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Pharmacokinetics of orally disintegrating tablets of perphenazine/hydroxypropyl-β-cyclodextrin inclusion complex in rabbits

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We investigated the pharmacokinetic behavior of orally disintegrating tablets (ODTs) containing perphenazine/hydroxypropyl-β-cyclodextrin inclusion complex (PPZ/ HP-β-CD) in rabbits and evaluated their bioequivalence with conventional tablets. In this study, a simple, sensitive and accurate high performance liquid chromatography method was developed for the determination of perphenazine concentration in rabbit plasma. The pharmacokinetic parameters were calculated by non-compartmental methods and the bioequivalence between PPZ/HP-β-CD ODTs with conventional tablets was determined by calculating 90% confidence interval (CI) for the ratio of logarithmic transformed C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ values. The pharmacokinetic parameters of test ODTs and reference tablets were as follows: C_{max}, 82.86 and 62.71 ng/mL; $AUC_{0\text{–}24}$, 480 and 397.56 ng/mL/h; $AUC_{0\text{-}\infty}$, 505 and 400.12 ng/mL/h; T_{max}, 1.04 and 3.83 h. The relative bioavailabilities of two formulations for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were 120.77% and 126.37%, respectively. The 90% CI statistical analysis demonstrated the two formulations were not bioequivalence. In conclusion, the ODTs showed faster absorption and higher peak concentration when compared with conventional tablets, which suggests ODTs could be promising oral formulations for PPZ.

1. Introduction

Nowadays, tablets are still the most popular and widely used dosage forms because of the advantages afforded both to the manufacturer and the patients (Sunada and Bi 2002). Nevertheless, difficulty in swallowing is common among all age patients, especially in geriatric, pediatric, psychotics and people and those with persistent nausea, resulting in a high incidence of noncompliance and ineffective therapy (Dobetti 2000a; Sastry et al. 2000b). In recent years, orally disintegrating tablets (ODTs) have attracted the interests of many researchers and are developed to meet the demands of the patients mentioned above (Bhardwaj et al. 2010a,b; Shaikh et al. 2012). This type of dosage form is placed in the mouth, allowed to rapidly disperse or dissolve in the saliva, and swallowed without the need for water. In addition, the dissolved drug can be directly absorbed through the cavity mucosa into the systemic circulation to elicit a rapid onset of action or improve the bioavailability for drugs that are susceptible to hepatic first-pass metabolism (Sastry et al. 2000). Perphenazine (PPZ), 2-{4-[3-(2-chlorophenothiazin-10-yl) propyl] piperazin-1-yl}-ethanol (Fig. 1), is a potent phenothiazine-type antipsychotic clinically used in the treatment of schizophrenia, anxiety and severe nausea or vomiting (Sweetman 2009). According to the Biopharmaceutic Classification System (BCS), PPZ belongs to the Class II drugs with poor solubility and high permeability (Lindenberg et al. 2004). Although PPZ is well absorbed after oral administration, its bioavailability is limited since a significant amount of the drug is lost through hepatic metabolism (Laitinen et al. 2009). Although numerous papers have highlighted the applicational value of PPZ, only a few studies have been conducted to develop proper formulations to overcome the obstacle. Turunena et al. (2011) reported increased bioavailability for PPZ after sublingual administration of PPZ/macrogol solid dispersion, PPZ/β-CyD complex and plain micronized PPZ in rabbits, respectively. The pharmacokinetic values of three formulations were compared with aqueous PPZ solution and all formulations could improve the adsorption of PPZ through three possible mechanisms. In our previous studies, a perphenazine/hydroxypropyl-β-cyclodextrin (PPZ/HP-β-CD) inclusion complex was investigated in order to improve the apparent solubility and dissolution rate of PPZ. Subsequently, ODTs containing PPZ/HP-β-CD were prepared by direct compression. The encouraging properties of ODTs such as

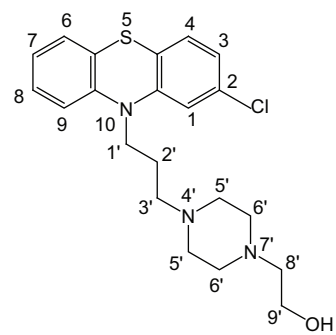


Fig. 1: Chemical structure of PPZ.

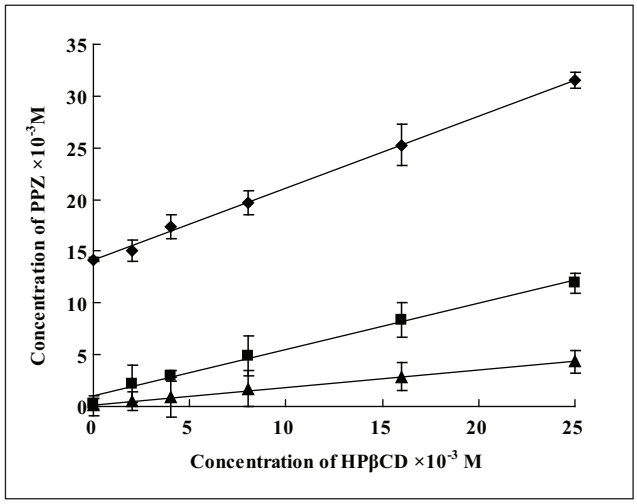


Fig. 2: Phase solubility diagrams of PPZ: HP-β-CD system in acetate buffer pH 4.5 (□), phosphate buffer pH 6.8 (■) and distilled water (▲) (n = 3). Error bars indicate the SD.

disintegration time, wetting time, and *in vitro* dissolution profile etc. were also investigated, which indicated possible improvement of PPZ in terms of *in vivo* absorption after oral administration (Wang et al. 2012). In order to demonstrate the *in vivo* performance of ODTs, a proper high performance liquid chromatography (HPLC) method was established to investigate the pharmacokinetics features of the ODTs after oral administration in rabbits. Pharmacokinetic parameters and bioequivalence of ODTs were also calculated and compared with conventional tablets for reference.

2. Investigations, results and discussion

2.1. Phase solubility studies

Cyclodextrins (CDs), with hydrophilic inner cavities and hydrophilic outer surfaces, are cyclic oligosaccharides containing 6, 7 or 8 D-(+)-glucopyranose units (α-, β-, γ- cyclodextrin) attached by α-1, 4-linkage (Wang et al. 2007). Particularly, β-cyclodextrin appears to be the most widely used CD in oral drug delivery and was considered to be a promising direct compression excipient (Pande and Shangraw 1994). Various derivatives were synthesized to modify its physicochemical properties, and hydroxypropyl derivatives (HP-β-CD) have been extensively used in pharmaceutical formulations due to their higher water solubility, parenteral safety and complexation ability (Suihko et al. 2001). Thus, HP-β-CD was chosen to improve the solubility and dissolution of PPZ.

The phase solubility diagrams obtained for PPZ/HP-β-CD are shown in Fig. 2. A linear increase of PPZ solubility was observed as a function of HP-β-CD and all diagrams showed A_L-type phase solubility curves ($r^2 > 0.99$), indicating the formation of 1:1 complexation between PPZ and HP-β-CD, and the solubility of PPZ was increased by 57.2 ± 1.7-fold for HP-β-CD at 25 mM in distilled water. The calculated K_s values in distilled water, acetate buffer pH 4.5, and phosphate buffer pH 6.8 were 2910.53 ± 165.46, 196.94 ± 33.91, and $3200.53 \pm 221.75\ M^{-1}$, respectively.

2.2. Preparation of ODTs containing PPZ/ HP-β-CD

The general technologies applied for the production of ODTs were freeze-drying, moulding, and direct compression. The great advantages of direct compression are the low manufacturing cost, the easy procedure, and the possibility to accommodate higher doses compared with other methods (Dobetti 2000). Consequently, ODTs containing PPZ/HP-β-CD inclusion complex were prepared by direct compression in this study. In many cases, disintegrants play a major role in the process of the disintegration of ODTs and the dissolution of drugs from ODTs, and act as the paramount factor for ensuring a high disintegration rate. Therefore, different kinds of disintegrants, such as L-HPC, Ac-Di-Sol, Kiccolate™ ND-200, and Polyplasdone XL-10, were selected by evaluating the disintegration time and wetting time of formulations. Finally, Polyplasdone XL-10 (8%, w/w) was chosen as the disintegrant. In addition, Pearlitol® 200 SD (67%, w/w) and Ceolus™ KG-802 (10%, w/w) were combined to use as the diluent owning to their good flow ability, refreshing sensation, and compactibility (Wang et al. 2012).

Table 1: Results of the intra-day and the inter-day precisions (n = 3)

C (ng/mL)	Intra-day		Inter-day	
	Mean ± SD (ng/mL)	RSD (%)	Mean ± SD (ng/mL)	RSD (%)
8	7.64 ± 0.68	8.90	7.28 ± 0.53	7.28
40	38.76 ± 2.81	7.25	39.01 ± 2.76	7.08
100	97.34 ± 5.64	5.79	101.04 ± 6.85	6.78

2.3. Method validation

2.3.1. Specificity

The specificity of the method for the interference of endogenous compounds was investigated by analyzing three plasma samples including one blank plasma sample, one plasma sample containing both PPZ and internal standard (I.S.), and one plasma sample collected after oral administration of test ODTs. Representative chromatograms are shown in Fig. 3. The retention times for PPZ and I.S. were approximately 11.7 and 15.5 min, respectively. Both PPZ and I.S. were completely separated from endogenous interferences.

2.3.2. Linearity of calibration curve and limit of detection

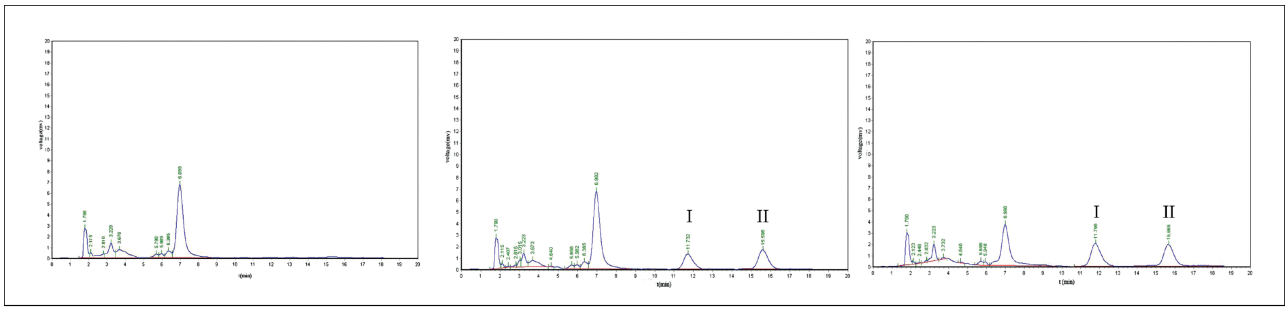
The linearity of the method was evaluated by a calibration curve in the range of 8 – 100 ng/mL of the PPZ (n = 6). The calibration curve was obtained by plotting peak area ratios of PPZ (As) to IS (Ais) versus the corresponding PPZ concentrations with the linear regression method. The linear regression equation was (As/Ais) = 0.0218C−0.0323 (r = 0.9989). The limit of the detection was 4 ng/mL, which was sufficient for investigations of pharmacokinetics after a single oral administration.

2.3.3. Precision

Results of the precision of the method are presented in Table 1. For intra-day precision, three replicate quality control samples at three concentrations (8, 40, and 100 ng/mL) were determined on the same day. The inter-day precision was assayed on three different days. The RSDs of both intra- and intro-day precision were less than 10% at any concentrations investigated.

2.3.4. Recovery

Both the analytical recovery and the absolute recovery were assessed at these concentrations of 8, 40, and 100 ng/mL, respectively. The analytical recovery was calculated by comparing the response of PPZ detected with the response of PPZ spiked while the absolute recovery was determined by comparing the peak



(A) (B) (C)

Fig. 3: Chromatograms of blank plasma (A), plasma containing perphenazine and clozapine (B), plasma sample after oral administration of test ODTs (C) □: clozapine □: perphenazine.

Table 2: Results of the relative recovery experiment (n = 3)

C(ng/mL)	Found (ng/mL)			Relative discovery (%)	RSD(%)
8	8.31	7.47	8.61	101.6 ± 7.39	7.27
40	38.8	41.7	36.8	97.8 ± 6.17	6.31
100	102.2	106.7	96.7	101.9 ± 5.01	4.92

areas of pre-treated plasma samples with those of standards prepared in the mobile phase without sample pre-treatment at the same concentration (Table 2) Table 3 (Lin and Ho 2009). Relative and absolute recoveries of PPZ at three concentrations ranged from 97.8 to 101.9% and 72.4 to 80.3%, respectively.

2.3.5. Stability

The stability of PPZ in plasma was investigated under three freeze-thaw cycles, short-term (at 4 h and 8 h, room temperature) and long-term (1 month, at −20 °C) storage conditions. No significant degradation of PPZ was observed in all conditions. Results of the stability in rabbit plasma are shown in Table 4.

2.4. In-vivo studies

In this study, the rabbit was chosen as the experimental animal due to the similarity of the thickness of buccal mucosa with the buccal mucosa of humans. According to the reference, the thickness of non-keratinized buccal mucosa of human is 0.50 − 0.60 mm, while those of rabbit, dog, pig were 0.60, 0.77, 0.77 mm, respectively, which indicates that the rabbit is the most suitable animal model for studying the pharmacokinetics of ODT containing drugs (Zhu 2011).

During the process of the blood sample preparation, several extraction solvents including ethyl acetate, dichloromethane, n-hexane, tert-butyl, ethyl ether, acetonitrile, n-hexane: dichloromethane: isopropanol (2:1:0.1, v/v) were evaluated and finally, ethyl ether was chosen as the extraction solvent due to the least amount of interference peaks and the best efficiency of extraction.

The mean plasma concentration-time profiles of PPZ after a single oral dose of the test and the reference formulations in rabbits are shown in Fig. 4. The pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\text{-}24}$, and $AUC_{0\text{-}\infty}$) are summarized in Table 5. Higher C_{max} and faster T_{max} were observed after peroral administration of ODTs compared with reference tablets, which could be due to the rapid disintegration of ODTs and the rapid dissolution of PPZ in the cavity, resulting in very fast absorption from the buccal mucosa and transformation into the blood circulation. In our previous studies, disintegration time (DT) of ODTs containing PPZ/HP-β-CD was 15.5 ± 1.9 s, which could favors the rapid disintegration in the cavity. In addition, the *in vitro* dissolution of the PPZ/HP-β-CD inclusion complex was carried out under both sink conditions and non-sink conditions. The results showed that PPZ dissolved, in the case of non-sink conditions (i.e. 3 mL of phosphate buffer pH 6.8), 74.7 ± 2.9% in 30 s, increasing up to 97.3 ± 3.4% after 4 min, which could improve the dissolution and absorption of insoluble PPZ (Wang et al. 2012).

Table 3: Results of the absolute recovery experiment (n = 3)

C(ng/mL)	Found (ng/mL)			absolute discovery (%)	RSD (%)
8	5.62	6.41	5.82	74.3 ± 5.13	6.91
40	27.5	30.7	28.7	72.4 ± 4.04	5.58
100	79.9	76.8	84.1	80.3 ± 3.66	4.56

2.5. Bioequivalence

ANOVA results found no period and sequence effects on log-transformed C_{max} and $AUC_{0\text{-}t}$, however, significant formulation effects were detected for C_{max} and $AUC_{0\text{-}t}$. The 90% CIs of the ratios of ODTs/reference tablets for the log-transformed C_{max} and $AUC_{0\text{-}t}$ were 128.9 to 139.5, 94.7 to 156.9, respectively, all of which missed the predefined bioequivalence criteria of 80% to 125%. The relative bioavailabilities of ODTs/reference tablets for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were 120.77% and 126.37%, respectively. T_{max} showed a significant difference between the test ODTs formulation and the reference tablet ($P < 0.05$). The greater bioavailability obtained from ODTs could be attributed to the absorption of PPZ from the buccal mucosa, resulting in decreased pre-systemic biotransformation due to either first-

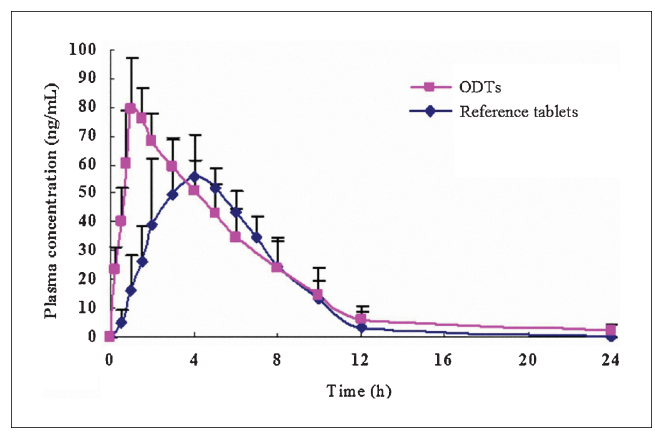


Fig. 4: Mean plasma concentration-time profile of perphenazine after peroral administration of ODTs and reference tablets in rabbits.

Table 4: Stability of perphenazine in rabbit plasma

	Storage conditions	Perphenazine (ng/mL)		
		8	40	100
Freeze-thaw(n = 3)				
1st cycle ng/mL		7.43 ± 0.40	36.88 ± 2.41	95.39 ± 5.17
(% of initial)		92.83 ± 4.95	92.20 ± 5.99	95.39 ± 5.17
2 st cycle ng/mL		7.45 ± 0.31	36.24 ± 2.55	94.12 ± 4.85
(% of initial)		93.17 ± 3.88	90.59 ± 6.37	94.12 ± 4.85
3 st cycle ng/mL		7.39 ± 0.28	35.78 ± 2.18	93.40 ± 5.78
(% of initial)		92.37 ± 3.53	89.45 ± 5.44	93.40 ± 5.78
Long-term (n = 3)	1 month, at −20 °C	7.37 ± 0.35	36.19 ± 2.94	92.81 ± 5.31
(% of initial)		92.08 ± 4.35	90.47 ± 7.35	92.81 ± 5.31
Short-term (n = 3)	4h, room temperature	7.42 ± 0.47	37.36 ± 2.32	92.13 ± 8.43
(% of initial)		92.75 ± 5.86	93.39 ± 5.81	92.13 ± 8.43
Short-term (n = 3)	8h, room temperature	7.35 ± 0.47	36.26 ± 2.48	90.61 ± 6.71
(% of initial)		91.83 ± 5.83	90.66 ± 6.21	90.61 ± 6.71

pass hepatic effect or metabolism in the gastrointestinal (GI) tract.

The current study has established a sensitive and accurate HPLC assay for the determination of PPZ in rabbit plasma after oral administration of ODT formulations. When compared with reference tablets, the bioequivalence of ODTs was enhanced owning to the rapid disintegrating and dissolution in the cavity and absorption from the buccal mucosa, which could also decrease the GI side effects of drug. Therefore, this study suggests that ODTs formulation could be an alternative to conventional formulations of PPZ (i.e. oral tablet) for the patients, especially those having difficulty in swallowing oral dosage forms.

3. Experimental

3.1. Chemicals and reagents

Perphenazine (PPZ) was obtained from Hubei Prosperity Galaxy Chemical Co., Ltd. (Wuhan, China). Hydroxypropyl-β-cyclodextrin (HP-β-CD, with an average molar substitution degree per anhydroglucose unit of 0.76), and Mannitol (Pearlitol® 200 SD) were kindly donated by Roquette (Lestrem, France). Crospovidone (Polyplasdone XL-10) was gifted by ISP Technologies, Inc. (Calvert City, KY, USA). The other excipients used were microcrystalline cellulose (Ceolus™ KG-802, Asahi Kasei Chemicals Corp., Tokyo, Japan), Low-substituted hydroxypropylcellulose (L-HPC, Shin-Etsu Chemical Co., Ltd., Japan), Croscarmellose Sodium (Ac-Di-Sol, FMC Biopolymer, Newark, DE, USA; Kiccolate™ ND-200, Asahi Kasei Chemicals Corp., Tokyo, Japan), lactose monohydrate (GranuLac® 200, Meggle, Wasserburg, Belgium), and magnesium stearate (Shanhe Pharmaceutical excipients Co., Ltd, Anhui, China). All other reagents used were of analytical grade.

3.2. Phase solubility studies

Phase solubility studies were carried out in distilled water, acetate buffer pH 4.5 (0.22 M^{-1} sodium acetate using acetic acid maintained the pH) and phosphate buffer pH 6.8 (0.2 M^{-1} potassium dihydrogen phosphate using NaOH solution maintained the pH). Briefly, excess amounts of PPZ (100 mg) were added to 10 mL of aqueous solutions containing serial concentrations of HP-β-CD (0∼25 mM). The suspensions were mechanically shaken (LSHZ-300, Huamei Biochemistry Instrument, Taicang, China) at 25 ± 1 °C for 3 days. After equilibrium attainment, the samples were filtered (0.45 μm membrane filter) and suitably diluted. The concentration of PPZ was determined with HPLC. Each experiment was carried out in triplicate for each buffer pH. Phase solubility diagrams were constructed by plotting the concentration of PPZ dissolved versus the concentration of HP-β-CD. The apparent stability constants (K_s) were calculated from the slope of the phase solubility digrams according to the following equation:

$$Ks = \frac{slope}{S_0(1 - slpoe)}$$

where S_0 is the solubility of PPZ in the absence of HP-β-CD.

Table 5: Pharmacokinetic parameters of perphenazine after peroral administration of ODTs and reference tablets in rabbits

Parameters	Unit	ODTs	Reference tablets
C_{max}	ng/mL	82.86 ± 12.96	62.71 ± 15.06
T_{max}	h	1.04 ± 0.24	3.83 ± 1.17
$AUC_{(0\text{-}t)}$	ng* h /mL	480.15 ± 149.56	397.56 ± 138.90
$AUC_{(0\text{-}\infty)}$	ng* h /mL	505.64 ± 142.05	400.12 ± 142.15

3.3. Preparation of ODTs containing PPZ/ HP-β-CD

The PPZ/HP-β-CD inclusion complex was prepared using the evaporation method in a 1:1 molar ratio (PPZ to HP-β-CD). Briefly, after dissolution of HP-β-CD (4.51 g) in 100 mL of 50% (v/v) ethanol-water solution, the stoichiometric proportion of PPZ (1.14 g) was added. The suspension was further sonicated for 15 min and the obtained clear solution was evaporated under vacuum at a temperature of 45 °C and 100 rpm in a rotary evaporator (RE-2000A, Kay Equipment Co., Ltd, Shanghai, China) almost until dryness. The solid residue was further dried at 40 °C for 48 h, then pulverized, sifted through 80-mesh sieve (pore size 180 μm) and stored in desiccator over silica gel at room temperature.

Tablet formulations containing PPZ/HP-β-CD complex (equivalent to amount of 2 mg of PPZ), Pearlitol® 200 SD (67%, w/w) and Ceolus™ KG-802 (10%, w/w) as suitable diluents and Polyplasdone XL-10 (8%, w/w) as the disintegrant were performed by direct compression using a GLZP-10A rotary tablet press (Beijing gylongli sci. & tech. Co., Ltd., China) equipped with flat faced 6 mm punches. The tablet weight was adjusted to 80 mg. The hardness was set to 30 N/mm using a 78X-2 Hardness tester (Huanghai drug test, China).

3.4. Analytical method

The concentration of PPZ was determined by a HPLC method. The HPLC system consisted of a pump (LC-10ATvp, shimadzu, Japan), an UV detector (SPD-10Avp, shimadzu, Japan), and a ODS C_{18} column (150 mm × 4.6 mm, 5 μm, Shimadzu, Japan). The mobile phase was composed of 70:30 (V/V) methanol-water with 0.4% (V/V) triethylamine (TEA) and adjusted to pH 6 with acetic acid. The flow rate was 1 mL/min, the detection wavelength was at 254 nm, and the injection volume was 20 μL at room temperature.

3.5. Preparation of reagents and solution

A 200 μg/mL stock solution of PPZ was prepared by dissolving 10 mg of PPZ in 50 mL of methanol, while a 800 μg/mL internal standard stock solution was prepared by dissolving 5 mg of the clozapine in 50 mL of methanol. The analytical PPZ standards (80, 120, 200, 400, 800, 1000 ng/mL) were prepared by diluting the PPZ stock solution with methanol. All the stock solutions were stored at −4 °C.

3.6. Blood sample preparation

0.1 mL of blood sample and 10 μL of IS solution was added into a tube and vortex-mixed for 10 s. After adding 1 mL of absolute ethyl ether, the tube

was vortex-mixed for 2 min, and centrifuged at 15000 rpm for 10 min. Upper organic phase of 0.9 mL was transferred to a clean tube and evaporated to dryness at 40 °C under water bath. The dry extract was reconstituted in 0.1 mL of methanol, vortex-mixed for 2 min, centrifuged at 15000 rpm for 10 min and the clear supernatant (20 μL) was injected into the HPLC system.

3.7. In vivo studies

All animal experiments conformed to institutional guidelines. Six male New Zealand white rabbits with a body weight range of 1.9 ∼ 2.1 kg were used in a randomized two-way cross-over study with a one-week washout period. The rabbits were divided into two groups in average. Before the experiments, rabbits were starved for 12 h but had free access to water. The first group required a single dose of three commercial conventional PPZ tablets (2 mg/tablet) perorally, whereas a single dose of three ODTs consisting of PPZ/HP-β-CD (2 mg/tablet) was given to the second group. Blood samples were collected in volumes of 1 mL from the ear marginal vein at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24 h and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24 h after drug administration, respectively. Subsequently, blood samples were centrifuged at 3000 rpm for 10 min to obtain the plasma, which was immediately removed and stored at −70 °C until being assayed.

3.8. Pharmacokinetics and statistical analysis

The following pharmacokinetics parameters were calculated using non-compartmental methods: area under the plasma concentration-time curve from zero to the last measurable PPZ concentration sample time (AUC_{0-t}), area under the plasma concentration-time from zero extrapolated to infinite time ($AUC_{0-\infty}$), maximum plasmatic drug concentration (C_{max}) and time to reach C_{max} (t_{max}). C_{max} and t_{max} were obtained from the data, AUC_{0-t} was calculated by using the linear trapezoidal method. $AUC_{0-\infty}$ was calculated as $AUC_{0-\infty} = AUC_{0-t} + C_t/k$, where C_t is the last measured concentration at the time t, and k is the terminal elimination rate constant (Armando et al. 2009).

C_{max}, AUC_{0-t}, and T_{max} were considered as primary variables for the purpose of assessing the bioequivalence between the test PPZ/HP-β-CD ODTs and reference conventional tablets. The logarithmic transformation of the C_{max} and AUC_{0-t} values were subjected to ANOVA to assess periods, formulation, and sequence effects using an F test, in which $P < 0.05$ was considers to be significant. The log-transformed parameters were calculated using the two 1-side t tests for acceptance of bioequivalence (Schuirmann 1987). The formulations were considered bioequivalent if the 90% confidence intervals (90% CI) for the ratio of C_{max} and AUC_{0-t} fell within 80−125% (US Food and Drug Administration 1993). The Wilcoxon rank sum test was used to exam statistically significant differences in T_{max}.

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