate (%)
MM(M)	0.606	9.6
MM1	0.601	6.4
CM	0.486	22.5
MCM	0.572	22.9

Each point represents the mean ($n=3$).

Table 2. Formulation of Tablets

Materials (%)	Granules				Physical mixture
	MM(M)-T	MM1-T	CM-T	MCM-T	PM-T
Furosemide	10	10	10	10	10
Maltitol	10	20	10	20	10
Mannitol	40	35	40	35	40
Crystalline cellulose (PH302)	40	35	40	35	40

Tablet Disintegration Time Tablet disintegration times are shown in Fig. 5. In all tablets excluding MM(M)−T, the disintegration time was prolonged as the compression pressure increased, but that of MM(M)−T did not change. At all compression pressures, the disintegration time of PM−T was the longest (15–20 s), followed by CM−T and MM1−T, while those of MM(M)−T and MCM−T were less than 10 s, indicating that the differences in the mannitol, crystalline cellulose, and MA contents did not affect the disintegration time.

Based on the above findings, and considing the hardness and masking effect, MM(M)−T and MCM−T are optimal orally disintegrating tablets with appropriate hardness, rapid disintegration, and good taste-masking effect.

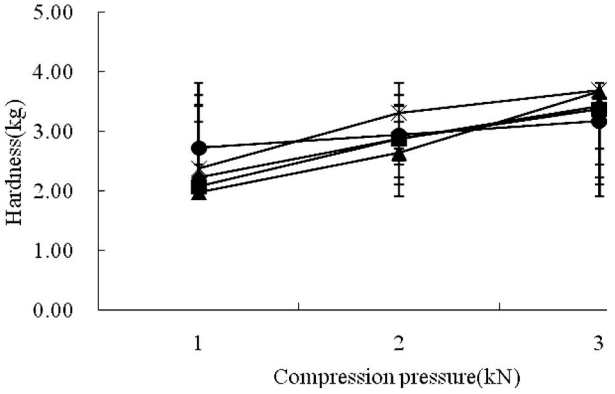

Fig. 4. Hardness of Tablets Prepared with Granules and Physical Mixture

◆, PM−T; ■, MM(M)−T; ▲, MM1−T; ●, CM−T; ×, MCM−T. Each point represents the mean±S.D. (n=6).

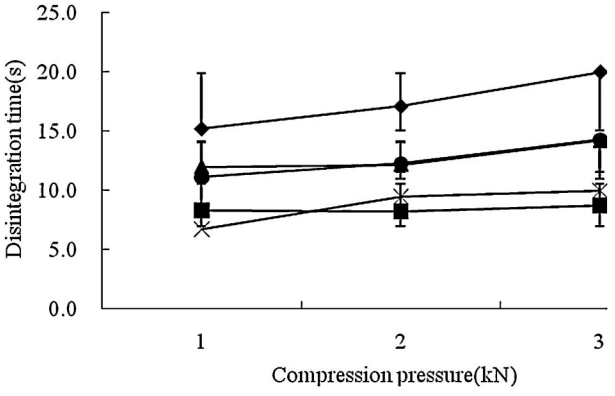

Fig. 5. Disintegration Time of Tablets Prepared with Granules and Physical Mixture

◆, PM−T; ■, MM(M)−T; ▲, MM1−T; ●, CM−T; ×, MCM−T. Each point represents the mean±S.D. (n=6).

Water Absorption Time of Tablets The water absorption times of the tablets are shown in Table 4. The water absorption time was extended as the compression pressure increased. It was the most rapid in MM(M)−T at all compression pressures, and changes with an increase in the compression pressure were slight. Among samples prepared by the same method, the absorption of water was slow in MM1−T with a high MA content. The absorption time in CM−T at 1 kN was 14 s, similar to that in MM(M)−T, but the water absorption was more markedly slowed by an increase in the compression pressure compared with that in MM(M)−T. In MCM−T, the water absorption was slower than that in all other tablets at all compression pressures, and changes with compression pressure elevation were marked. One cause of the slower water absorption with greater compression pressure may have been the reduction of porosity. In addition, different distributions of insoluble FU and highly water-soluble MA may have affected it.

It was assumed that in MM(M)−T granules prepared by the mixing method, FU and MA were mixed in the tablet, and soluble MA incorporated water into the tablet, facilitating water permeation and subsequent disintegration. When the MA content increased, as in MM1−T, dissolved MA may have inhibited water permeation and slowed the water absorption, prolonging the disintegration time. In contrast, in CM−T, MA may have surrounded FU. With this distribution, water permeated relatively quickly

Table 4. Water Absorption Time of Tablets Prepared with Granules and Physical Mixture

Compression pressure (kN)	Water Absorption Time (s)[a]				
	PM-T	MM-T	MM1-T	CM-T	MCM-T
1	22.5±3.5	13.3±2.9	33.7±7.8	14.0±3.6	60.3±1.5
2	87.0±4.2	21.3±4.2	63.7±6.0	33.3±6.1	146.8±7.6
3	71.2±9.8	38.3±3.5	93.7±4.0	56.0±7.2	259.7±35.2

a) Each point represents the mean±S.D. (n=7).

because MA guided the water, but the localized presence of insoluble FU may have affected the water absorption time and disintegration time. In MCM–T, although FU and MA were mixed, the MA surrounding them may also have been abundantly present, as in MM1–T, and dissolved MA inhibited and slowed water absorption. However, since FU and MA were mixed, dissolved MA may have disruped the binding network and facilitated disintegration. In PM–T, unlike MM(M)–T, FU, MA, mannitol, and crystalline cellulose were distributed over the tablet, in which FU may have affected the water absorption and disintegration.

CONCLUSION

Using insoluble FU with an unpleasant taste, the preparation of orally disintegrating tablets with a masked taste was investigated. Granules were prepared using different MA–adding methods and subjected to taste testing. The masking effect was favorable when granules were prepared by the mixing and mixing/coating methods. Tablets composed of granules were prepared using mannitol and crystalline cellulose as fillers, and the strength and disintegration property were investigated. The tablets prepared by the mixing and mixing/coating methods showed appropriate strength and disintegration. In granules prepared by the mixing method, the disintegration time was prolonged as the MA content increased, showing that the MA level should be determined to mask taste and lead to rapid disintegration. The present findings suggest that orally disintegrating tablets of insoluble drugs with an unpleasant taste may be produced using granules prepared with MA by the mixing or mixing/coating method.

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