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Research Article

Preparation and Evaluation of Orally Disintegrating Tablets Containing Taste-Masked Microcapsules of Berberine Hydrochloride

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Abstract. The purpose of this study was to prepare and evaluate a taste-masked berberine hydrochloride orally disintegrating tablet for enhanced patient compliance. Taste masking was performed by coating berberine hydrochloride with Eudragit E100 using a fluidized bed. It was found that microcapsules with a drug–polymer ratio of 1:0.8 masked the bitter taste obviously. The microcapsules were formulated to orally disintegrating tablets and the optimized tablets containing 6% (*w*/*w*) crospovidone XL and 15% (*w*/*w*) microcrystalline cellulose showed the fastest disintegration, within 25.5 s, and had a pleasant taste. The dissolution profiles revealed that the taste-masked orally disintegrating tablets released the drug faster than commercial tablets in the first 10 min. However, their dissolution profiles were very similar after 10 min. The prepared taste-masked tablets remained stable after 6 months of storage. The pharmacokinetics of the taste-masked and commercial tablets was evaluated in rabbits. The C_{max}, T_{max}, and AUC_{0-24} values were not significantly different from each other, suggesting that the taste-masked orally disintegrating tablets are bioequivalent to commercial tablets in rabbits. These tablets will enhance patient compliance by masking taste and improve patients' quality of life.

KEY WORDS: berberine hydrochloride; microcapsule; orally disintegrating tablet; 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 (1). It has been reported that around 26–50% of patients find it difficult to swallow tablets and hard gelatin capsules (2). To address this problem, orally disintegrating tablets (ODTs) have been developed as a user-friendly new dosage form. ODTs have remarkable disintegration properties: They disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue and can be swallowed without water or chewing (3). ODTs offer ease of administration and improved compliance, particularly in certain populations such as pediatric, elderly, and patients with swallowing difficulties. ODTs are also useful for those who have little or no access to water, such as travelers.

In the last decade, ODTs have prospered enormously as a convenient, safe, and acceptable alternative to conventional tablets and capsules. The commercial success and viability of such products requires the development of robust formulations with excellent palatability, disintegration times, physicochemical stability, and pharmacokinetic profiles which should be applicable and bioequivalent to conventional oral dosage forms (4). Palatability plays a key role in the commercial success of the finished dosage form. Because unlike conventional tablets, ODTs allow patients to taste the active drug, and unpleasant- or bitter-tasting drugs often leads to patients' non-compliance and reduction of QOL (5). Addition of flavors and sweeteners is a conventional and simple masking approach; however, it may not be efficient enough to mask the unpleasant taste of some drugs. A wide variety of new masking technologies have been developed in order to mask the taste of bitter active substances. These approaches include the use of ion exchange resins (6,7), the use of inclusion complexes with cyclodextrins (8), and drug–polymer complexes (9,10). In recent years, as an efficient taste-masking approach, microencapsulation has become an increasingly attractive strategy for taste masking by creating a physical barrier around the bitter drug to prevent them from direct contact with the taste buds present on the tongue (4,11).

However, because forming a polymer layer around the drug, microencapsulation can also undesirably reduce the release of drug in the gastrointestinal tract. Furthermore, the taste-masked drug product may no longer be bioequivalent to the free drug product since slow drug dissolution may cause low bioavailability (11–13). Eudragit E100 is a pH-dependent polymer and is only soluble at a pH of less

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than 5. So the polymer is expected to keep intact in buccal cavity (pH5.8–7.4) with good taste masking, but dissolve quickly in stomach (pH1–3) without influencing the dissolution or bioavailability of the drug (9,14).

Berberine hydrochloride (Ber) is a yellow plant alkaloid with a long history of medicinal use in China. Ber has been proven to be effective against acute diarrhea and is usually given to pediatric and elderly patients and carried by travelers. Thus ODT is an appropriate dosage form for Ber. Unfortunately, the drug has intensely bitter taste. Therefore, taste masking of Ber is a challenge for the successful development of this dosage form.

Ber is not available in the dosage form of ODT in the market. To the best of our knowledge, there is no published article on the formulation of Ber ODT. Thus, in the present study, an attempt has been made to develop a taste-masked Ber ODT for improving the compliance and clinical value of Ber. Firstly, taste-masked microcapsules were prepared by coating Ber with Eudragit E100. Then, after taste-masked Ber ODT was optimized and formulated, the palatability, disintegration time, and physicochemical stability were evaluated. The pharmacokinetics in rabbits of taste-masked Ber ODTs was conducted compared to the commercial Ber tablets.

MATERIALS AND METHODS

Materials

Ber was purchased from Sichuan Yabao Guangtai Pharmaceutical Co., Ltd. (Sichuan, China). Hydroxypropylmethylcellulose (HPMC–Pharmacoat® 603, viscosity grade is 3 cP) was a gift from Shin-Etsu Chemical Co., Ltd (Tokyo, Japan). Eudragit E100 was a gift from Degussa Chemicals Co., Ltd (Germany). Low-substituted hydroxypropylcellulose was a gift from JRS (Germany). Crospovidone XL was a gift from ISP Technologies, Inc. (U.S.A.). Croscarmellose sodium and microcrystalline cellulose PH101 were gifts from FMC BioPolymer (U.S.A.). Sodium starch glycolate was a gift from JRS (Germany). Spray-dried mannitol was a gift from Roquette (China) Co., Ltd. (Nanning, China). Aspartame was purchased from Shanghai Dasheng Co., Ltd. (Shanghai, China).

Preparation of Ber Microcapsules

Ber powder was forced through a 100-mesh sieve to remove large particles. Sieved powder was granulated with 3% (*w*/*w*) hydroxypropylmethylcellulose (HPMC) aqueous solution using the side-spray method in a fluidized bed (EPL-1, Jinggong Pharmaceutical Machinery, China). The operating conditions were as follows: inlet air temperature was 75–80°C, sample temperature was 54–60°C, spray pressure was 0.1 MPa, diameter of the spray nozzle was 1.2 mm, flow rate was 3.2–6.4 ml/min, and disk rotation speed was 160–200 rpm. The drug load was 800 g and the time of granulation was about 3 h.

After granulation, the resultant granules were removed from fluid bed and the fluid bed chamber was cleaned thoroughly. Then the granules were coated with 8% Eudragit E100 alcohol solution in the fluidized bed. The operating conditions were as follows: inlet air temperature was 40–45°C, sample temperature was 35–40°C, spray pressure was 0.1 MPa, the diameter of the spray nozzle was 1.2 mm, and the flow rate was 3.2–8 ml/min. The duration of the coating process was variable depending on the drug to Eudragit ratio and it was about 8 h when the ratio was 1:0.8.

Evaluation of Microcapsule Characteristics

Roughness and Bitterness

Evaluation of the sensation of roughness and bitterness for Ber microcapsules was carried out in six healthy human volunteers, from whom informed consent was first obtained. The volunteers thoroughly rinsed their mouths with purified water, and then the microcapsules equivalent of 25 mg Ber were held in the mouth for 30 s and then spat out. The roughness levels were recorded on a numerical scale ranging from 0 to 3 where 0 indicated no roughness and 3 indicated pronounced roughness. Bitterness was recorded immediately and at several intervals for 10 min on a bitterness intensity scale from 0 to 3 where 0 indicated no bitterness and 3 indicated strong bitterness (10,15,16). Microcapsules coated with different amounts of Eudragit E100 were evaluated for the sensation of roughness and bitterness.

Particle Size

Particle size distribution was determined by sieve analysis with a series of sieves.

Surface State

The surfaces of the Ber granules and Ber microcapsules coated with Eudragit E100 were observed using scanning electron microscopy (S-3000N, Hitachi Limited, Japan).

Drug Entrapment Efficiency and Loading

Drug entrapment efficiency and loading were determined by dissolving 20 mg of Ber microcapsules in 100 ml of 0.1 mol/l HCl and analyzing the diluted sample using UV spectrophotometer (UV-160A, Shimadzu) at 263 nm. Drug entrapment efficiency and loading were calculated using the following equations.

$$\text{Drug entrapment efficiency}\ (\%) = \frac{\text{Weight of drug in microcapsules}}{\text{Weight of drug fed initially}} \times 100\%$$

$$\text{Drug loading}\ (\%) = \frac{\text{Weight of drug in microcapsules}}{\text{Weight of microcapsules}} \times 100\%$$

Dissolution Study

Dissolution study of Ber microcapsules was performed by placing microcapsules equivalent to 50 mg Ber in 1,000 ml purified water (pH6.3) and in 0.1 mol/l HCl, using the paddle method at 100 rpm and 37±0.5°C. Dissolution medium (5 ml) was withdrawn at specified time intervals and analyzed at 263 nm.

Preparation of ODTs

Before formulation, low-substituted hydroxypropylcellulose (L-HPC), crospovidone XL (PVPP XL), croscarmellose sodium (CCNa), and sodium starch glycolate (CMS-Na) were assessed as disintegrants. Tablets were prepared in various batches containing different disintegrants in the same concentration 6% (*w*/*w*) and a blend of microcrystalline cellulose and spray-dried mannitol (1:5) as a diluent. Subsequently, tablets containing the disintegrant screened in different concentrations: 4, 6, 8, 10, and 15% (*w*/*w*). The most effective disintegrant was then used at its optimal concentration for the final formulation of tablets (Table I). As reference, a conventional ODT containing free Ber and a great quantity of aspartame was prepared (Table I). Tablets were prepared by direct compression using a 9-mm retuse punch. The gross weight of each tablet was 200 mg and the pressure was adjusted to maintain an appropriate hardness of the tablet around 3 kg (measured on a 78X-2 multifunctional determinator for tablets, Huanghai Drug Testing Instrument Co. Ltd, Shanghai, China).

Evaluation of Tablet Characteristics

Physical Properties

Twenty tablets were randomly selected and weighed using an electronic balance (BS 124S, Sartorius, Germany). Their average weight and variations in weight were determined. Hardness of the tablets was determined using a hardness tester. The mean hardness of ten tablets was calculated.

Water Uptake

The apparatus used for measuring water uptake was a modification of a design by Kawashima *et al.* (17). A schematic representation of the apparatus is shown in Fig. 1. A glass dropper without the rubber cap and a glass pipette were connected by a rubber tubing and filled with purified water. A small piece of filter paper (diameter similar to that of the glass dropper) was kept on the glass dropper and saturated with purified water. One tablet was placed on the filter paper. The amount of water taken up by the tablet was recorded at appropriate times by observing the reduction of water in the pipette. The mean amount of water taken up by six tablets was calculated.

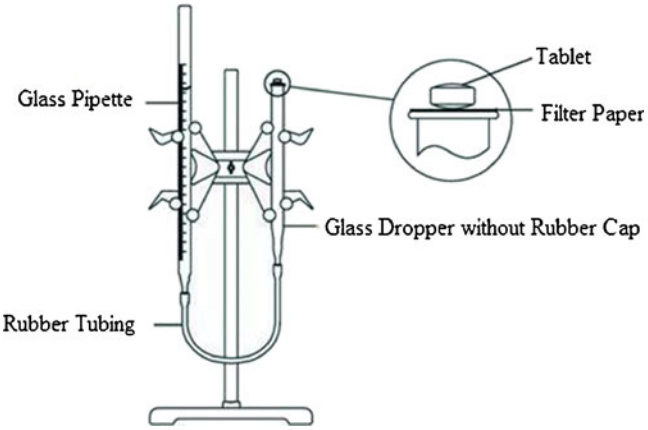

Fig. 1. Water uptake and wetting time test apparatus

Wetting Time

While measuring the water uptake of tablets, the time required for the water to diffuse from wet filter paper throughout the entire tablet was recorded as the wetting time. The mean wetting time was calculated.

Disintegration Time

A relatively simple and suitable method of evaluating the *in vitro* disintegration of ODTs was developed here. Each individual tablet was dropped into a 5-ml glass beaker (2 cm diameter) containing 2 ml purified water, and the time required for complete disintegration was observed visually and recorded using a stopwatch. Then the glass beaker was emptied onto a 24-mesh sieve. The presence of any remaining particles on the 24-mesh sieve was taken to indicate that the disintegration was incomplete, and the test was repeated. The mean disintegration time of six tablets was calculated. The limit for the disintegration time was 60 s. ODTs that required more than 60 s were disqualified. *In vivo* disintegration was performed on six healthy human volunteers, from whom informed consent was first obtained. The volunteers rinsed their mouths thoroughly with purified water and each held one tablet in the mouth. The time required for complete disintegration of the tablet was recorded. The mean disintegration time was calculated. *In vivo* disintegration times were determined and compared with the results obtained from the United States Pharmacopeia (USP) method and the new *in vitro* method.

Table I. Composition of the ODTs

	Batch						
	F0	F1	F2	F3	F4	F5	F6
Ber (mg)	25	–	–	–	–	–	–
Ber microcapsules (mg)	–	45.5	45.5	45.5	45.5	45.5	45.5
Crospovidone XL (mg)	12	12	12	12	12	12	12
Microcrystalline cellulose (mg)	20	10 (5%)	20 (10%)	30 (15%)	40 (20%)	60 (30%)	140 (70%)
Spray-dried mannitol (mg)	116	131	121	111	101	81	–
Aspartame (mg)	25	–	–	–	–	–	–
Polyethylene glycol 6000 (mg)	1.5	1.5	1.5	1.5	1.5	1.5	2.5

Table II. Roughness and Bitterness of Microcapsules with Various Drug–Eudragit E100 Ratios

		Drug/Eudragit E100				
		1:0	1:0.4	1:0.6	1:0.8	1:1
Degree of roughness		0	0.5	1	1	2
Degree of bitterness after time	30 s	3	2	1	0.5	0.5
	1 min	3	2	1	0.5	0.5
	2 min	3	2	1	0	0
	5 min	3	2	1	0	0
	10 min	2	1	0.5	0	0

Roughness and Bitterness

Evaluation of the sensations of roughness and bitterness for the Ber ODTs was carried out in six healthy human volunteers, from whom informed consent was first obtained. The volunteers rinsed their mouths with purified water and each held one tablet in the mouth. The tablet was then spat out. Roughness and bitterness levels were recorded.

Dissolution Study

Dissolution study of prepared Ber ODTs and commercial Ber tablets was performed in 1,000 ml 0.1 mol/l HCl, using the paddle method at 100 rpm and 37±0.5°C. Dissolution medium (5 ml) was withdrawn at specified time intervals and analyzed at 263 nm. Fresh dissolution medium (5 ml) was added to keep the volume of the dissolution medium constant and to maintain the sink conditions.

Stability Study

The ODTs (F3) was stored at 60±2°C, 92.5±5% RH and 4,500±500 lx for 10 days without package. Then the tablets were packed and sealed in 30-cm^3 high-density polyethylene (HDPE) bottles and stored at 40±2°C/75±5% RH and 25±2°C/60±5% RH for 6 months for accelerated and long-term stability study, respectively. Samples were withdrawn at different time and evaluated for taste, average weight, drug content, disintegration time, and dissolution.

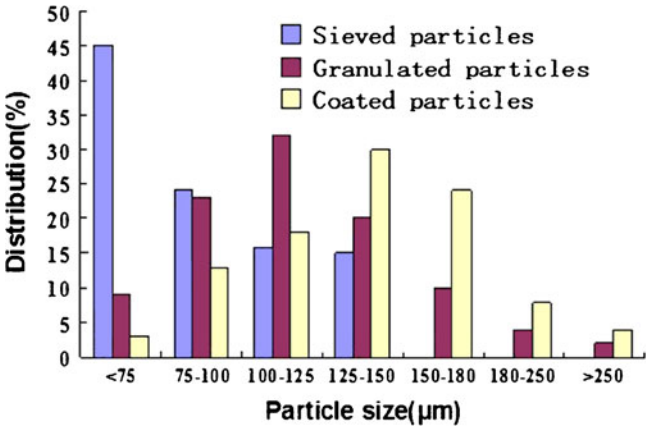

Fig. 3. Particle size distribution for sieved drug, granulated particles, and coated microcapsules

***In Vivo* Study**

The study was carried out in accordance with Animal Ethical Guidelines for investigations in laboratory animal and the study protocol was approved by the Animal Ethics Committee of Chongqing Medical University. Six healthy male New Zealand white rabbits weighing 2±0.5 kg were used for the *in vivo* study. The study was conducted according to a two-period, two-sequence crossover design with 2-week wash out period between the phases. The rabbits were randomly divided into two groups of three rabbits each. All the rabbits were fasted for 12 h with *ad libitum* access to water. One group received taste-masked ODTs (F3) whereas the other group received commercial tablets.

The tablets were administered at 50 mg/kg per animal using a gastric intubation tube. Two milliliters of blood sample were then withdrawn from marginal ear vein into heparinized Eppendorf tubes at time intervals of 0.5, 1, 2, 3, 5, 7, 12, and 24 h. The blood was immediately centrifuged at 4,000 rpm for 15 min and plasma was stored at −20°C until HPLC analysis.

To 0.5 ml of plasma, 0.75 ml of acetonitrile was added and vortex mixed for 1 min and then centrifuged at 4,000 rpm for 15 min. The supernatant (0.4 ml) was vortex mixed with equal volume mobile phase and then centrifuged at 14,000 rpm for 10 min and 50 μl of the supernatant was injected into the HPLC system.

The HPLC method was performed on a Shimadzu chromatographic system (SPD10A, Shimadzu, Japan) and an ODS

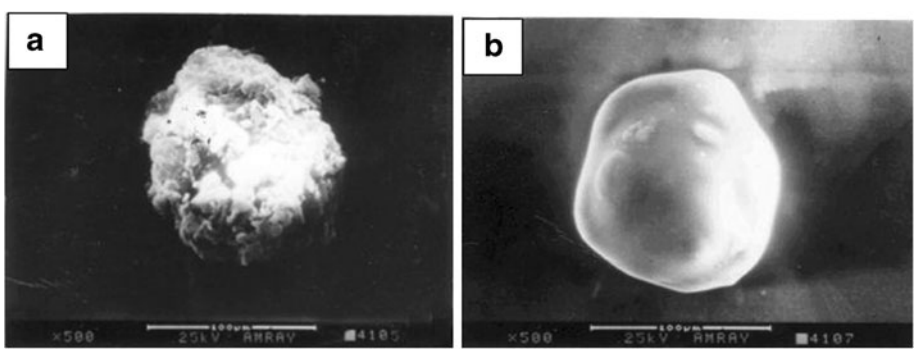

Fig. 2. Scanning electron micrographs of Ber microcapsules (×500): **a** granulated particle; **b** coated microcapsule

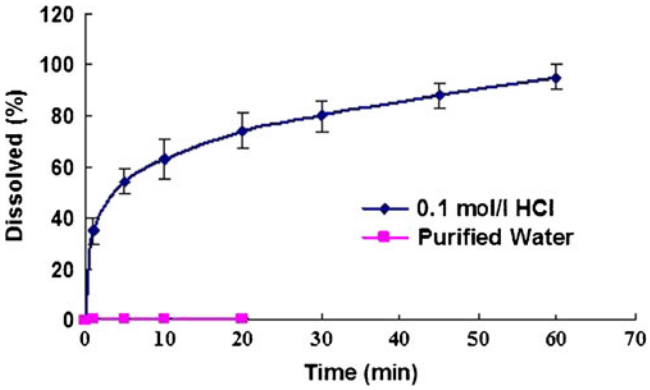

Fig. 4. Dissolution profile of Ber microcapsules in 0.1 mol/l HCl and purified water (mean±S.D., n=6)

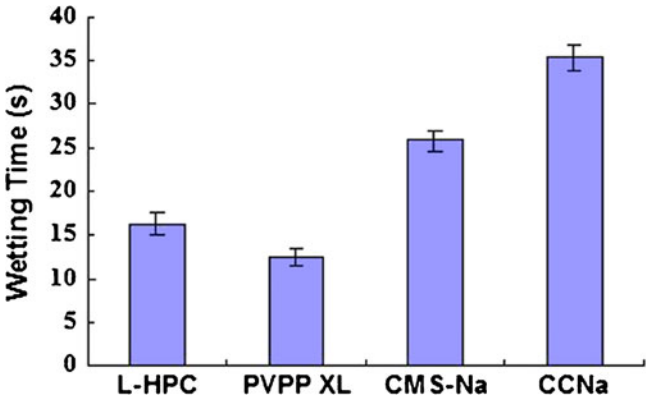

Fig. 6. Wetting times of tablets containing different disintegrants (mean±S.D., n=6)

C18 column (4.6×250 mm, 5 μm, Dalian Elite Analytical Instruments Co., Ltd., China) was used. Acetonitrile–0.033 mol/L potassium dihydrogen phosphate (30:70, *v*/*v*) was used as mobile phase at a flow rate of 1 ml/min. The ultraviolet detection was at 263 nm. The calibration curve was $y=58.691x-197.03$ (r= 0.9996, n=6), it exhibited an excellent linearity over a concentration range of 20–500 ng/ml of berberine hydrochloride.

The pharmacokinetic parameters, namely maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve from 0 to 24 h (AUC_{0-24}) was calculated by the trapezoidal rule. The values of C_{max} and AUC_{0-24} were analyzed statistically using analysis of variance (ANOVA) after logarithmic transformation. The T_{max} values were analyzed using Wilcoxon signed-rank test for paired samples. A statistical significant difference was considered at $p<0.05$.

RESULTS AND DISCUSSION

Preparation of Microcapsules

The taste masking of bitter active substances is a major challenge for the successful development of ODTs. Taste masking can be achieved by microencapsulation technology through forming a thick polymer layer around the drug particle and prevent direct contact of the active substance with the taste buds. In this study, to mask the bitterness of Ber, microcapsules were prepared by coating Ber with Eudragit E100 using a fluidized bed.

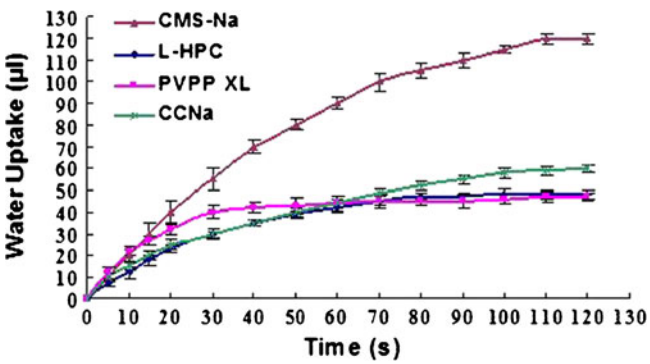

Fig. 5. Water uptake profiles of tablets containing different disintegrants

To obtain homogenous coating for all particles, the number of small particles less than 50 μm in size that kept floating in the coating vessel or adhering to the wall surface in the coating process must be minimized (18). Granulation of Ber with 3% (*w*/*w*) HPMC solution was performed using the side-spray method before coating.

In order to find the appropriate composition of the microcapsules, various drug-Eudragit E100 ratios were used to prepare microcapsules and then the sensations of roughness and bitterness was evaluated. Table II shows that when the drug-Eudragit E100 ratio was increased from1:0 to 1:0.8, the sensation of bitterness of the microcapsules decreased obviously. The sensation of bitterness was very slight when the drug-Eudragit E100 ratio was 1:0.8. Further increase in the amount of Eudragit E100 did not cause further decrease in bitterness. On the other hand, increase in the amount of Eudragit E100 increased the sensation of roughness. This is because Eudragit E100 is insoluble in the oral cavity. Therefore, the ratio 1:0.8 was considered to be the most suitable.

Evaluation of Microcapsules

Surface State and Particle Size

Scanning electron microscopy photographs showed that particles of Ber had an uneven surface and irregular

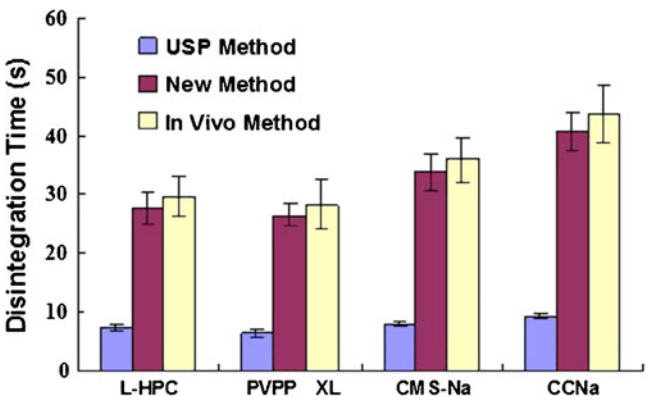

Fig. 7. *In vitro* (USP method and new method) and *in vivo* disintegration times of tablets prepared with different disintegrants (mean± S.D., n=6)

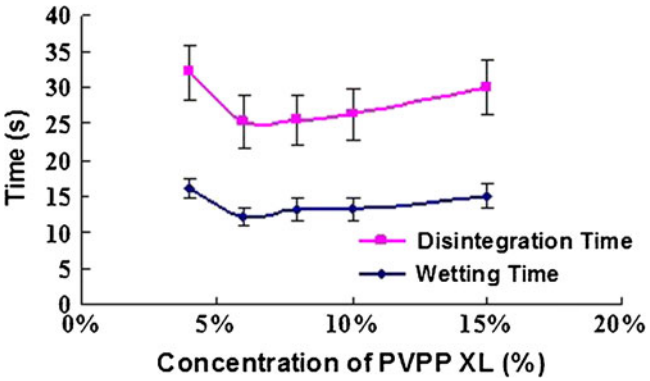

Fig. 8. Wetting times and disintegration times of tablets containing PVPP XL in different concentrations (mean±S.D., n=6)

shape (Fig. 2a). After coating with Eudragit E100, however, the microcapsules were almost spherical, with regular shapes and smooth surfaces (Fig. 2b). Particle size distribution of Ber after sieving, granulation, and coating is shown in Fig. 3. The median diameter was 105 μm before coating and 145 μm after. This increase of 40 μm was considered to be due to the thickness of the coating layer.

Entrapment Efficiency and Drug Loading

The entrapment efficiency of Ber microcapsules was found to be 82.8% with a drug loading of 55.0%. The lower entrapment efficiency could be due to a portion of the small and light particles escaping through the exhaust of the fluid bed during the microcapsule preparation process.

Dissolution Study

Figure 4 shows the dissolution profiles of Ber microcapsules in 0.1 mol/l HCl and purified water. The dissolution profiles showed that Ber microcapsules dissolved more than 50% within 5 min when placed in 0.1 mol/l HCl but only 0.56% within 20 min in purified water. These results suggested that after being coated with Eudragit E100, Ber was released hardly in the saliva but quickly in gastric juice. This method was therefore concluded to mask the bitter taste of Ber without reducing its dissolution or absorption of drug in gastrointestinal track.

Preparation and Evaluation of ODTs

Initially, tablets containing disintegrants in the same concentration were tested for water uptake, wetting time, and disintegration time. The results are given in Figs. 5, 6, and 7, respectively. Tablets containing PVPP XL required only minimal time to become saturated during water uptake, about 30 s. The next were L-HPC, CCNa, and CMS-Na. Tablets containing PVPP XL showed quick wetting and disintegration followed by L-HPC, CMS-Na, and CCNa. The results were similar to that observed by Khan *et al.* (10) and Sheshala *et al.* (19). It might be attributed to rapid water absorbing nature of crospovidone, involving both capillary and swelling mechanisms which build up the pressure internally leading to the faster disintegration (20). A coincident relationship was observed between the wetting time and disintegration time of the tablets with four disintegrants. The tablets with shorter wetting times disintegrated faster. This showed that the wetting time plays an important role in the disintegration of ODTs.

Tablets containing PVPP XL at concentrations 4, 6, 8, 10, and 15% (*w*/*w*) were evaluated with respect to wetting time and disintegration time using the new method, and the results are shown in Fig. 8. Tablets containing 6% PVPP XL showed the shortest wetting and disintegration times. Further increase in concentration did not decrease wetting or disintegration times. It was observed that wetting and disintegration time increased when the concentration of PVPP XL increased to 15%. The delays in wetting and disintegration may be because the gel induced by a large amount of PVPP XL hindered further water penetration into the tablets.

A combination of microcrystalline cellulose and mannitol was used as the diluents in all formulations. Microcrystalline cellulose can increase the porosity of tablets, thus promoting capillary action. An evaluation of tablets containing microcrystalline cellulose in concentrations of 5, 10, 15, 20, 30, and 70% (*w*/*w*) is presented in Table III. It was observed that increase in the concentration of microcrystalline cellulose led to decrease in disintegration time at concentrations less than 20%, but batches F4 to F6, which contained higher concentrations of microcrystalline cellulose, showed slightly increased disintegration times. Tablets containing 15% microcrystalline cellulose showed the shortest disintegration time. This may be because of competition between microcrystalline cellulose and PVPP XL for water absorption. A large amount of microcrystalline cellulose absorbed most of the water, delaying water absorption and swelling of PVPP XL which increased disintegration time. In addition, the tablets containing the higher concentrations of microcrystalline

Table III. Evaluation of the ODTs

	Batch						
	F0	F1	F2	F3	F4	F5	F6
Weight, mg, n=20	202.0±1.1	201.5±1.4	198.1±1.3	201.2±1.2	200.2±1.4	203.4±1.0	202.4±1.1
Hardness, kg, n=10	2.96±0.03	2.91±0.04	2.97±0.06	3.02±0.03	3.05±0.05	3.03±0.03	3.06±0.04
DT, s, n=6	42.4±3.2	39.4±3.7	34.5±3.0	25.5±3.4	26.7±2.5	28.2±3.7	30.2±3.3
Degree of roughness	0	0.5	0.5	0.5	1	1.5	2
Degree of bitterness	3	0+	0+	0+	0+	0+	0

"+" indicates palatable
DT in vitro disintegration time

cellulose caused more of a sensation of roughness because the microcrystalline cellulose absorbed the saliva and did not dissolve in the oral cavity (Table III). For this reason, 15% microcrystalline cellulose was selected for the formulation of ODTs.

Conventional ODTs (F0), to which a great quantity of aspartame had been added, had an intensely bitter taste. In contrast, with microencapsulation technology, none of the taste-masked ODTs (batch F1–F6) tasted bitter, even though no aspartame was used (Table III). ODTs with added mannitol (F1–F5) tasted good. Mannitol has good aqueous solubility, negative heats of solution, and sweet taste (21). These attributes decrease the sensations of roughness and bitterness, improving the perceived taste of the ODTs.

Tablets of batch F3 containing 6% (*w*/*w*) PVPP XL and 15% microcrystalline cellulose disintegrated the fastest, within 25.5 s, and had a pleasant taste. Thus, formulation F3 was considered as the optimized formulation.

Disintegration Study

Many reports indicated the unsuitability of the conventional disintegration test apparatus for ODTs (22–25). The conditions of the conventional disintegration test do not reflect those of the oral cavity, where a very limited volume (0.35–1.0 ml/min) of saliva is available for a maximum of 5 to 7 ml/min after stimulation (26). Also, the raising and lowering of the basket in the USP method accelerates tablet disintegration, resulting in a disintegration time skewed toward shorter values. A relatively simple method, as previously described, was developed to evaluate the disintegration time of ODTs. In this method, the temperature (37±1°C) of the distilled water was similar to that of the oral cavity. The small volume of water (2 mL) used for tablet disintegration evaluation approximate the volume of saliva secreted under normal conditions and in the relatively static environment, the disintegration process of ODT was in its natural state. Therefore this method simulates the temperature of the oral cavity, the small volume of saliva, and the natural disintegration process of ODT in the oral cavity. A 24-mesh sieve (850 μm) was to determine whether the ODT was completely disintegrated and dispersed using method of determination the dispersion fineness of dispersible tablets described in *Chinese Pharmacopoeia* (2010).

Figure 7 shows disintegration times determined by three methods. There was a significant difference between the USP method and the *in vivo* method ($P<0.05$), but the disintegration times of tablets from all batches determined using the new *in vitro* method were nearly the same as the *in vivo* disintegration results. The difference in disintegration times between the new *in vitro* method and *in vivo* method was statistically insignificant ($P>0.05$). The new *in vitro* method was concluded to be accurate and suitable for use in ODTs.

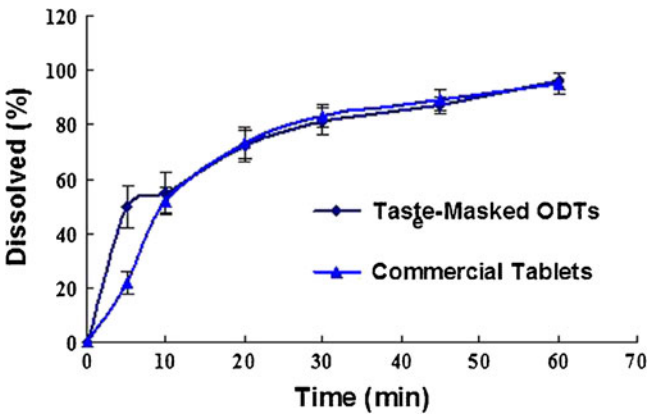

Fig. 9. Dissolution profiles of taste-masked ODTs (F3) and commercial Ber tablets (mean±S.D., $n=6$)

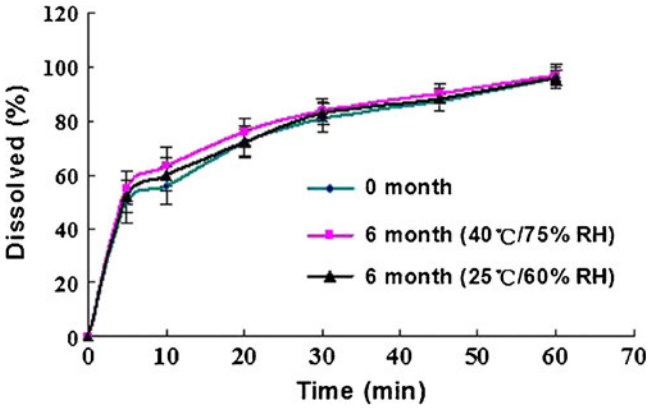

Fig. 10. Dissolution profiles of optimized Ber ODTs (F3) stored at different temperature and humidity for 6 months (mean±S.D., $n=6$)

Dissolution Study

Figure 9 shows *in vitro* drug release profiles of taste-masked ODTs (F3) and commercial Ber tablets. It revealed that in the first 10 min, the drug released from taste-masked ODTs was faster than from commercial Ber tablets. However, their dissolution profiles were very similar after 10 min. This was because taste-masked ODTs disintegrated quickly and Eudragit E100 dissolved fast in 0.1 mol/l HCl; thus, the initial release of the drug from taste-masked ODTs was very quick. The initial release of drug from commercial Ber tablets was slow because of the slow disintegration of these conventional tablets. After 10 min, the commercial Ber tablets disintegrated and dispersed completely, and so exhibited similar release profiles with taste-masked ODTs.

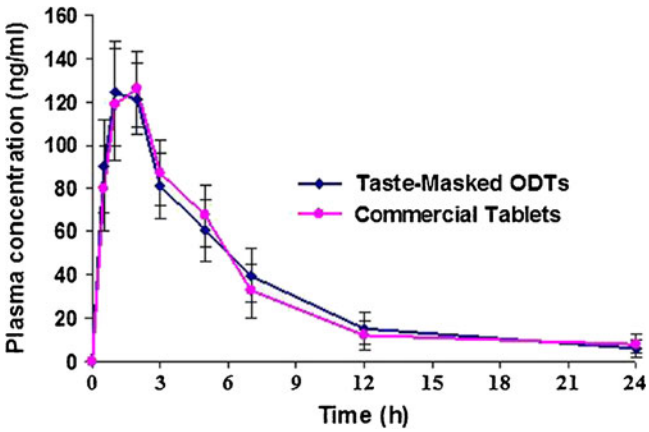

Fig. 11. Plasma concentration-time profiles of Ber after oral administration of taste-masked ODTs (F3) and commercial Ber tablets in rabbits (mean±S.D., $n=6$)

Stability Study

The stability results demonstrated that there was no significant change in the taste, average weight, drug content, disintegration time, or dissolution time after 10 days of exposure to 60°C and to 4,500 lx. Some changes were observed in the ODTs after 10 days of exposure to 92.5% RH. These tablets thickened and increased in weight by an average of 18 mg (9.0%), and disintegration time shortened by 5 s. These results show that the ODTs absorbed moisture easily and that this reduces disintegration time. After 6 months of storage, there was no significant change in the taste, average weight, drug content, disintegration time, and or dissolution characteristics of these tablets ($P>0.05$). The dissolution profiles of optimized formulation (F3) stored for 6 months are shown in Fig. 10. There was no significant difference in dissolution profiles before and after storage. Thus, the formulation F3 was proven to remain stable for at least 6 months.

In Vivo Study

The plasma concentration–time profiles of Ber taste-masked ODTs and commercial tablets were shown in Fig. 11. The pharmacokinetic parameters, C_{max}, T_{max}, and AUC_{0-24} values were 125.96±26.56 ng/ml, 1.02±0.44 h, and 699.29±44.75 ng·h/ml, respectively for taste-masked ODTs and 129.49±24.54 ng/ml, 1.09±0.37 h and 675.84±47.34 ng·h/ml, respectively for commercial tablets. The C_{max}, T_{max}, and AUC_{0-24} values were not significantly different from each other, indicating that the Ber taste-masked ODTs are bioequivalent to commercial Ber tablets in rabbits.

CONCLUSIONS

This study demonstrated that preparing microcapsules with Eudragit E100 was an effective means of masking the bitter taste of Ber. The ODTs containing Ber microcapsules had pleasant taste, disintegrated rapidly, and were bioequivalent to commercial Ber tablets in rabbits. The taste masking and rapid disintegration may possibly help in administration of Ber in a more user-friendly form without water, and will improve treatment compliance and QOL. This technology also can be applied to other bitter-tasting drugs. In addition, during this study, we developed a simple *in vitro* disintegration method, and it was found to be suitable for ODTs.

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REFERENCES

1. Kawano Y, Ito A, Sasatsu M, Machida Y. 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. Yakugaku Zasshi. 2010;130:81–6.
2. Anderson O, Zweidorff OK, Hjelde T. Problems when swallowing tablets. A questionnaire study from general practice. Tidsskr Nor Laegeforen. 1995;20:947–9.
3. USFDA, Center for Drug Evaluation and Research (CDER). 2008. Guidance for industry orally disintegrating tablets. http://www.fda.gov/cder/guidance. Accessed 15 July 2010.
4. Douroumis D. Orally disintegrating dosage forms and taste-masking technologies; 2010. Expert Opin Drug Deliv. 2011;8:665–75.
5. Kawano Y, Ito A, Sasatsu M, Machida Y, Onishi H. Preparation and evaluation of taste masked orally disintegrating tablets with granules made by the wet granulation method. Yakugaku Zasshi. 2010;130:1737–42.
6. Lu MY, Borodkin S, Woodward L, Li P, Diesner C, Hernandez L, *et al*. A polymer carrier system for taste masking of macrolide antibiotics. Pharm Res. 1991;8:706–12.
7. Bhise K, Shaikh S, Bora D. Taste mask, design and evaluation of an oral formulation using ion exchange resin as drug carrier. AAPS PharmSciTech. 2008;9:557–62.
8. Szejtli J, Szente L. Elimination of bitter, disgusting tastes of drugs and foods by cyclodextrins. Eur J Pharm Biopharm. 2005;61:115–25.
9. Ishikawa T, Watanabe Y, Utoguchi N, Matsumoto M. Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter-taste-masked granules by the compression method. Chem Pharm Bull. 1999;47:1451–4.
10. Khan S, Kataria P, Nakhat P. Taste masking of ondansetron hydrochloride by polymer carrier system and formulation of rapid-disintegrating tablets. AAPS PharmSciTech. 2007;8:E46.
11. Yan YD, Woo JS, Kang JH, Yong CS, Choi HG. Preparation and evaluation of taste-masked donepezil hydrochloride orally disintegrating tablets. Biol Pharm Bull. 2010;33:1364–70.
12. Löbenberg R, Krämer J, Shah VP, Amidon GL, Dressman JB. Dissolution testing as a prognostic tool for oral drug absorption: dissolution behavior of glibenclamide. Pharm Res. 2000;17:439–44.
13. Yoshida T, Tasaki H, Maeda A, Katsuma M, Sakoa K, Uchidac T. Salting-out taste-masking system generates lag time with subsequent immediate release. Int J Pharm. 2009;365:81–8.
14. Shah PP, Mashru RC, Rane YM, Badhan AC. Design and optimization of artemether microparticles for bitter taste masking. Acta Pharm. 2008;58:379–92.
15. Ishikawa T, Mukai B, Shiraishi S, Utoguchi N, Fujii M, Matsumoto M, *et al*. Preparation of rapidly disintegrating tablet using new types of microcrystalline cellulose (PH-M series) and low substituted-hydroxypropylcellulose or spherical sugar granules by direct compression method. Chem Pharm Bull. 2001;49:134–9.
16. Uchida T, Nakamura T, Tanigake A, Miyanaga Y, Ogawa T. The effect of various substances on the suppression of the bitterness of quinine-human gustatory sensation, binding, and taste sensor studies. Chem Pharm Bull. 2002;50:1589–93.
17. Kawashima Y, Takeuchi H, Hino T, Niwa T, Lin TL, Sekigawa F, *et al*. Low-substituted hydroxypropylcellulose as a sustained-drug release matrix base or disintegrant depending on its particle size and loading in formulation. Pharm Res. 1993;10:351–5.
18. Sugao H, Yamazaki S, Shiozawa H, Yano K. Taste masking of bitter drug powder without loss of bioavailability by heat treatment of wax-coated microparticles. J Pharm Sci. 1998;87:96–100.
19. Sheshala R, Khan N, Darwis Y. Formulation and optimization of orally disintegrating tablets of sumatriptan succinate. Chem Pharm Bull. 2011;59:920–8.
20. Battu SK, Repka MA, Majumdar S, Madhusudan RY. Formulation and evaluation of rapidly disintegrating fenoverine tablets: effect of superdisintegrants. Drug Dev Ind Pharm. 2007;33:1225–32.
21. Madan J, Sharma AK, Singh R. Fast dissolving tablets of *Aloe vera* gel. Trop J Pharm Res. 2009;8:63–70.

22. Morita Y, Tsushima Y, Termoz R, Ajioka J, Takayama K. Evaluation of disintegration time of rapidly disintegrating tablets *via* a novel method utilizing a CCD camera. Chem Pharm Bull. 2002;50:1181–6.
23. Shibata Y, Yamamoto Y, Fujii M, Kondoh M, Watanabe Y. A novel method for predicting disintegration time in the mouth of rapidly disintegrating tablet by compaction analysis using TabAll. Chem Pharm Bull. 2004;52:1394–5.
24. Narazaki R, Harada T, Takami N, Kato Y, Ohwaki T. A new method for disintegration studies of rapid disintegrating tablets. Chem Pharm Bull. 2004;52:704–7.
25. Rawas-Qalaji MM, Simons FE, Simons KJ. Fast-disintegrating sublingual tablets: effect of epinephrine load on tablet characteristics. AAPS PharmSciTech. 2006;7:E41.
26. Diem K, Lentner C. Scientific tables. Basle: Ciba-Geigy Limited; 1971.