

Preparation and Evaluation of Tablets Rapidly Disintegrating in Saliva Containing Bitter-Taste-Masked Granules by the Compression Method¹⁾

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The aim of this study was to prepare, using taste-masked granules, tablets which can rapidly disintegrate in saliva (rapidly disintegrating tablet), of drugs with bitter taste (pirenzepine HCl or oxybutynin HCl). The taste-masked granules were prepared using aminoalkyl methacrylate copolymers (Eudragit E-100[®]) by the extrusion method. None of the drugs dissolved from the granules (% of dissolved, <5%) even at 480 min at pH 6.8 in the dissolution test. However, the drugs dissolved rapidly in the medium at pH 1.2 in the dissolution test. Rapidly disintegrating tablets were prepared using the prepared taste-masked granules, and a mixture of excipients consisting of crystalline cellulose (Avicel PH-102[®]) and low-substituted hydroxypropylcellulose (L-HPC, LH-11[®]). The granules and excipients were mixed well (mixing ratio by weight, crystalline cellulose:L-HPC=8:2) with 1% magnesium stearate, and subsequently compressed at 500—1500 kgf in a single-punch tableting machine. The prepared tablets (compressed at 500 kgf) containing the taste-masked granules have sufficient strength (the crushing strength: oxybutynin tablet, 3.5 kg; pirenzepine tablet, 2.2 kg), and a rapid disintegration time (within 20 s) was observed in the saliva of healthy volunteers. None of the volunteers felt any bitter taste after the disintegration of the tablet which contained the taste-masked granules. We confirmed that the rapidly disintegrating tablets can be prepared using these taste-masked granules and excipients which are commonly used in tablet preparation.

Key words rapidly disintegrating tablet; taste-masked granule; Eudragit E-100[®]; compression method

Recently, pharmaceutical preparations used for elderly patients have been investigated to improve the treatment compliance and quality of life (QOL) of such patients.²⁾ A tablet which can rapidly disintegrate in saliva (rapidly disintegrating tablet) is an attractive dosage form and a patient-oriented pharmaceutical preparation.³⁻⁵⁾ We previously confirmed the preparation method of rapidly disintegrating tablets consisting of crystalline cellulose and low-substituted hydroxypropylcellulose (L-HPC) which are commonly used in the manufacture of conventional tablets; the rapidly disintegrating tablet can be prepared by direct compression at a low compression force (100—300 kgf).⁶⁾ Tablets prepared thus disintegrated rapidly in saliva (a small amount of water) and the disintegration was complete at 20—30 s. Furthermore, we succeeded in the preparation of high-porosity compressed tablets of drug soluble in saliva, using mannitol of water-soluble excipient.⁷⁾ The dissolution time of the tablet prepared using only mannitol by the compression method was long (>120 s). However, highly porous tablets could be prepared by subliming camphor after compression of the mixture of drug, mannitol and camphor particles. High-porosity tablets prepared thus completely dissolved in saliva within 10—20 s.⁷⁾ The above-mentioned tablets contained meclizine (HCl salt, powder), an antiemetic and antivertigo agent,⁸⁾ as the active component. These tablets of meclizine can be taken for motion sickness even when water is not available. Thus, this tablet preparation is highly useful for the treatment of kinetosis. In the case of rapidly disintegrating tablets, however, we often encounter the problem of bitter taste of the drug due to dissolution of the active component in the mouth. Fortunately, no such problem was encountered when the above-mentioned meclizine tablets dissolved in the mouth, because of the not-so-bitter taste of the drug. However, it is necessary to investigate taste masking before

preparation of rapidly disintegrating tablets of drugs with bitter taste. In the present study, we chose pirenzepine (HCl salt) and oxybutynin (HCl salt) which are extremely bitter as the model drugs and investigated the preparation method for rapidly disintegrating tablets using taste-masked granules such as the aminoalkyl methacrylate copolymers. Pirenzepine and oxybutynin have antimuscarinic effects, and are used as antispasmodic agent.⁹⁾

Materials and Methods

Materials Pirenzepine (HCl salt powder) and oxybutynin (HCl salt powder) were obtained by Daito Co. (Tokyo, Japan). Crystalline cellulose (Avicel PH-102[®]) and L-HPC (LH-11[®]) were kindly supplied by Asahi Chemical Industry Co. (Tokyo, Japan) and Shin-Etsu Chemical Co. (Tokyo, Japan), respectively. Aminoalkyl methacrylate copolymer (Eudragit E-100[®]) was supplied by Rohm GmbH (Darmstadt, Germany). Ethanol (≥99%) and magnesium stearate were purchased from Shinwa Alcohol Industry Co. (Tokyo, Japan) and Wako Pure Chemical Industry Co. (Tokyo, Japan), respectively. All other reagents used were of analytical grade.

Preparation of Taste-Masked Granules and Rapidly Disintegrating Tablets A schematic representation of the preparation procedure of the taste-masked granules is illustrated in Fig. 1. The composition of each tablet tested is listed in Table 1. Each of the drugs (pirenzepine or oxybutynin) was mixed with powdered Eudragit E-100[®] using a mixing machine (high-speed elliptical-rotor-type powder mixture, θ -composa[®], Tokujin Co., Kanagawa, Japan). Then 10% ethanol was added to the mixture of each drug with Eudragit E-100[®] in a glass beaker. Then a gel containing the mixture of the drug and Eudragit E-100[®] was prepared; using this prepared gel, the taste-masked granules were prepared by the extrusion method. The prepared gel was manually extended (pressed out) using a syringe (Nipro Syringe, Nissho Co., Tokyo, Japan). After extrusion of the gel, ethanol was removed by evaporation overnight and subsequently the solidified gel in the shape of a string was crushed into granules using a mortar.

A schematic illustration of the method for the preparation of the taste-masked tablets is shown in Fig. 2. For tableting, the tablet-hitting pressure displacement measuring system (model N-20E, Okada Seiko, Tokyo, Japan) was used as a single punch tableting machine. The taste-masked tablets were prepared using the taste-masked granules, excipient⁶⁾ mixture for the rapid disintegrating tablet, crystalline cellulose and L-HPC, at mixing ratios by

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weight of crystalline cellulose : L-HPC=8 : 2, and magnesium stearate (1%). On the other hand, we prepared tablets using a powder mixture of the drug and Eudragit E-100[®], (without granulation) and magnesium stearate (1%), as the control tablet. Tablets (R-faced, 8 mm diameter) were prepared using at a compression force of 500—1500 kgf.

Evaluation of the Tablets The crushing strength of the tablets in diametrical compression was measured with the digital crushing strength measuring machine (Handy cheker HC-20[®], Okada Seiko, Japan).

The *in vitro* disintegration time⁶⁾ was measured using the JP XIII disintegration test apparatus. One tablet was placed in each tube of the basket, and light-weight disks were added to each tube. Then, the basket with the bottom surface made of a stainless-steel screen (10 mesh) was immersed in water (37±2 °C). The time required for complete disintegration of the tablet in each well of the basket was determined using a stopwatch.⁶⁾

The *in vitro* dissolution test was followed by JP XIII. The materials (tablet contents and masked granules) were dried overnight in a desiccator and subjected to the dissolution test in a machine equipped with an autosampling apparatus (Toyama Sangyo Co., Osaka, Japan). The JP XIII dissolution test basket was attached to a spindle and placed in a dissolution bath containing 900 ml of JP XIII 1st fluid (pH 1.2), 2nd fluid (pH 6.8) for the disintegration test or citric acid–NaOH buffer solution (pH 5.0),¹⁰⁾ maintained at 37±0.5 °C. The spindle was rotated at 100 rpm, and the samples were withdrawn and analyzed by UV spectrometry (pirenzepine: λ_{max}=280 nm, oxybutynin: λ_{max}=244 nm).

For determination of the *in vivo* disintegration time, six healthy volunteers, from whom informed consent was first obtained, randomly took one tablet containing pirenzepine or oxybutynin (Table 1) and the time required for complete disintegration of the tablet in the mouth, without biting and without drinking water, was measured.^{6,7)} The sensory test for bitter taste described by Kimura *et al.*,¹¹⁾ was applied with slight modification. Briefly, the same six volunteers mentioned above at the same time as the determination of the disintegrating time in saliva, held disintegrated materials in the mouth for 30 s. Immediately after the *in vivo* disintegration test, volunteers rinsed their mouth without ingesting the disintegrated particles.

Results and Discussion

1. Dissolution Profiles of Pirenzepine and Oxybutynin from the Taste-Masked Granules Prepared from the Aminoalkyl Methacrylate Copolymer Aminoalkyl methacrylate copolymer (Eudragit E-100) dissolved under acidic pH (low pH region) but not in the neutral pH region. Therefore, Eudragit E-100 was used as an acid-soluble (gastric soluble) coating material for the compound. Granules containing pirenzepine or oxybutynin were prepared by the method illustrated in Fig. 1. In the preliminary study, the taste-masked granule using Eudragit E-100 at various mixing ratios by weight was prepared. Although the mixing ratio of the active component and Eudragit E-100 was set arbitrarily, the ratio was finally assumed to be pirenzepine : Eudragit E-100=1 : 3 and oxybutynin : Eudragit E-100=1 : 14 in consideration of the dose of the active component in the tablets (Table 1). Figure 3 shows the dissolution profiles of the drugs from the prepared granule. The prepared granules scarcely dissolved in the JP XIII 2nd fluid (pH 6.8) and the granule shape was maintained. Consequently, none of the drugs dissolved from the granules (% of dissolved, <5%) even at 480 min after the beginning of the dissolution test. On the other hand, the dissolution of the drug was rapid in the JP XIII 1st fluid (pH 1.2). The drug dissolution was complete at 15 min after the beginning of the test. When the pH in stomach is increased (low gastric acidity) by drugs for instance, pirenzepine,¹²⁾ or foods and in patients with anacidity, dissolution of drug from the taste-masked granules would be decreased. Therefore, we tested dissolution of pirenzepine or oxybutynin from each taste-masked granule in buffer solution at pH 5.0. Consequently, a similar profile of rapid dissolution was obtained at pH 5.0 (Fig. 3). From the results

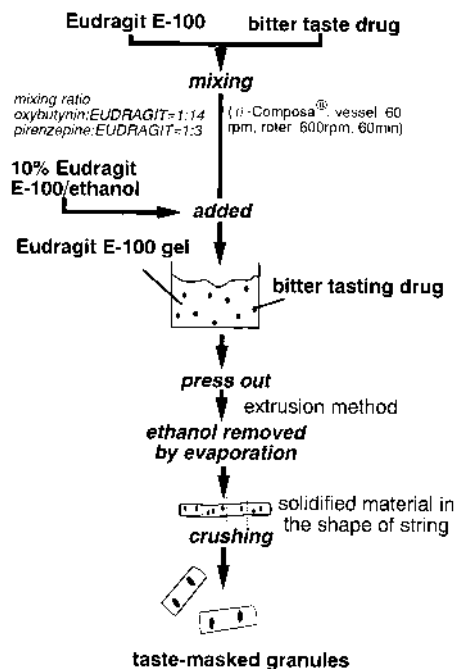


Fig. 1. Schematic Illustration of Preparation of Taste-Masked Granules

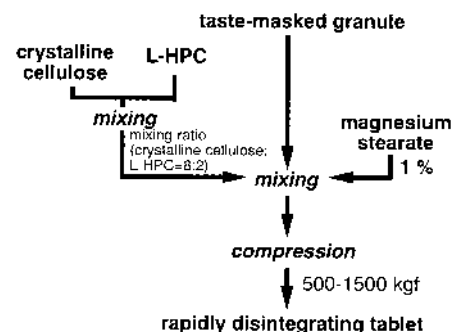


Fig. 2. Schematic Illustration of the Method of Preparation of the Tablet

Table 1. Composition of the Tablets

Material	Pirenzepine tablet	Oxybutynin tablet
Drug	25 (mg)	2 (mg)
Eudragit E-100	75	28
Crystalline cellulose	78	134
L-HPC	20	34
Magnesium stearate	2	2
Total	200	200

of the dissolution test, it was inferred that pirenzepine and oxybutynin do not dissolve from the prepared granules in saliva whose pH is in the neutral region, but they rapidly dissolve in the gastric juice where the pH is acidic. As shown in Table 2, the volunteers who took the prepared granules (drug content: pirenzepine, 25 mg; oxybutynin, 2 mg) did not feel the bitter taste of the drugs. Therefore, we concluded that the taste-masked granules can be prepared using of Eudragit E-100.

2. Evaluation of the Rapidly Disintegrating Tablets Prepared Using the Taste-Masked Granules and Excipients of Crystalline Cellulose and L-HPC The preparation

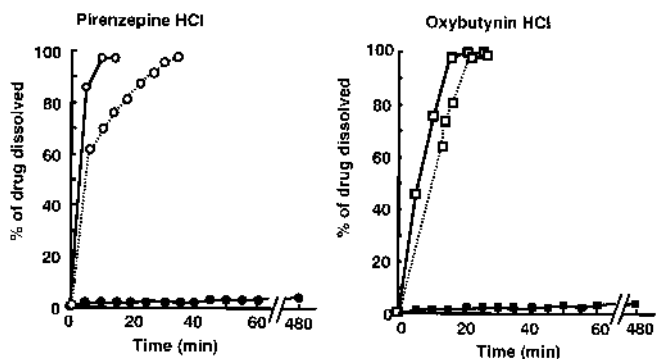


Fig. 3. Percent of the Drug Dissolved from the Taste-Masked Granules as a Function of Time Elapsed (Pirenzepine or Oxybutynin) Using Eudragit E-100

Dissolution medium: —○— and —□—, JP XIII 1st fluid (pH 1.2); —●— and —■—, JP XIII 2nd fluid (pH 6.8); ---○--- and ---□---, citric acid-NaOH buffer (pH 5.0).

Table 2. Disintegration Time (s) in the Mouth and Sensory Test for the Taste-Masked Tablet (200 mg) Containing Taste-Masked Granules

Volunteer	Pirenzepine (25 mg)		Oxybutynin (2 mg)	
	Masked tablet	Control tablet	Masked tablet	Control tablet
A	24 (-)	19 (+)	27 (-)	28 (+)
B	26 (-)	22 (+)	13 (-)	16 (+)
C	23 (-)	23 (+)	20 (-)	24 (+)
D	28 (-)	24 (+)	15 (-)	20 (+)
E	23 (-)	29 (+)	17 (-)	13 (+)
F	25 (-)	26 (+)	18 (-)	18 (+)
Mean ± S.D.	25 ± 2	24 ± 3	18 ± 5	20 ± 6

Bitter taste: -, no; +, yes.

method of the rapidly disintegrating tablets using the taste-masked granule and excipients (Table 2) is illustrated in Fig. 2. The contents of pirenzepine and oxybutynin in the tablets were chosen to be equal to the a dose of each. Crystalline cellulose and L-HPC were used as the excipients for the rapidly disintegrating tablet.^{6,13)}

Figure 4 shows the relationship between the compression force on the mixture of the taste-masked granules and excipients and the crushing strength of the prepared tablet. In the case of the oxybutynin tablet (shown as filled square), the crushing strength was about 4 kg for the tablet compressed at 500 kgf while it exceeded 6 kg for the tablets compressed at 1500 kgf. In the case of pirenzepine tablets (shown as filled circles), the compounding ratio of the taste-masked granule is increased because the dose of pirenzepine is larger than that of oxybutynin. The compressibility decreased when the content of Eudragit E-100 increased as compared with those of other excipients (crystalline cellulose and L-HPC). Consequently, the crushing strength of the prepared pirenzepine tablets (shown as filled circles) was lower than that of the oxybutynin tablets.

Figure 5 illustrates the relationship between the compression force and the *in vitro* disintegration time of the prepared tablet. When the compression force was increased, the crushing strength increased markedly and also the *in vitro* disintegration time was prolonged. To date, the best criteria of the disintegrating time for the rapidly disintegrating tablet is still

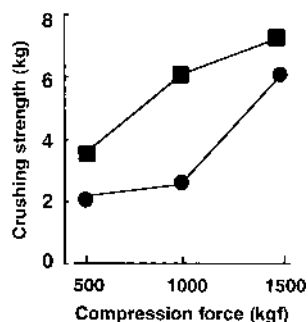


Fig. 4. Relationship between Compression Force and Crushing Strength of the Tablets (Pirenzepine or Oxybutynin)

Key: —●—, pirenzepine tablet; —■—, oxybutynin tablet.

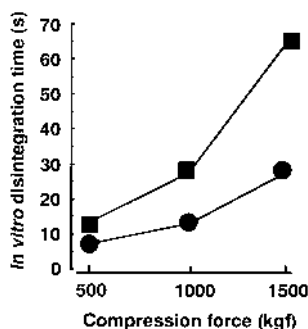


Fig. 5. Relationship between Compression Force and *in Vitro* Disintegration Time of the Tablets (Pirenzepine or Oxybutynin)

Key: —●—, pirenzepine tablet; —■—, oxybutynin tablet.

not confirmed. We intended to achieve a maximum disintegration time of 30 s. As for the tablets in this study, rapid disintegration of the prepared tablets can be achieved by use of a mixture of the taste-masked granule and excipients at various compounding ratios when the compression force is adjusted to below 1000 kgf. It was noted that the disintegration times of both pirenzepine and oxybutynin tablets were less than 20 s *in vitro* when the compression force was 500 kgf. To examine the disintegration of the prepared tablet in the mouth, the *in vivo* disintegration time was measured by the method described in Materials and Methods. At the same time, a sensory test was preliminarily performed to evaluate the degree of taste masking. For the control tablet, each containing the drug and excipients without granulation, the mixture of the active component, crystalline cellulose, L-HPC and Eudragit E-100 was compressed at the same force as for the case of tablets containing the taste-masked granule. The results are summarized in Table 2. The disintegration time in the mouth of pirenzepine or oxybutynin tablets containing the taste-masked granules prepared using a compression force of 500 kgf was approximately 20 s. Fortunately, none of the volunteers felt any bitter taste after disintegration of the tablets containing the taste-masked granules, but they strongly felt the bitter taste when the control tablet disintegrated in the mouth. These results in the sensory test suggest that formation of Eudragit E-100 matrices (granules) plays an essential role in the screening of the bitter taste. Although dissolution in the stomach was not examined in the volunteers, it would seem that rapid dissolution would occur in the gastric juice. Concerning the mechanisms of rapid disintegration by the excipients of crystalline cellulose and L-HPC,

we previously discussed that a higher value of porosity of the compressed tablets using crystalline cellulose and L-HPC is preferable for disintegration in a small amount of water.⁶⁾ Bi *et al.*, suggested that the disintegration of crystalline cellulose: L-HPC tablet is affected mainly by tablet porosity, hydrophilicity, swelling ability and interparticle force.¹³⁾

In conclusion, we succeeded in masking the taste of bitter drugs using granules of Eudragit E-100. Furthermore, we confirmed that rapidly disintegrating tablets can be prepared using taste-masked granules and excipients which are commonly used in tablet preparation. The preparation method designed in this research is useful for the preparation of rapidly disintegrating tablets containing drugs with strong bitter taste.

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