Design and Evaluation of an Economic Taste-Masked Dispersible Tablet of Pyridostigmine Bromide, a Highly Soluble Drug with an Extremely Bitter Taste

Qunyou Tan, Li Zhang, Liangke Zhang, Yongzhen Teng, and Jingqing Zhang

Department of Thoracic Surgery, Institute of Surgery Research, Daping Hospital, Third Military Medical University; Chongqing 400042, P. R. China; and Medicine Engineering Research Center, Chongqing Key Laboratory of Biochemical & Molecular Pharmacology, Chongqing Medical University; Chongqing 400042, P. R. China.

Received July 18, 2012; accepted September 25, 2012

Pyridostigmine bromide (PTB) is a highly soluble and extremely bitter drug. Here, an economic complexation technology combined with direct tablet compression method has been developed to meet the requirements of a patient friendly dosage known as taste-masked dispersible tablets loaded PTB (TPDPTs): (1) TPDPTs should have optimal disintegration and good physical resistance (hardness); (2) a low-cost, simple but practical preparation method suitable for industrial production is preferred from a cost perspective. Physicochemical properties of the inclusion complex of PTB with beta-cyclodextrin were investigated by Fourier transformed infrared spectroscopy, differential scanning calorimetry and UV spectroscopy. An orthogonal design was chosen to properly formulate TPDPTs. All volunteers regarded acceptable bitterness of TPDPTs. The properties including disintegration time, weight variation, friability, hardness, dispersible uniformity and drug content of TPDPTs were evaluated. The dissolution profile of TPDPTs in distilled water exhibited a fast rate. Pharmacokinetic results demonstrated that TPDPTs and the commercial tablets were bioequivalent.

Key words pyridostigmine bromide; taste-masked; dispersible tablet; inclusion complex; bioequivalence

British Pharmacopoeia defined dispersible tablets (DPTs) as the uncoated tablets or film-coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion. DPTs usually disintegrate within three minutes when put in a small amount (5 to 10 mL) of liquid (clean water or milk). It is easy for caregivers to prepare and easy for sick children to take.1–3) It is well established that DPTs may be a good dosage form of choice for geriatric, pediatric, bedridden, traveler, soldier, nauseous or non-compliant patients. DPTs can also give a new lease of life to an existing drug for line extension or/and patenting new dosage form. Up to now, pharmaceutical companies have marketed various types of dispersible dosage forms, such as Afeksin® by Actavis Ltd., Coartem® by Novartis and Medicines,1) Amotaks® by Polfa Tarchomin SA.4) Pyridostigmine bromide (PTB; C9H13BrN2O2; molecular weight 261.12; very soluble; c log P -3.1; Fig. 1), also called 3-(dimethylcarbamoyloxy)-1-methylpyridinium bromide, functions as a reversible competitive carbamate type of acetylcholinesterase inhibitor. PTB has been used to treat myasthenia gravis for many years.5) The indication for prophylaxis against intoxication with nerve agents (such as sarin and soman) has been recently approved by the U.S. Food and Drug Administration (FDA) and the French Drug Agency.6) So far, the formulations of PTB used clinically are the sugar-coated tablet, sustained release tablet, injection and syrup. DPT may be an appropriate alternative dosage form of PTB. However, PTB is a highly soluble drug with a bitter taste, and thus effectively taste masking is critical to patient compliance, and it is also the first and foremost challenging task in the preparation of DPT.7) In brief, in terms of PTB (a highly soluble drug with an extremely bitter taste), it is a big challenge to develop a taste-masked dispersible tablet (TPDPTs) suitable for industrial production. Here, economic complexation technology combined with direct tablet compression method has been developed to meet the requirements of TPDPTs: (1) TPDPTs should have optimal disintegration and good physical resistance (hardness); (2) low-cost, simple but practical preparation methods are preferred from a cost perspective.

Fig. 1. The Chemical Structure of PTB (A) and βCD (B), and the Proposed Structure Model of PTBβCD (C)

*To whom correspondence should be addressed. e-mail: zjqrae01@163.com

© 2012 The Pharmaceutical Society of Japan
Taste-masking technologies\(^8\) that have commonly been used in drug solid formulations, in general, include micronization,\(^{9,10}\) solid dispersion,\(^{11-13}\) and complexation.\(^{14}\) Betacyclodextrin (CD) is a cyclic oligosaccharide composed of seven dextrose units joined through \(\alpha\)-1,4-glucosidic bonds.\(^{15}\) Being a non-toxic and low-cost excipient with some favourable characteristics, βCD has been recorded in many national pharmacopoeias (such as United States Pharmacopoeia, Chinese Pharmacopoeia and Japanese Pharmacopoeia). It has been successfully used to improve the solubility, dissolution rate and bioavailability of poorly water-soluble drugs,\(^{16}\) enhance the physicochemical stability of unstable drugs,\(^{17}\) and eliminate the undesired taste of the bitter drug.\(^{18-20}\) Regarding the application of βCD to mask the bitter taste of drugs, the effects of βCD on both the tablet hardness and disintegration time should be considered simultaneously: in general, tablet hardness increases with the increased amount of βCD, and the disintegration time increases with the increase in hardness.\(^{21}\) So, in order to produce taste-masked DPTs with optimal disintegration and good physical resistance (hardness), it is important to use effective disintegrants combined with suitable amounts of drug inclusion complexes with βCD.

In the experiments, complexation technology was employed to develop an alternative drug delivery system with a favorable taste for PTB (a highly soluble drug with an extremely bitter taste) for increasing patient compliance and guaranteeing the effectiveness of the therapy. The objectives of this study were as follows: (1) PTB complexed with βCD (PTBCDs) were prepared by using the kneading method. Physicochemical properties of PTBCDs were investigated by Fourier transformed infrared (FT-IR) spectroscopy, differential scanning calorimetry (DSC) and UV (UV) spectroscopy. (2) Taste-masked PTB DPTs (TPDPTs) were prepared by direct compression, and a four-factor, three-level orthogonal design was chosen to properly formulate TPDPTs. (3) The properties including the bitter taste, disintegration time, weight variation, friability, hardness, dispersible uniformity and drug content of TPDPTs were evaluated. (4) The dissolution in vitro and pharmacokinetics in vivo were evaluated for the tested TPDPTs compared to the commercial tablets.

### Experimental

**Materials** PTB was obtained from Yuancheng Technology and Development Co., Ltd. (Wuhan, China). Lactose was kindly donated by Meggle Co., Ltd. (Bavaria, Germany). From Fisher Scientific U.K., Ltd. (Loughborough, U.K.). Other reagents were analytical grade and used as received.

**Preparation of PTBCDs** The PTBCDs were prepared according to the kneading method reported previously.\(^{22,23}\) Weighed amounts of PTB and βCD with a 1:1 molar ratio were mixed with the dropwise addition of 5 mL of water to form a homogenous paste. The paste was further ground for 60 min and dried. The obtained mass was washed three times with absolute ethanol and the solvent was eliminated by vacuum evaporation at 55°C. The final product was pulverized and sieved with an 80 mesh filter.

**FT-IR Spectroscopy of PTBCDs** The FT-IR spectroscopic experiments were carried out with a FT-IR spectrophotometer (Spectrum One NTS, PerkinElmer Instruments Inc., Massachusetts, U.S.A.). The samples (PTB, βCD, the physical mixture and PTBCDs) were compressed into KBr pellets and then scanned over the frequency range of 400–4000 cm\(^{-1}\).

**Differential Scanning Calorimetry (DSC) of PTBCDs** The samples, sealed in the aluminum crimp cell, were heated at the speed of 10°C min\(^{-1}\) from 30 to 200°C under a nitrogen atmosphere.\(^{24}\) The phase transition onset temperatures of pure PTB, βCD, the physical mixture and PTBCDs were determined and compared with the help of a differential scanning calorimeter (Netzsch STA-449C, Selb, Germany).

**UV Spectroscopy of PTBCDs** The complex formation composed of PTB and βCD in water was studied using the spectral shift method.\(^{25}\) The concentration of PTB was 180 μmol/L while the βCD concentration varied from 180 to 720 μmol/L (PTB and βCD with 1:0, 1:1, 1:2, 1:3, 1:4 molar ratios, respectively). The mixtures were kneaded for 1 h and the UV absorption spectra were recorded with a UV-3150 spectrophotometer (Shimadzu, Kyoto, Japan).

### Table 1. Optimal Formulation of TPDPTs

<table>
<thead>
<tr>
<th>Ingredient (prescription analysis)</th>
<th>Content (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTBCDs equivalent to 30 mg PB (principle or active agent)</td>
<td>40</td>
</tr>
<tr>
<td>Anhydrous citric acid (effervescent disintegrants)</td>
<td>10</td>
</tr>
<tr>
<td>Sodium bicarbonate (effervescent disintegrants)</td>
<td>8</td>
</tr>
<tr>
<td>MCC (disintegrant and diluent)</td>
<td>10</td>
</tr>
<tr>
<td>L-HPC (superdisintegrant)</td>
<td>6</td>
</tr>
<tr>
<td>Talc (anti-adherent)</td>
<td>2</td>
</tr>
<tr>
<td>Aspartame (sweetener)</td>
<td>2</td>
</tr>
<tr>
<td>Menthol (sweetener)</td>
<td>2</td>
</tr>
<tr>
<td>Mannitol (diluent)</td>
<td>to 100</td>
</tr>
</tbody>
</table>

### Table 2. Factors and Levels of Orthogonal Design

<table>
<thead>
<tr>
<th>Factor</th>
<th>A (mg)</th>
<th>B</th>
<th>C (mg)</th>
<th>D (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>20</td>
<td>PVPP</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Level 2</td>
<td>40</td>
<td>CMS-Na</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Level 3</td>
<td>60</td>
<td>L-HPC</td>
<td>24</td>
<td>12</td>
</tr>
</tbody>
</table>

\(A\), amount of MCC; \(B\), type of superdisintegrant; \(C\), amount of superdisintegrant; \(D\), amount of talc.
Preparation of TPDPTs  The TPDPTs containing the equivalent of 60 mg of PTB were compressed on a single rotary tabletting press (ZDY-8, Shanghai Far-east Pharmaceutical Machinery Co., Shanghai, China) using an 12-mm flat faced punch by direct compression. The PTB and excipients for 100 tablets were weighed according to the proportions listed in Table 1, and then passed through 80 meshes and blended to uniformity. The requisite quantity of the powder mixture was added into a die, and the pressure was adjusted to form the round tablets of hardness ca. 400 mg. The tablet weight was adjusted to ca. 400 mg.

Orthogonal Experimental Design (OED)  Preliminary experimental results revealed that the factors of the amount of MCC (A, mg), kind of superdisintegrant (B), amount of superdisintegrant (C, mg), and amount of talc (D, mg) had relatively great influence on the disintegration time (T, s). Thus, a four-factor, three-level OED was used to determine the optimal factors of the formulation for TPDPTs26,27 (Table 2). In order to study the influence of the tablet formulation on the disintegration time in vivo, TPDPTs with various formulations were prepared according to the orthogonal design (Table 3). The data was analyzed using the statistical package StatView, version 5.0 (SAS Institute, Inc., Cary, U.S.A.)

Disintegration Time of TPDPTs  The disintegration time was determined by Chinese Pharmacopoeia (CHP) 2010. Briefly, Six tablets were placed in a disintegration apparatus (ZB-ID, Taijin Tiandatianfa Scientific Co., Ltd., Tianjin, China). The core barrels were immersed in 1000 mL of water at 37±1°C, and kept moving up and down at 30–32 rpm. The disintegration time was recorded as the time when all granules passed through the sieve.

The Taste Evaluation of TPDPTs  The sensory evaluation was performed in 18 healthy volunteers (9 males and 9 females). Each volunteer was asked to wash his/her mouth well with distilled water prior to testing. Every tablet was dispersed in 10 mL of water before administration giving a homogeneous dispersion. One milliliter of the resulting dispersion was placed on the center of the tongue and retained in the mouth for 10 s, and then spat out. The bitterness was recorded according to the bitterness intensity scale: no bitterness, slight bitterness (slightly bitter but acceptable), and strong bitterness (strongly bitter and unacceptable). Reference conventional tablets (containing PTB instead of PTBCDs) were prepared by the method described above. Informed consents from the volunteers were first obtained. The trial in human was conducted according to the protocol approved and reviewed by the Institutional Ethics Committee.

Dissolution Test of TPDPTs  Dissolution studies were carried out with a dissolution apparatus (ZBR-6B, Huanghai Drug Examine Instrument Factory, Shanghai, China) according to the specifications of the CHP (2010 edition, paddle method). Dissolution flasks were immersed in 200 mL of distilled water at 37±0.5°C. The dissolution medium was continuously stirred at 100 rpm. The TPDPTs and the reference commercial tablet (SUNV26, conventional tablet) equivalent to 30 mg of PTB were added on the surface of the stirred dissolution medium. At different time intervals, 2 mL of samples were withdrawn and filtered using 0.22 μm cellulose nitrate membranes, and then analyzed by UV. Equal quantity of fresh distilled water was supplemented into the corresponding flasks.

A similar factor \( f_2 \) method was investigated for dissolution profile comparison in our experiments.28 The \( f_2 \) value was calculated using the following formula (Eq. 1):

\[
f_2 = 50 \log_2 \left[ 1 + \left( 1/n \right) \sum W_t (\bar{X}_d - \bar{X}_a)^2 \right]^{-1/2} \times 100
\]

where \( f_2 \) was the similar factor, \( \bar{X}_d \) and \( \bar{X}_a \) were drug cumulative release at time \( t \) of the two dissolution curves, respectively, \( n \) was the number of the sample point, \( W_t \) was the weight and set as 1 here.

When the two profiles are identical, the \( f_2 \) value is equal to 100. In the case of an average difference of 10% at all sampling time points, the \( f_2 \) value changes to 50. The Food and Drug Administration (United States) has set a common criterion of \( f_2 \) value (50–100) to illustrate similarity between a pair of dissolution curves. The higher the value of a similar factor the closer the similarity. On the other hand, there is a significant difference between two curves when the \( f_2 \) value is below 50.

The PTB concentrations were determined with a UV
spectrophotometer (UV-3150, Shimadzu, Kyoto, Japan). The calibration curve was linear in the range of 16–40 μg/mL ($A = 1.79 \times 10^{-7}C + 6.5 \times 10^{-3}$, $r = 0.9999$, $n = 7$). $A$ means the absorbance of PTB at 269 nm, and $C$ means the concentration of PTB. The recoveries of PTB are (99.46 ± 1.54)% (mean ± S.D., $n = 9$). The UV method provided an assay that was both sensitive and specific for quantifying PTB.

**Evaluation of Weight Variation, Friability, Hardness, Dispersible Uniformity and Drug Content of TPDPTs** The TPDPTs were determined for weight variation, friability, hardness, dispersible uniformity and drug content as per the CHP (2010 edition) method of tablet evaluation. Briefly, (1) Twenty randomly selected tablets were weighed individually (Metller Toledo, Greifensee, Switzerland). The average weight and the relative standard deviation were calculated. (2) Sixteen tablets (about 0.65 g) were accurately weighed and placed in the drum of friabilator (CJY-300C, Shanghai Huanghai Drug Inspection Instrument Co., Shanghai, China). The tablets were rotated at 25 rpm for 4 min. After 100 revolutions, the tablets were removed, carefully dedusted and accurately reweighed. The percentage of weight loss was calculated and the friability was evaluated. (3) The hardness (fracture strength) of TPDPTs was measured with a hardness tablet tester (YP-200A, Shanghai Huanghai Drug Inspection Instrument Co., Shanghai, China). (4) Dispersible uniformity of TPDPTs was determined as follows: six tablets were placed in 100 mL of distilled water at 15–25°C and shaken for 3 min. Each tablet should disintegrate within 3 min and pass through 24 meshes (the aperture size is (850 ± 29)μm). (5) Twenty tablets were crushed and the powder equivalent to 30 mg of PTB was dissolved by distilled water, transferred into a 100 mL of volumetric flask, fixed and sonicated for 15 min. The resulting solution was filtered through a 0.45μm microfilter and the filtrate was analyzed by the UV method described above. The drug content was then calculated.

**Preliminary Evaluation of Suspension Stability of TPDPTs** DPTs are expected to disintegrate within 3 min in water, disperse into small granules, and eventually form a uniform suspension before administration. In case of a conventional suspension formulation, the suspension stability is, and the higher the suspension stability is. The recoveries of PTB are (99.46 ± 1.54)% (mean ± S.D., $n = 9$). The UV method provided an assay that was both sensitive and specific for quantifying PTB.

**Pharmacokinetics Study in Vivo** Animal facilities and protocols were in accordance with the National Institute of Health’s guidelines regarding the principles of animal care (2004). To evaluate the effects of TPDPTs on the release profiles *in vivo*, 12 male New Zealand White (NZW) rabbits weighing 2.5–3.0 kg were used. In a single-dose, randomized, open-label, two-period crossover trial, all the rabbits were divided into two groups and fasted for overnight (26,30). The test TPDPTs were dispersed in 5 mL of water and immediately administered by gastric perfusion. The reference commercial tablets (SUNV®, conventional tablets) were placed in the pharynx, and swallowed whole with 5 mL of water. (By the way, the reason that the conventional PTB-loaded commercial tablet not PTB-loaded dispersible tablet was used as reference tablets in our study is because that no PTB-loaded dispersible tablet is available on the market, it has been neither reported.) The concentrations of PTB from the rabbits at the predetermined timepoints post-administration were measured by HPLC. The peak concentration ($C_{\text{max}}$) and peak time ($t_{\text{max}}$) were derived directly from the concentration–time curve. The other pharmacokinetic parameters were calculated using the DAS 2.1.1 statistical software (Mathematical Pharmacology Professional Committee of China, Shanghai, China).

A 1.0 mL aliquot of ear vein blood was collected from the rabbits at the predetermined time points after dosing. The plasma samples obtained from the upper layer after centrifugation (15 min, 1500 rpm) were stored at −80°C until HPLC analysis. The plasma samples were pre-treated as follows: a 100 μL aliquot of internal standard solution (Prostigmin, 208 μg·mL⁻¹), 200 μL of picric acid (0.1 mM) in 0.1 M sodium hydroxide (pH adjusted to 7), and 1.0 mL of water-saturated dichloromethane was added to each plasma sample (100 μL). The resulting mixture was vortexed for 3 min and then centrifuged at 12000 rpm for 10 min. After 200 μL of tetrabutyl ammonium bromide (1 mM) was added to the solution below, this mixture was shaken for 1 min and centrifuged at 12000 rpm for 5 min. Aliquots of the supernatant were injected into the HPLC system for further analysis.

The plasma concentrations of PTB were determined by using the reversed-phase HPLC (Shimadzu System). The stationary phase (Hypersil ODS-2 column, 250 mm × 4.6 mm, 5 μm) was kept at 30°C. The mobile phase was a mixture, with ratio of acetonitrile:aqueous buffer (10 mM sodium dihydrogen phosphate, 10 mM sodium heptanesulfonate, 0.5% triethylamine) = 20:80 (v/v, pH adjusted to 3.0 with phosphoric acid). The flow rate was 1.0 mL/min. The sample injection volumes were 20 μL and PTB detection was performed using the UV detector at a wavelength of 270 nm. The calibration curve was linear in the range of $C = 20–2000$ ng/mL ($Y = 0.5500C + 0.07546$, $r = 0.9996$, $n = 7$). $Y$ means the peak area ratio between PTB and prostigmin. The limit of detection (LOD) was 5 ng/mL. The HPLC method provided an assay that was both sensitive and specific for quantifying PTB.
Results and Discussion

FT-IR Spectroscopy of PTBCDs
The FT-IR spectra of PTB, βCD, physical mixtures and PTBCDs in the transmittance mode were depicted in Fig 2. The peaks of βCD at 3403 cm⁻¹, 2923 cm⁻¹, 1657 cm⁻¹, 1158 cm⁻¹ and 1081 cm⁻¹ were assigned to the O–H stretching vibrations, the C–H stretching vibrations, the H–O–H bending vibrations, the C–O stretching vibration and the C–O–C stretching vibration, respectively. The peaks of PTB at 2945 cm⁻¹, 3044 cm⁻¹, 1000–1200 cm⁻¹, 1200–1500 cm⁻¹ and 1734 cm⁻¹ were assigned to the C–H stretching vibration of the methyl group, the C–H stretching vibration of pyridine ring, the C–N stretching vibration of the tertiary amine, the skeleton vibration of the pyridine ring and C=O stretching vibration of the ester carbonyl, respectively. The FT-IR spectrum of the physical mixtures showed overlapping effects of PTB and βCD, accompanying with the attenuation of the PTB peaks. However, in the spectrum of PTBCDs, the characteristic peaks of βCD remain strong while the peaks of PTB almost disappear. The results suggested the modification of the drug environment and that the guest molecules (PTB) were entrapped inside the cavities of the host molecules (βCD) through forming an inclusion complex. These FT-IR spectroscopy change phenomena happened to the PTBCDs were similar to what happened to the simvastatin/hydroxypropyl-βCD inclusion complex reported by Jun et al. 35)

Differential Scanning Calorimetry (DSC) of PTBCDs
It was believed that the DSC spectra could be used for the recognition of the inclusion complex. 36) When the guest molecules were embedded into the cavity of the host molecules (βCD), their melting or boiling points generally disappeared or shifted to a different temperature. In our study, the thermograms of PTB, βCD, physical mixture and the inclusion complex were depicted in Fig. 3. Pure βCD showed a broad endothermic peak at 70.2°C, as corresponding to the dehydration process. The free PTB showed a sharp endothermic peak at 153.3°C, as corresponding to the melting point of the drug. The DSC curve of the physical mixtures mainly showed overlapping effects of PTB and βCD, accompanying with the reduction of the PTB peak, while the DSC curve of the PTBCDs showed that the characteristic endothermal peak of PTB disappeared, indicating the inclusion of PTB into βCD cavity.

UV Spectroscopy of PTBCDs
The effect of βCD on the UV absorption of PTB in the aqueous solution was showed in Fig. 4. PTB alone in aqueous solution exhibited one absorption peak at 269 nm, while the UV absorption of βCD alone in aqueous solution was negligible at 200–400 nm. No red shift or blue shift of the UV absorption spectra was observed when
different amounts of βCD were added into the PTB solution. The absorbance of PTB at 269 nm decreased gradually with the addition of βCD. The more βCD was added, the lower the absorbance of PTB was obtained. The profiles of absorbance at 269 nm against the concentration of βCD (Fig. 4B) indicated that the PTB absorbance decreased with the increase of the βCD concentration in a linear fashion (the correlation coefficient was 0.9887). These absorbance changes suggested the chromophore groups of PTB might be partially masked by βCD through the inclusion complexation. The UV results, considering together with the above described DSC and FT-IR profiles, indicated that PTB molecules might get into and remain in the βCD cavities (Fig. 1C). The bitter taste of PTB might be caused by the dimethylcarbamylxy group since the variation, friability, hardness, dispersible uniformity drug content unifor-

![Fig. 5. The Dissolution Profiles of the TPDPTs and the Reference Commercial Tablet (n=6)](image)

Table 4. Properties of TPDPTs Prepared Under the Optimal Conditions (Mean±S.D., n=3)

<table>
<thead>
<tr>
<th>Properties</th>
<th>Batch 1</th>
<th>Batch 2</th>
<th>Batch 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disintegration time (s)</td>
<td>48.5±4.76</td>
<td>49.2±3.60</td>
<td>48.2±2.64</td>
</tr>
<tr>
<td>Weight uniformity (mg)</td>
<td>406.34±1.55</td>
<td>409.13±2.24</td>
<td>402.77±0.87</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.52</td>
<td>0.50</td>
<td>0.47</td>
</tr>
<tr>
<td>Hardness (N)</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Content uniformity (%)</td>
<td>97.55±0.43</td>
<td>99.46±0.75</td>
<td>99.64±0.93</td>
</tr>
<tr>
<td>Slope K (×10⁻²)</td>
<td>1.09</td>
<td>1.13</td>
<td>1.06</td>
</tr>
</tbody>
</table>

Slope K is the slope of the regression curve (see the regression Eq. 2).

Table 5. Results of Taste Evaluation

<table>
<thead>
<tr>
<th>Bitterness test</th>
<th>The number of volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPDPTs</td>
<td>Conventional tablets</td>
</tr>
<tr>
<td>No bitterness</td>
<td>12</td>
</tr>
<tr>
<td>Slight bitterness</td>
<td>6</td>
</tr>
<tr>
<td>Strong bitterness</td>
<td>0</td>
</tr>
</tbody>
</table>

![Fig. 6. PTB Plasma Concentration versus Time Profiles after Oral Administration of TPDPTs and the Commercial Tablets (n=12)](image)

contained a substantial of βCD. To prevent the punch from sticking, talc (as an effective anti-stick agent) was added into the formulation. However, excessive talc with very low water solubility would prevent water from infiltrating and wetting the tablet, and consequently prolonged the disintegration time. It was very important to use the right amount of talc. The function of each ingredient in the formulation was analysed (Table 2).

Apparently, the best formulation had the shortest disintegration time. As shown in Table 3, the optimal levels of formulation were found to be A₁B₁C₁D₁, that is, the optimal values for the amount of MCC (A, mg), the kind of superdisintegrant (B), the amount of superdisintegrant (C, mg), and the amount of talc (D, mg) should be 40mg, L-HPC, 24mg and 4mg, respectively. Particularly, our study suggested that MCC (disintegrant and diluent) should be used in combination with L-HPC (superdisintegrant) to obtain the rapidly disintegrating tablet with a short disintegration time. Similar results were reported in former documents. The disintegration time of three batches of TPDPTs prepared under the described optimal protocol (Table 1) was recorded as (48.63±0.51) s (Table 4). Other properties of three batches of TPDPTs prepared under the optimal conditions were also presented in Table 4.

Characterization of TPDPTs The properties like weight variation, friability, hardness, dispersible uniformity drug content, and suspension stability of TPDPTs of three batches were found to be within acceptable limits (Table 4). A attempt had been made to mask the bitterness of PTB in TPDPTs by complexing it with βCD and combining the resultant complex with flavoring agents. As shown in Table 5, all volunteers regarded acceptable bitterness of TPDPTs but only about 5% of volunteers thought so in the case of conventional tablets (reference tablets). The dissolution profiles of the TPDPTs and the reference commercial tablet (SUNV®, conventional tablet) were depicted in Fig. 5.
drug in TPDPTs were released in the first 5 min, indicating that TPDPTs could be dissolved in the distilled water at 37°C immediately. As for the reference commercial tablet, under the same conditions, only (7.51±1.30%) (n=6) was released. The dissolution profile of TPDPTs exhibited a faster rate of PTB C

formulations. For example, the few differences between the plasma exposure profiles of two are similar. However, it should be noted that there were still a test TPDPTs do not change the PTB permeability or the

dissolution rate were successfully prepared using inclusion disintegrating time, fine dispersible uniformity and rapid

drug in TPDPTs were released in the first 5 min, indicating that TPDPTs could be dissolved in the distilled water at 37°C immediately. As for the reference commercial tablet, under the same conditions, only (7.51±1.30%) (n=6) was released. The dissolution profile of TPDPTs exhibited a faster rate of PTB C

formulations. For example, the few differences between the plasma exposure profiles of two are similar. However, it should be noted that there were still a test TPDPTs do not change the PTB permeability or the


dissolution rate were successfully prepared using inclusion disintegrating time, fine dispersible uniformity and rapid

drug in TPDPTs were released in the first 5 min, indicating that TPDPTs could be dissolved in the distilled water at 37°C immediately. As for the reference commercial tablet, under the same conditions, only (7.51±1.30%) (n=6) was released. The dissolution profile of TPDPTs exhibited a faster rate of PTB C

formulations. For example, the few differences between the plasma exposure profiles of two are similar. However, it should be noted that there were still a test TPDPTs do not change the PTB permeability or the


dissolution rate were successfully prepared using inclusion disintegrating time, fine dispersible uniformity and rapid

drug in TPDPTs were released in the first 5 min, indicating that TPDPTs could be dissolved in the distilled water at 37°C immediately. As for the reference commercial tablet, under the same conditions, only (7.51±1.30%) (n=6) was released. The dissolution profile of TPDPTs exhibited a faster rate of PTB C

formulations. For example, the few differences between the plasma exposure profiles of two are similar. However, it should be noted that there were still a test TPDPTs do not change the PTB permeability or the


dissolution rate were successfully prepared using inclusion disintegrating time, fine dispersible uniformity and rapid

drug in TPDPTs were released in the first 5 min, indicating that TPDPTs could be dissolved in the distilled water at 37°C immediately. As for the reference commercial tablet, under the same conditions, only (7.51±1.30%) (n=6) was released. The dissolution profile of TPDPTs exhibited a faster rate of PTB C

formulations. For example, the few differences between the plasma exposure profiles of two are similar. However, it should be noted that there were still a test TPDPTs do not change the PTB permeability or the


dissolution rate were successfully prepared using inclusion disintegrating time, fine dispersible uniformity and rapid

drug in TPDPTs were released in the first 5 min, indicating that TPDPTs could be dissolved in the distilled water at 37°C immediately. As for the reference commercial tablet, under the same conditions, only (7.51±1.30%) (n=6) was released. The dissolution profile of TPDPTs exhibited a faster rate of PTB C

formulations. For example, the few differences between the plasma exposure profiles of two are similar. However, it should be noted that there were still a test TPDPTs do not change the PTB permeability or the


dissolution rate were successfully prepared using inclusion disintegrating time, fine dispersible uniformity and rapid

drug in TPDPTs were released in the first 5 min, indicating that TPDPTs could be dissolved in the distilled water at 37°C immediately. As for the reference commercial tablet, under the same conditions, only (7.51±1.30%) (n=6) was released. The dissolution profile of TPDPTs exhibited a faster rate of PTB C

formulations. For example, the few differences between the plasma exposure profiles of two are similar. However, it should be noted that there were still a test TPDPTs do not change the PTB permeability or the


dissolution rate were successfully prepared using inclusion disintegrating time, fine dispersible uniformity and rapid

drug in TPDPTs were released in the first 5 min, indicating that TPDPTs could be dissolved in the distilled water at 37°C immediately. As for the reference commercial tablet, under the same conditions, only (7.51±1.30%) (n=6) was released. The dissolution profile of TPDPTs exhibited a faster rate of PTB C

formulations. For example, the few differences between the plasma exposure profiles of two are similar. However, it should be noted that there were still a test TPDPTs do not change the PTB permeability or the


dissolution rate were successfully prepared using inclusion disintegrating time, fine dispersible uniformity and rapid

drug in TPDPTs were released in the first 5 min, indicating that TPDPTs could be dissolved in the distilled water at 37°C immediately. As for the reference commercial tablet, under the same conditions, only (7.51±1.30%) (n=6) was released. The dissolution profile of TPDPTs exhibited a faster rate of PTB C