Preparation and Evaluation of Taste-Masked Donepezil Hydrochloride Orally Disintegrating Tablets

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Received June 11, 2009; accepted May 9, 2010

The purpose of this research was to prepare and evaluate a non-bitter donepezil hydrochloride (DH) orally disintegrating tablet (ODT) for enhanced patient compliance. Taste masking was done by preparing microspheres with different ratios of drug and Eudragit® EPO using spray drying method. The entrapment of the drug into microspheres was confirmed by scanning electron microscope (SEM) and X-ray powder diffraction. It was found that microspheres with a drug-polymer ratio of 1 : 2 could mask the taste obviously by inhibiting the release of DH in simulated salivary fluid. Microspheres-loaded tablets containing Polyplasdone NF and Low substituted Hydroxypropyl Cellulose (L-HPC) both at a 10% level showed rapid disintegration, in vitro (15.5 s) and in vivo (19.8 s), which were faster than that of marketed tablets (36.7, 41.3 s, respectively). Results from taste evaluation in human volunteers revealed that the ODTs with taste-masked microspheres had significantly enhanced palatability. Dissolution in vitro and pharmacokinetics in rats were evaluated for the tested ODTs compared to the donepezil hydrochloride commercial product (ARICEPT®). Both tablets showed comparable dissolution patterns in vitro and similar area under curve from 0 to 24 h (AUC0–24, Cmax, and Tmax of DH in vivo to each other, suggesting that the tested ODTs might give the similar drug efficacy in rats compared to that of ARICEPT®. Thus, it was concluded that DH ODTs with masked taste were obtained by Eudragit® EPO-based microspheres, drug loaded microspheres neither decreased the bioavailability nor delayed the release of DH.

Key words donepezil hydrochloride; orally disintegrating tablet; taste masking; microsphere; pharmacokinetics

In recent decades, the demand for development of orally disintegrating tablet (ODT) is enormously increased as it can facilitate ease of medication, offering an advantage for populations who have difficulty in swallowing or chewing. Ideally, an ODT formulation should disintegrate rapidly in the saliva without water and then form a smooth, non-gritty, and easy-to-swallow suspension with favorable taste and mouthfeel. However, many therapeutic agents are bitter and thus taste masking for these active substances challenges the development of this dosage form to achieve patient acceptability.

The techniques most often employed for achieving effective taste-masking have been described in literature when the addition of flavors or sweeteners is limited and may not be efficient enough to mask the unpleasant taste of some drugs. These approaches include the use of ion exchange resins, the use of inclusion complexes with cyclodextrins, and drug-polymer complexes. In recent years, the entrapment of bitter drug substance into polymer-based microspheres or microcapsules has become an increasingly attractive strategy for taste masking by creating a physical barrier around the bitter drug to keep them from coming in contact with the patients’ taste buds. It has also been reported that these microparticles remained intact without undergoing significant merging or rupturing during tabletting. However, a taste masking by microencapsulation which prevents release of a bitter-tasting drug in the oral cavity can also undesirably reduce the rate of drug release in the gastrointestinal tract. Furthermore, because of the slower drug release, the taste-masked drug product may no longer be bioequivalent to the immediate-release product. To avoid this undesirable consequence, in this study, a novel promising copolymer called Eudragit® EPO was selected as a carrier to prepare taste masked microspheres. It is a pH dependent material and is only soluble at a pH below 5.5, by taking the advantage of this unique property, we can prevent the release of the bitter drug from the microspheres in saliva (pH 6.2) thus masking the bitterness induced by the drug in oral cavity, however, active drug is then rapidly released afterwards in gastric fluids (pH 1.2), in which Eudragit® EPO is dissolved with no more microspheres existing. Taste masking by using this said polymer is expected not to affect the dissolution or absorption of drug in gastrointestinal track.

Donepezil hydrochloride (DH) is clinically used for the treatment of mild to moderate dementia due to Alzheimer’s disease occurring primarily in individuals over 55 years of age. Thus ODT is an appropriate dosage form for these target patients. Unfortunately, the drug has a very bitter taste that leads to reduced compliance of commercially available product (ARICEPT® ODT) and consequently the market value for this product is lessened significantly. So it is necessary that taste masking is carried out during the formulation process.

The purpose of this work was to develop a non-bitter orally disintegrating tablet for DH. Firstly, the taste masked microspheres were prepared and characterized using scanning electron microscope (SEM), and X-ray powder diffraction. And then, after DH ODT was optimized and formulated, taste evaluation, dissolution and pharmacokinetics in rats were conducted compared to the commercial product of ARICEPT®.

MATERIALS AND METHODS

Materials

Donepezil hydrochloride (DH, Batch No. 08DNP-PF01001) and ARICEPT® ODT (Lot. 003614) were donated by Hanmi Pharm. Co., Ltd. (Seoul, Republic of Korea). Aminoalkyl methacrylate copolymer (Eudragit® EPO) and colloidal silicone dioxide (AEROSIL, 200Pharm)

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were purchased from Degussa Co., Ltd. (Germany). Icarin was purchased from Xi’an Xiao Cao Botanical Development Co., Ltd. (China). The diluents used were microcrystalline cellulose (Celos KS 802, Asahi Kasei Chemicals Corp., Tokyo, Japan), mannitol (ManninexTM, Cargill, U.S.A.). The disintegrants were crospovidone (Polyplasdone NF, ISP Technologies, Inc., Calvert, KY, U.S.A.) and Low Substitution Hydroxypropylcellulose (SHMI-04, Shanghai Shenmei Pharmaceutical Technology Co., Ltd., China). Magnesium stearate, aspartame and orange flavor were obtained from Hanmi Pharm. Co., Ltd. (Seoul, Republic of Korea). Ace-tonitrile (HPLC grade) was obtained from Mallinckrodt Baker, Inc. Phillipsburg, U.S.A. Other reagents were analytical grade and used as received. All other chemicals used in the study were of analytical grade.

Preparation of Microspheres The microspheres were obtained by spray drying method using a Büchi 191Mini Spray Dryer (Büchi Laboratoriums-Technik AG, Flawil, Switzerland). At first, the drug and Eudragit® EPO in various ratios (as shown in Table 1) were co-dissolved in 95% (v/v) ethanol followed by the suspending of colloidal silicon dioxide in the drug solution, then the resulting suspensions were delivered to the nozzle at a flow rate of 5 ml/min using a peristaltic pump and thereafter spray dried under the following processing conditions: inlet temperature: 80 °C, airflow rate: 600 NL/h and aspirator setting: 85%, Fitted with a standard 0.7 mm two-fluid nozzle.

The colloidal silicon dioxide was used as both carriers and glidend to enhance the performance of spray drying. In all the suspensions, the ratio of colloidal silicon dioxide to DH was fixed at 1:1.

In Vitro Taste Evaluation of Microspheres Standard Solution for Evaluation of the Bitter Taste Threshold of Donepezil Hydrochloride The bitter taste threshold value of DH was determined based on the bitter taste recognized by six volunteers. One milliliter of standard aqueous solution with various concentrations (i.e. 2.5, 5.0, 10.0, 15.0, 20.0 μg/mL) was placed on the center of the tongue and retained in the mouth for 60 s, and then the mouth was thoroughly rinsed with distilled water. The threshold value was correspondingly selected as the lowest concentration that had a bitter taste.17)

Estimation of the Bitter Taste of Microspheres and Marketed Product in Vitro In vitro taste was evaluated by determining drug release in simulated salivary fluid (SSF) (pH 6.2) to predict release in the human saliva.17,18) Microspheres or marketed tablets containing about 5 mg DH were placed in 10 ml of SSF and shaken for 60 s. The amount of drug released was assayed by HPLC.

The HPLC method was performed on The Waters Alliance HT Chromatography System (Waters Corp., Milford, MA, U.S.A.) and an ODS-3 C18 column (250 mm×4.6 mm i.d., 5 μm, Inertsil, Japan) was used. Chromatography was conducted at room temperature using a 10 min run time. Acetonitrile-0.02 M phosphate buffer-trimethylamine (50 : 50 : 0.5, v/v/v) was used as mobile phase at a flow rate of 1 mL/min. The injection volume was 20 μl and ultraviolet detection was at 271 nm.26) The calibration curve was y = 25300x−63080 (r²= 0.9999, n= 5). It showed that the absorbance was linear to the DH concentration within the range of 0.5—10 μg/ml.

Characterization of Microspheres. Percentage Yield The percentage yield of microspheres was calculated using the following formula:

\[
\text{yield} = \frac{\text{theoretical yield}}{\text{practical yield}} 
\]

Drug Entrapment Efficiency of the Microspheres The amount of drug entrapped was estimated by dissolving the microspheres in 95% (v/v) ethanol and determined in triplicate. The percentage of drug entrapment efficiency (% DEE) was calculated using the following formula:

\[
\text{% DEE} = \frac{\text{amount of drug actually present}}{\text{theoretical drug expected}} \times 100
\]

Particle Size Analysis of the Microspheres The particle size analysis and particle size distribution of microspheres were carried out by means of Scanning Electron Microscopy method under 1000 magnification. The images were obtained automatically and were analyzed with an image analysis system.

Scanning Electron Microscopy Analysis of the Microspheres The microspheres were characterized further using a scanning electron microscope (S-400, Hitachi, Japan). Shapes and surface characteristics of the microspheres were investigated and photographed. The microspheres were fixed on a brass specimen club using double-side sticky tape and made electrically conductive by coating in a vacuum (6 Pa) with platinum (6 nm/min) using a Hitachi Iron Sputter (E-1030) for 30 s at 15 mA.

X-Ray Powder Diffraction Analysis of the Microspheres The physical states of the pure DH, silicon dioxide, Eudragit® EPO, physical mixture and formed DH microspheres were evaluated with X-ray powder diffraction (XRPD). Diffraction patterns were obtained using a BRUKER D8 FOCUS High Resolution Powder Diffractometer (BRUKER AXS, Germany) equipped with a scintillation counter detector and a divergent beam. This beam employed a Cu-Kα radiation source with a wavelength of λ = 1.5418 containing 2 mm slits over a range of 10—50° 2-theta. X-Ray diffraction data were collected at room temperature and scanned with a step size of 5° 2-theta and a dwell time of 12 min at each step. The values and the intensities of the peaks were compared for pure ingredients and microsphere system. The generator was set to 40 kV and 40 mA. Fourier transform (FT) IR spectra were obtained on a Bruker T.

Optimization of the Formulation and Preparation of the ODTs Commonly used Polyplasdone NF and L-HPC ingredients were used as the main disintegrant in consideration of their good swelling property as well as low price and easy access. Various concentrations of the disintegrants were blended uniformly with diluents screened from microcrystalline cellulose, lactose and/or mannitol as designed in Table 2, and then the tablets were prepared by direct compressing using an 8-mm flat faced punch. The pressure was adjusted to maintain an appropriate hardness of the tablet around 35N.

The optimized formulation was then used for the final formulation of tablets. When microspheres equivalent of 5 mg of the model drug were added, the same amount of microcrystalline cellulose was excluded accordingly. In the development of formulation, the commonly used aspartame and orange flavor were added for the further enhancement of tablets’ palatability.

Evaluation of the ODTs. Wetting Time and Hardness To measure tablet wetting time, a piece of tissue paper was
placed in a small culture dish (i.e., 5 cm) containing 6 ml of water, a pre-weighed tablet was put on the paper, and the time for complete wetting was measured. The wetted tablet was weighed and the water absorption ratio \( R \) was calculated according to the equation \( R = \frac{W_f - W_0}{W_f} \), where \( W_0 \) and \( W_f \) were the weights of the tablet before and after study.

For each formulation, the fracture strength, which is defined as the force, required to break a tablet by radial compression, was measured with a Monsanto tablet hardness tester. The mean hardness was calculated and expressed as N.

**In Vitro Disintegration**  
In vitro disintegration time for ODts was determined using an apparatus described by Khan et al.,\(^{19}\) which was considered to be more suitable for ODts with 900 ml of SSF (pH 6.2) as the disintegrating medium. The basket volume used was 6 ml. The disintegrating medium was maintained at 37±2°C and stirred by a magnetic bead placed at the bottom at a speed of 50 rpm. Disintegration time was determined when the tablets had completely disintegrated and passed through the mesh.

**In Vitro Drug Release of ODts**  
The drug release study on both tested ODts (optimized formulation) and marketed tablets (ARICEPT® ODT, used as a reference) was performed using 900 ml of 0.1 N HCl for 30 min using the paddle method under sink conditions. The speed of the paddle was adjusted to 50 rpm and then the tablets were added to a dissolution medium kept at 37±0.5°C. Samples were then collected at 5, 10, 15, 20, and 30 min time point. After suitable dilution, the samples were analyzed by the HPLC method described above.

**In Vivo Disintegration and Taste Evaluation**  
In vivo disintegration was performed by six volunteers who were asked to rate the bitter taste of the tablets. One tablet was placed on the center of the tongue after rinsing and the time required for complete disintegration of the tablet was recorded; the disintegrated material was held in the mouth for another 60 s, and then spat out. The mouth was thoroughly rinsed with distilled water. Finally, bitterness was recorded according to the bitterness intensity scale from 0+ to 3 where 0+ 0, 1, 2, and 3 indicate increased palatability, no, slight, moderate, and high bitterness, respectively. Only when the score was 1 or less, the taste was considered as acceptable.

The trial in human was conducted according to the protocol approved and subject to review by Institutional Ethics Committee, the ethical principles that have origins in the Declaration of Helsinki and the Good Laboratory Practice (GLP) regulatory requirements.

**Pharmacokinetics Study in Rats**  
To evaluate the effects of the microspheres on the release profile in vivo, twelve male Sprague-Dawley rats weighing 260±20 g were used. All the rats were divided into two groups and fasted for 10—12 h prior to the experiments but allowed free access to water. The commercial product (ARICEPT®) was reconstituted with 100 ml of mobile phase and 50 ml of the resulting solution was analyzed.

The HPLC method was performed on the same Alliance HT Chromatography System and column as described mentioned above. The mobile phase was comprised of 70% acetonitrile and 30% 10 mm ammonium acetate, adjusted to pH 5.0 (v/v) with glacial acetic acid, at a flow rate of 0.7 ml/min. Separation was carried out isocratically, at ambient temperature (25±1°C) with ultraviolet (UV) detection at 315 nm.

Student’s t-tests were performed to evaluate any possible difference between two kinds of tablets. Values were reported as mean±S.D. and the data were considered statistically significant at \( p<0.05 \).

**RESULTS AND DISCUSSION**

**The Bitter Threshold of Donepezil Hydrochloride**  
The bitter threshold of DH recognized by the volunteers was between 15.0 and 20.0 \( \mu \)g/ml. If the drug concentration dissolved in 10 ml simulated salivary fluid from the microspheres after vibration for 60 s was below the threshold value, no bitter taste could be identified by the taste buds. Accordingly, the bitter taste of donepezil hydrochloride was considered to be masked effectively by the polymer.

**Taste-Masking Ability of the Microspheres**  
As mentioned above, the amount of the drug released from the microspheres in simulated salivary fluid could be considered as an indicating parameter to determine whether the bitterness had been masked or not. Thus, in order to find the appropriate composition of the microspheres, various drug/polymer ratios were used to prepare microspheres and then the taste was evaluated by determining drug release in simulated salivary fluid in 60 s. A yield of about 40% was consistently produced by these sets of experimental processes. Drug entrapment efficiency varied from 92.5 to 98.5%. Different extents of retard release were shown for all the microspheres (as shown in Table 1). When the drug/polymer ratio was increased from 1:3 to 1:2, microspheres showed almost the same drug release profile of DH (1.49% and 1.55%, respectively). However, if the ratio was changed from 1:2 to 1:1, a sharp increase of drug release was observed (6.15%) and correspondingly the concentration of DH in 10 ml simulated salivary fluid (30.8 \( \mu \)g/ml as calculated) was above the bitter threshold value. Therefore, the ratio 1:2 was considered to be the most suitable with respect to taste masking, and microspheres consisting of donepezil hydrochloride, Eudragit® EPO and silicon dioxide (1:2:1) were prepared for further research and evaluation.

On the other, the drug released from the marketed tablets in the same medium was as high as 25.86% (as shown in Table 1), the resulted concentration (129.5 \( \mu \)g/ml) was more...
than 6 times higher than the upper bitter threshold limit, making taste masking urgently needed.

Characterization of Microspheres The microspheres prepared by the optimal composition were subjected to particle size distribution analysis. The size of microspheres varied within a range of 1—22 μm and the weighted mean size was 4.35 μm as shown in Fig. 1, more than 80% of microspheres displayed a diameter well within 6 μm, and a few larger particles observed irregular in shape were considered to be a result of aggregation of two or more fine microspheres. Increased polymer/drug ratio was expected to increase the number and particle size of aggregated microspheres as a consequence of higher solution viscosity caused by polymers during the spray drying process.5,17) At selected ratio level, the small mean size and narrow size distribution were both acceptable, considering that larger microspheres were more likely to suffer from merging or rupturing during tabletting, thus inducing gritty in the mouth.

The particle structural and surface morphology of the microspheres were evaluated by a scanning electron microscope. The representative scanning electron microscopy (Fig. 2) confirmed the encapsulation of the raw material. The spray dried particles showed the regularly spherical nature of microspheres with a narrow size distribution, whereas in DH raw material particles there existed flake shaped crystals and broad particle size distribution was also observed (Fig. 3).

The X-ray diffraction (XRD) provided the information on the crystallinity and crystal orientation, and the shape of the XRD patterns reflected the state of regular arrangement of molecules inside the crystals. Figure 4 showed the results of the XRD analysis. Many diffraction peaks with high intensity were observed on the diffraction pattern of DH raw material.

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**Table 1. Taste Masking Results of Microspheres with Various Drug : Polymer Ratios (n=3, Mean Value±S.D.)**

<table>
<thead>
<tr>
<th>Tested items</th>
<th>Drug : Polymer</th>
<th>Percentage yield (%)</th>
<th>Drug entrapment efficiency (%)</th>
<th>Drug release in simulated salivary fluid in 60 s (%)</th>
<th>Taste evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microspheres</td>
<td>1 : 1</td>
<td>45.21±4.52</td>
<td>98.54±0.71</td>
<td>6.15±0.17</td>
<td>Bitter</td>
</tr>
<tr>
<td></td>
<td>1 : 2</td>
<td>40.37±3.58</td>
<td>96.67±2.43</td>
<td>1.55±0.16</td>
<td>Insipid</td>
</tr>
<tr>
<td></td>
<td>1 : 3</td>
<td>38.24±4.73</td>
<td>92.53±1.24</td>
<td>1.49±0.05</td>
<td>Insipid</td>
</tr>
<tr>
<td>Marketed tablets</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>25.86±7.24</td>
<td>Bitter</td>
</tr>
</tbody>
</table>

a) Insipid=drug detected in SSF below the threshold of bitterness of DH; Bitter=drug detected in SSF above the threshold of bitterness of DH.
due to its crystallinity. On the other hand, the microspheres prepared by the spray drying processes showed a peak similar to the excipients pattern in which none of diffraction peaks were observed and any peaks for crystalline DH were not observed. This result was similar to that from the SEM, suggesting the entrapment of DH in microspheres by this spray drying process.

**Optimization of the Formulation** Attempts were made to formulate the orally disintegrating tablet exhibiting desirable characteristics. The formulation was optimized so that an adequate hardness was obtained while maintaining quick disintegration time of the tablet.

At first, Polyplasdone NF and L-HPC at a concentration of 10 or 20% wt/wt were examined as the disintegrants for blank orally disintegrating tablets (Table 2). The results showed that Polyplasdone NF had better disintegration ability than L-HPC. When the concentration of Polyplasdone NF increased from 10 to 20%, the disintegration time was shortened from 13.3 to 9.2 s. However, one unexpected observation was made when larger amounts of Polyplasdone NF were added into the formulation: although all the particles passed through the #12 mesh, ultimately relatively larger particles were generated during the process of testing disintegration. A proper amount of microspheres equivalent to 5 mg of DH (about 20 mg) were added into the formulation: although all the particles passed through the #12 mesh, ultimately relatively larger particles were generated during the process of testing disintegration. Given this, the combination use of Polyplasdone NF and L-HPC both at a 10% level (both of them were 15 mg/tablet as shown in Table 2) was considered to be a favorable choice. Furthermore, in an attempt to enhance the palatability of the tablet, some amount of microcrystalline cellulose was substituted with mannitol as indicated in formulation 6 and formulation 7. Unfortunately, a significant increase of disintegration time was observed from 10.5 s (formulation 3) to 19.0 s and 25.5 s when 20% and 40% level of mannitol were added, respectively.

As a result, formulation 3 showing a disintegration time of 10.5 s and a minimal occurrence possibility of larger particles was selected as the optimized one.

**Evaluation of ODTs** A proper amount of microspheres equivalent to 5 mg of DH (about 20 mg) were added into the optimized blank formulation (formulation 3). To maintain the same total weight of the tablet, the amount of microcrystalline cellulose was adjusted accordingly. As expected, the disintegration time in vitro had a tendency to be prolonged after the loading of DH-loaded microspheres. Even when disintegrants were kept at the same level as blank formulation, the disintegration time was changed from 10.5 to 15.5 s after drug loading (see Tables 2, 3, respectively). It might be explained by the substitution of microcrystalline cellulose, which itself had disintegration function by swelling.

Properties of drug loaded ODTs including hardness, friability, weight variation, and content uniformity of tablets were found to be within acceptable limits (see Table 3).

A further retarded disintegration was observed when the tablets were tested for disintegration in vivo. The disintegration was delayed by 4.3 s compared with that of in vitro. A longer disintegration time is reasonable and predictable considering the actual situation that less water in the mouth is available to be absorbed by the tablet. This result coincides with the findings of Khan et al.\(^\text{18}\)

A significant difference was observed when the wetting time, disintegration time both in vitro and in vivo were compared with the commercial tablets (\(p<0.01\)). The prepared ODTs showed a faster disintegration and water absorption rate than that of the reference tablets. As shown in Table 3, a disintegration time of less than 20 s was achieved both for in vitro and in vivo (15.5 s and 19.8 s, respectively) using the modified disintegration test method, shorter than the commercial samples (36.7 s and 41.7 s, respectively).

Results from taste evaluation in human volunteers of both the tested and commercial ODTs showed considerable masking of the bitter taste of DH. The scores given by 6 individuals were all below the threshold value (1.0) for the tested tablets. On the other hand, the commercial tablets were evaluated to be bitter by all the tested subjects (Table 4), these findings were consistent with the results of taste evaluation in vitro (Table 1), in which the drug released in simulated saliva fluid was far above bitter threshold value of DH. Therefore, the taste-masked tablets were proved to be more palatable than the marketed product.

Table 3. Comparative Evaluation of DH ODTs and Marketed Products (\(n=10\), Mean Value±S.D.)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Tested ODTs (Lot: 081220)</th>
<th>Marketed products (Lot: 003263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (mg)</td>
<td>152.6±2.1</td>
<td>284.7±3.8</td>
</tr>
<tr>
<td>Hardness (N)</td>
<td>35.4±6.0</td>
<td>88.0±6.9^{**}</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.5±0.1</td>
<td>0.2±0.02*</td>
</tr>
<tr>
<td>Content uniformity (%)</td>
<td>103.1±1.8</td>
<td>99.7±2.4</td>
</tr>
<tr>
<td>Wetting time (s)</td>
<td>21.4±0.9</td>
<td>61.5±4.3^{**}</td>
</tr>
<tr>
<td>Disintegration time in vitro (s)</td>
<td>15.5±1.0</td>
<td>36.7±3.5^{**}</td>
</tr>
<tr>
<td>Disintegration time in vivo (s)</td>
<td>19.8±2.5</td>
<td>41.7±3.4^{**}</td>
</tr>
</tbody>
</table>

*The hardness of the marketed product was higher than that of the prepared ODTs (\(p<0.01\)) and the subsequent friability is less (\(p<0.05\)). But all the parameters were well within the corresponding limits according to USP. \^{**}The statistically significant difference was observed (\(p<0.01\)) between two groups.

Table 2. Composition of the Blank Orally–Disintegrating Tablets

<table>
<thead>
<tr>
<th></th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcrystalline cellulose (mg)(^a)</td>
<td>129</td>
<td>114</td>
<td>114</td>
<td>99</td>
<td>114</td>
<td>84</td>
<td>54</td>
</tr>
<tr>
<td>Mannitol (mg)</td>
<td>—</td>
<td>—</td>
<td>15</td>
<td>15</td>
<td>30</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Polyplasdone NF (mg)</td>
<td>15</td>
<td>30</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>L-HPC (mg)</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Orange flavor (mg)</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Aspartame (mg)</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
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<tr>
<td>Magnesium stearate (mg)</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Characterization of the tablets</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Hardness (N)</td>
<td>32.5±3.2</td>
<td>34.9±5.0</td>
<td>35.1±4.7</td>
<td>35.8±3.5</td>
<td>31.6±2.8</td>
<td>34.5±3.7</td>
<td>33.7±3.8</td>
</tr>
<tr>
<td>Disintegration time in vitro</td>
<td>13.3±2.1</td>
<td>20.3±3.1</td>
<td>10.5±1.8</td>
<td>10.2±2.2</td>
<td>9.2±1.2</td>
<td>19.0±2.3</td>
<td>25.5±4.0</td>
</tr>
</tbody>
</table>

\(^a\) Designed total tablet weight is 150 mg, the amount of microcrystalline cellulose was adjusted according to the change of disintegrants.
Dissolution Study  The dissolution tests in simulated gastric fluid for 30 min were performed to compare the release profile of taste-masked tablets and commercial products. Compared with marketed samples, only a slight delayed effect was found in 5 min time period (Fig. 5), and the accumulative release values for optimized tablet and commercial tablets in 5 min time period were 84.3% and 96.5%, respectively. However, when all the data were analyzed, this minor difference in dissolution was not found to be significant. Both tablets released drugs completely in 10 min, showing rapid drug release patterns.

In Vivo Study  The pharmacokinetic parameters and the plasma concentration–time profiles of DH following single-dose oral administration of commercial product (ARICEPT®) and test tablets were shown in Table 5 and Fig. 6, respectively. Because the orally disintegrating tablet (ODT) system is orally administered in gastrointestinal tracts after disintegrating or/and dissolving in the saliva, they were dispersed in water and immediately orally administered through oral gavage to compare their pharmacokinetic parameters in this study. The area under curve from 0 to 24 h (AUC[0–24]), Cmax and Tmax of DH were not significantly different from each other as well as Kel and t1/2 values. Thus, the tested ODTs might be bioequivalent to commercial product in rats.

From the pharmacokinetic view, the taste masked tablets might give the similar drug efficacy compared to the commercial product in rats; the drug loaded microspheres neither decrease the bioavailability nor delay the release of DH significantly.

CONCLUSION  Eudragit® EPO could be used as a taste masking material, microspheres with a drug–polymer ratio of 1:2 prepared by spray drying method showed less drug release in simulated salivary fluid in 60 s than the bitter threshold value of DH. SEM and X-ray powder diffraction analysis confirmed the entrapment of drug into microspheres.

This study demonstrated that the prepared DH orally disintegrating tablets had significantly improved taste and shortened disintegration time both in vitro and in vivo while maintaining comparable dissolution patterns and pharmacokinetic behaviors in rats to the marketed products, suggesting that the tested ODTs also released the drug in a manner bioequivalent to the commercial product.

The research in this paper provides a promising approach for the orally disintegrating tablets development of bitter drugs, which disintegrate rapidly with good organoleptic properties in oral cavity and still release the drug rapidly within the gastrointestinal tract. This patient-friendly dosage form is expected to improve convenience and efficacy by enhancing compliance with the dosing regimen.

Acknowledgement  This work was supported by Mid-Career Researcher Program through NRF Grant funded by the MEST (No. 2010-0000363) and a Grant from the Korean Health Technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea (A092018).

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