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In vitro and *in vivo* evaluation of novel immediate release carbamazepine tablets: Complexation with hydroxypropyl-β-cyclodextrin in the presence of HPMC

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ABSTRACT

Carbamazepine (CBZ)–hydroxypropyl-β-cyclodextrin (HP-β-CD) complex in the presence of HPMC was prepared and characterized by differential scanning calorimetry (DSC) and X-ray diffractometer intended for improving the dissolution rate of CBZ. The phase-solubility method was used to investigate the effect of HP-β-CD and HPMC on the solubility of CBZ. Tablets of the resulting complex were prepared using direct compression method and the bioavailability was evaluated in beagle dogs using a UPLC/MS/MS method. The results showed solubility of CBZ was increased up to 95 times by complexation with HP-β-CD in the presence of 0.1% HPMC. The results of DSC and X-ray diffraction proved a formation of complex between CBZ and HP-β-CD. Dissolution rate of CBZ was notably improved from complex tablets with more than 97.39% released within 10 min; whereas for the commercial tablets, around 60% was released within 30 min. Using commercial tablets as the reference formulation, the bioavailability of complex tablets was considerably increased by 1.5-fold ($P < 0.05$) and T_{max} was reduced to 0.88 h compared with 1.25 h for commercial tablets. Furthermore, a lower inter-subject variability (49.9%) was observed compared with that of the commercial tablets (39.7%). It is evident from the results herein that complexation with HP-β-CD in the presence of HPMC is a feasible way to prepare a rapidly acting and better absorbed CBZ oral product.

1. Introduction

Carbamazepine (CBZ) is a widely used anticonvulsant drug. Due to its very low water solubility and dissolution rate-limited absorption, absorption of immediate-release tablets is generally slow and irregular. It was well documented that its rate of absorption varied markedly with different pharmaceutical formulations (Martindale, 1982). It has been reported that time to peak concentration (T_{max}) of CBZ immediate-release tablets vary from 4 h to 8 h (Bertilsson, 1978).

The poor aqueous solubility of CBZ has been overcome by many techniques, such as solid dispersion with polyethylene glycols (PEG); coprecipitation with phospholipids (PL) (Hind et al., 1998) and complexation with cyclodextrin (CD) (Brewster et al., 1991; Choudhury and Nelson, 1992; Betlach et al., 1993; El-Gindy et al., 2002; Smith et al., 2005). Among them, CD complexation has been proved to be especially useful to improve the oral bioavailability of CBZ. Koester et al. (2004) have reported using β-CD to improve the solubility of CBZ *in vitro* and the bioavailability *in vivo*, while Betlach et al. (1993) and Brewster et al. (1997) have reported using HP-β-CD as complexation material to improve the bioavailability of CBZ in dogs.

Among the complexation material, HP-β-CD was considered to be moderate oral and intravenous doses (Irie and Uekama, 1997; Thompson, 1997). In addition to increasing solubility, HP-β-CD was much more toxicologically benign than the natural β-CD (Gould and Scott, 2005). However, the use of CD in the solid oral dosage forms is limited to low-dose drugs because of the mass limitations of oral dosage units (Rajewski and Stella, 1996). Therefore, it is very important to find effective methods for enhancing CD complexing and solubilizing abilities. Many work demonstrated the ability of water-soluble polymers to enhance both the aqueous solubility of the complex and the CD complexation efficiency (Faucci and Mura, 2001; Loftsson and Friðriksdóttir, 1998; Smith et al., 2005; Cirri et al., 2009). Therefore, complexation with HP-β-CD in the presence of water soluble polymer is a possible way to prepare a rapidly acting and better absorbed CBZ oral product. However, all studies reported are restricted to the evaluation of the interactions in solution and in the solid states of such ternary systems. To the best of our knowledge, no reports regarding the evaluation of the bioavailability of CBZ tablets containing CBZ-HP-

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β-CD complex in the presence of water soluble polymer have been found.

In this context, the effect of water-soluble polymers, such as PVP and HPMC, on the complexation efficiency of CBZ with HP-β-CD was investigated. The solid complex was prepared by the solvent method and characterized by DSC and X-ray diffractometer. Furthermore, the bioavailability of the complex tablets was evaluated in beagle dogs using UPLC/MS/MS method.

2. Materials and methods

2.1. Materials

CBZ (molar weight = 236.27 g/mol) was purchased from Zhejiang Jiuzhou Pharmaceutical Co., Ltd. The commercial CBZ tablet was purchased from Shaihai fuhua Pharmaceutical Co., Ltd. (100 mg, Batch No. 091214). Phenacetin as internal standard was obtained from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Hydroxypropyl-β-cyclodextrin (HP-β-CD molar weight = 1396 g/mol) was purchased from Shandong Xinda Fine Chemical Co., Ltd. The following excipients were obtained from the company indicated in parentheses: HPMC (E5, Colorcon, China), $PVP_{K\text{-}30}$ (BASF, Germany), lactose (Flowlac 100, Meggle, Germany), MCC (Aricel pH302, Asahi Kasei Corporation, Japan), CMS-Na (Anhui ShanHe Pharmaceutical Excipients Co., Ltd.), Aerosil (Degussa, Germany). Methanol (HPLC-grade) was purchased from Fisher Scientific (Pittsburgh, PA, USA). Formic acid was purchased from Concord Chemical (Tianjin, China).

2.2. Phase solubility studies

Aqueous solutions were prepared containing HP-β-CD (0–50%, w/v) and PVP (0, 0.1%, 0.25%, 0.5%, w/v) or HPMC (0, 0.1%, 0.25%, 0.5%, w/v). An excess amount of drug was added. The suspensions were equilibrated at constant temperature on a tumbling mixer. After equilibrium, the suspensions were filtered and the solutions were assayed spectrometrically at 286 nm.

The equilibrium constants of the inclusion complex were determined from the phase-solubility diagrams according to Higuchi and Connors (1965). As the slope of these diagrams was <1, it was assumed that a 1:1 stoichiometric complex was formed. The apparent stability constants (*Ks*) were then determined from Eq. (1)

2.3. Preparation of CBZ-HP-β-CD complex in the presence of HPMC

According to the literature, the inclusion complex of CBZ–HP-β-CD in the solid state was prepared by the solvent method (Hind et al., 1998). Briefly, CBZ and HP-β-CD (in a 1:1 molar ratio) were dissolved separately in ethanol, adding 0.1% HPMC, and then mixed. The solvent was evaporated at 60 °C, and the resultant film was stored in a desiccator at room temperature. Prior to *in vitro* evaluation, CBZ content in the resulting powder was assayed and was found to be 13.8%.

2.4. Differential scanning calorimetry (DSC)

DSC analysis was carried out with a DSC-60 (Shimadzu, Japan). Samples (5–10 mg) of solid complex, simple physical mixture, pure CBZ and HP-β-CD were heated at a scanning rate of 10 °C/min, from 25 °C up to 250 °C.

2.5. X-ray diffractometry

X-ray diffraction for pure CBZ, HP-β-CD, CBZ-HP-β-CD complex in the presence of HPMC, and CBZ-HP-β-CD physical mixture were performed using Rigaku D/max-2400PC apparatus. The measuring conditions were as follows: filter, Kβ; target, Cu Kα; voltage, 56 kV; current, 182 mA.

Table 1
Formulation of complex tablets.

Composition	Weight % (w/w)
CBZ–HP-β-CD–HPMC complex	36.5
MCC	13.5
Lactose	45
CMS-Na	8
Aerosil	2

2.6. Preparation of tablets

Tablets of complex containing CBZ 50 mg were prepared by direct compression technique. Table 1 presents the formula composition. A single punch Korsch EK-0 machine, equipped with flat 15.0 mm punches was employed. The tablets were evaluated regarding dissolution rate *in vitro*.

2.7. In vitro dissolution test

A dissolution test was performed using a ZRS-8G dissolution apparatus coupled to a SPEKOL 1200 Spectrophotometer at 37 °C in 1000 mL and 500 mL dissolution medium. The paddle rotation speed was maintained at 150 rpm. Different dissolution media were used as water, 0.1 mol/L HCl, pH 4.5 acetate buffers, pH 6.8 phosphate buffers, pH 7.2 phosphate buffers, and 0.065 mol/L HCl. Samples were withdrawn at 5, 10, 20, 30, 40 and 60 min. Each sample solution was filtered through a 0.22 μm millipore filter and analyzed spectrometrically at 286 nm to determine the dissolution rate of CBZ.

2.8. In vivo study

All animal experiments were performed in accordance with institutional guidelines and were approved by the University Committee on Use and Care of Animals, Shenyang Pharmaceutical University. Six female beagle dogs weighting 8–12 kg were used in this randomized, crossover study with a washout phase of 1 week between the two study periods. The dogs were fasted overnight prior to oral administration of the drug. The treatments consisted of a single oral 100 mg dose with 40 mL water: a commercial tablet (100 mg, Shanghai fuhua Pharmaceutical Co., Ltd.) and two tablets containing CBZ–HP-β-CD complex. During all experiments, water was allowed ad libitum. Solid meals were given 8 h after administration of drug.

Blood samples of 2.0 mL were withdrawn from forefoot vein at 0, 10, 20, 30, 45, 60, 75, 90, 120, 180, 240, 360, 480 min after administration of the drug and centrifuged for 10 min at 3500 rpm. The plasma was stored at −20 °C until analysis.

2.9. Analysis of CBZ concentration in the plasma

A Waters ACQUITY TQD system was employed for the determination of the analytes. Chromatography was performed on a ACQUITY UPLC™ BEH C_{18} column (50 mm × 2.1 mm, 1.7 μm, Waters Corp., Milford, MA, USA), using mobile phase of methanol–water–formic acid (65:35:0.1, v/v/v). The flow rate was 0.2 mL/min. The column temperature was maintained at 35 °C. A Waters TQD triple quadrupole mass spectrometer equipped with an ESI source was used for mass analysis and detection. The mass spectrometer was operated in the positive ion electrospray ionization (ESI+). Quantification was carried out using

Table 2
Saturated solubility of CBZ (mmol/L) with HP-β-CD and HPMC.

HPMC (% w/v)	HP-β-CD % w/v (mol/L)								
	0(0)	1(0.00609)	2(0.0122)	5(0.0304)	10(0.0608)	20(0.122)	30(0.183)	40(0.243)	50(0.304)
0	1.78	2.89	4.92	13.1	25.8	50.8	91.0	105.2	132.3
0.1	3.23	5.93	10.2	24.5	40.0	73.1	110.1	138.4	169.2
0.25	3.19	5.43	10.3	23.9	45.6	74.3	107.2	137.2	168.6
0.5	3.20	5.77	11.2	24.3	46.7	75.9	109.1	132.9	170.8

the multiple reaction monitoring (MRM) mode. The fragmentation transitions for MRM were *m/z* 237.3 → 194.3 for CBZ and *m/z* 180.3 → 110.1 for phenacetin. The optimal MS parameters were as follows: desolvation gas flow: 550 L h^{-1}; cone gas flow: 50 L h^{-1}; source temperature: 120 °C; desolvation gas temperature: 350 °C; capillary voltage: 3.22 kV; cone voltage: 43 V.

A 50 μL aliquot of plasma was spiked with 50 μL mobile phase and mixed thoroughly with 50 μL internal standard solution (500 ng/mL of phenacetin). Then, add 1 mL ether and mix vigorously for 30 s. After centrifugation at 3500 rpm for 10 min, the supernatant was separated and the organic solvent was evaporated under a nitrogen stream at 40 °C. The residue was reconstituted in 500 μL mobile phase and a 5 μL aliquot was injected into the UPLC/MS/MS system.

2.10. Pharmacokinetic and statistical analysis

The maximum plasma concentration (C_{max}) and the time to reach peak concentration (T_{max}) were obtained directly from the concentration–time data of each dog. The elimination rate constant (K_e) was obtained from the least-squares fitted terminal log-linear portion of the plasma concentration–time profile. The elimination half-life ($t_{1/2}$) was calculated from 0.693/K_e, while the area under the curve to the last measurable concentration (AUC_{0-t}) was calculated by the linear trapezoidal rule. The area under the curve extrapolated to infinity ($AUC_{0-\infty}$) was obtained as $AUC_{0-t} + Ct/K_e$.

The significance of the differences observed for the mean pharmacokinetic parameters of test and reference tablets was evaluated using analysis of variance (ANOVA) at a significance level of $P < 0.05$.

3. Results and discussion

3.1. Phase solubility studies

To investigate the effect of HP-β-CD on the solubility of CBZ in the presence or the absence of water-soluble polymer as PVP and HPMC, the saturated solubilities of CBZ were determined in different solutions.

As seen in Table 2, as expected, with the increase in HP-β-CD concentration in the solution, the saturated solubility of CBZ increased from 1.78 to 132.4 mmol/L, indicating that complexation with HP-β-CD is an effective way to improve the solubility of CBZ. When this complexation process occurred together with HPMC, remarkable increase in solubility was obtained. For example, in 50% w/v HP-β-CD solution, the solubility of CBZ is 132.4 mmol/L; correspondingly, with the addition of 0.1% w/v HPMC, the solubility value is 169.2 mmol/L, CBZ solubility was increased to up to 95 times by molecular complexation with 0.1% HPMC and HP-β-CD. At each concentration point of HP-β-CD, the solubilities of CBZ were increased around by 1.5-fold after the addition of HPMC. Similarly, it has been reported (Smith et al., 2005) that the solubility of CBZ was increased when HPMC combined with SBE7-β-CD and this synergistic improvement in CBZ solubility was due to HPMC increasing the concentration of free CBZ available in solution to interact with the HP-β-CD. Katzhendler et al. (1998) assumed the increased solubility due to an interaction between HPMC and CBZ in solution, and considered this occurred by hydrogen bonding. However, further increased HPMC concentration as 0.25% and 0.5% (w/v), CBZ solubility is similar to that observed in 0.1% HPMC (w/v).

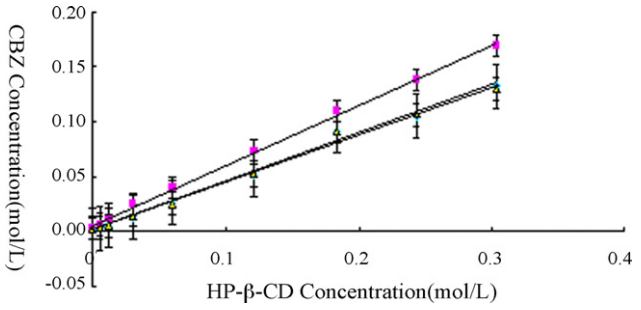

Fig. 1. Phase solubility diagram of CBZ with HP-β-CD alone (-♦-), and with 0.1% HPMC (■), 0.1% PVP (▲).

Concerning PVP, seen from Table 3, significant difference in CBZ solubility was not found within the concentration levels of 0.1–0.5% (w/v) studied. This result reveals that the presence of the hydrophilic polymer favorably improved the solubilizing effect of HP-β-CD toward CBZ, but depending on the type of polymer. In this work, combined strategy of HP-β-CD complexation and hydrophilic polymer HPMC improved CBZ solubilization effectively and thereby can greatly reduce the amount of HP-β-CD in formulation.

The phase solubility diagrams were presented in Fig. 1. As expected, with the increase in concentration of HP-β-CD, the solubility of CBZ was increased and there is a linear relationship between CBZ solubility and HP-β-CD concentration with the slope <1, both in the presence and in the absence of HPMC or PVP, indicating formation of the inclusion complex with a 1:1 molar stoichiometry, concurrent with the previously reported 1:1 complexation of CBZ and HP-β-CD (Hoshino et al., 1993). While the corresponding stability constant *Ks* values were found to be 435.2 mol^{-1}, 687.2 mol^{-1}, 444.1 mol^{-1} in the presence of PVP, HPMC and absence of both of them, respectively.

Table 3
Saturated solubility of CBZ (mmol/L) with HP-β-CD and PVP.

PVP (% w/v)	HP-β-CD % w/v (mol/L)								
	0(0)	1(0.00609)	2(0.0122)	5(0.0304)	10(0.0608)	20(0.122)	30(0.183)	40(0.243)	50(0.304)
0	1.78	2.89	4.92	12.1	24.8	50.8	75.0	96.2	120.0
0.1	1.73	2.70	4.84	13.7	22.1	51.2	74.3	95.4	117.2
0.25	1.74	2.81	4.79	13.4	23.4	49.7	73.2	94.2	119.6
0.5	1.72	2.67	4.88	12.7	23.8	50.3	75.1	93.9	120.8

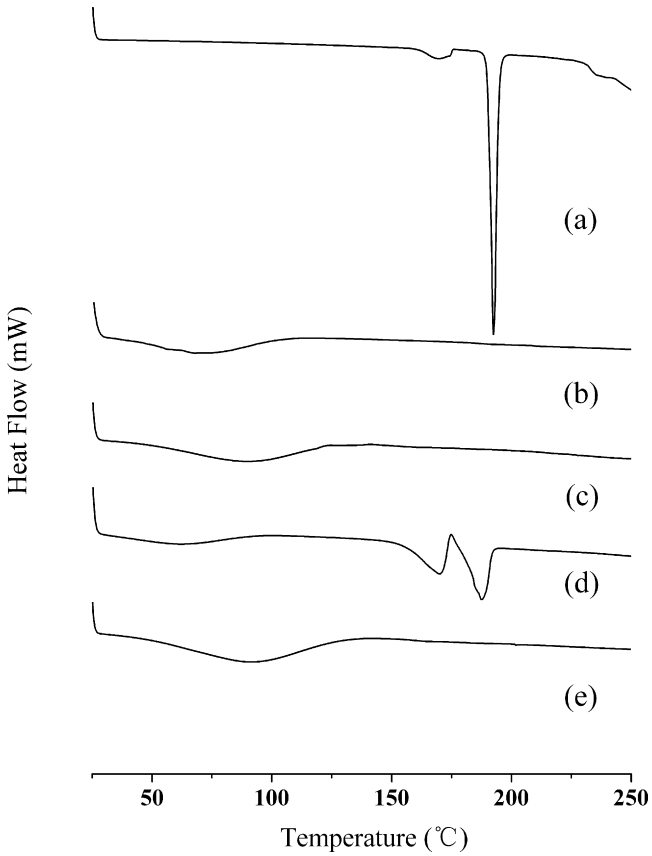

Fig. 2. DSC spectra of CBZ (a), HP-β-CD (b), HPMC (c), CBZ–HP-β-CD–HPMC physical mixture (d) CBZ-HP-β-CD complex combined with HPMC (e).

Obviously, the addition of polymers to the solution did not influence the type of the phase solubility diagram. While an increase in the stability constant *Ks* value was observed as the HPMC added, thereby revealing an improvement in the complexation efficiency of HP-β-CD. Regarding combination of HP-β-CD and PVP, negligible differences in solubility of CBZ and *Ks* value were observed. It has been reported by Loftsson et al. (1996) when adding HPMC to various drugs with HP-β-CD, the increase or decrease in solubility of drug was drug dependent. This experiment suggests the possible interaction of drug and water soluble polymer during the complexation process of drug and HP-β-CD.

3.2. DSC and X-ray diffractometry studies

Evidence for the complex formulation in the solid state was obtained by differential scanning calorimetry (DSC) and X-ray diffractometry analysis. Fig. 2 illustrates the DSC profile of pure CBZ, HP-β-CD, HPMC, physical mixture and complex. The DSC thermogram of CBZ characterized by a sharp melting peak at 192 °C typical of a pure, anhydrous substance, while the thermogram of HP-β-CD show a large endothermic band ranging between 48 °C and 100 °C, which could correspond to the loss of water molecules from the cyclodextrin cavity, and the thermogram of HPMC also show a large endothermic band ranging between 55 °C and 122 °C. The thermogram of CBZ, HP-β-CD and HPMC physical mixture shows two peaks, the endothermic band ranging between 48 °C and 100 °C is due to HP-β-CD decomposition; and the endothermic peak at 192 °C is caused by the melting of CBZ. The thermogram of CBZ-HP-β-CD complex combined with HPMC was similar to HP-β-CD alone. These thermal behavior changes indicate the formation of the inclusion complex through molecular interactions between the CBZ and HP-β-CD, resulting in the amorphous dispersed form of CBZ.

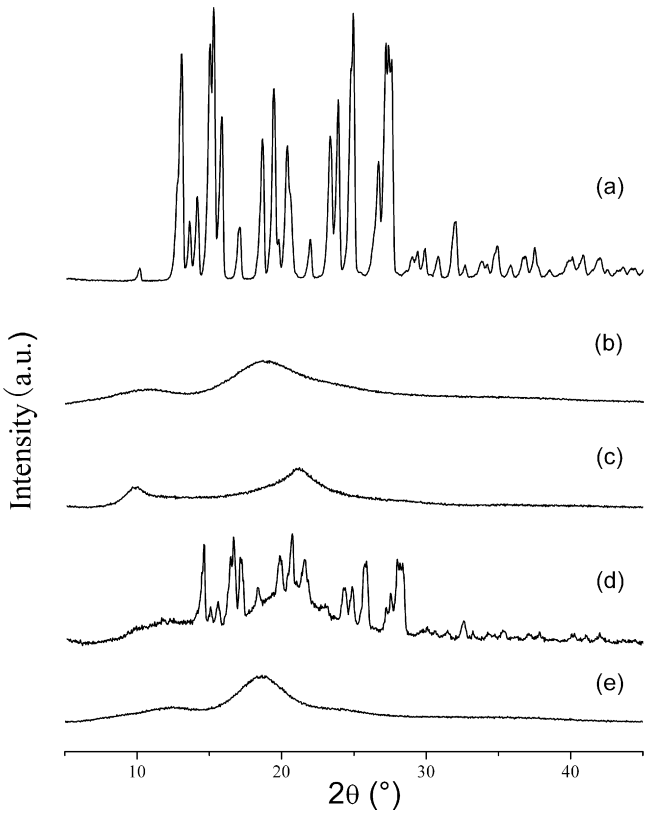

Fig. 3. X-ray diffractograms of CBZ (a), HP-β-CD (b), HPMC (c), CBZ–HP-β-CD–HPMC physical mixture (d), CBZ–HP-β-CD complex combined with HPMC (e).

Fig. 3 shows the XRPD spectra of CBZ, HP-β-CD, HPMC, physical mixture and the complex, respectively. The pattern of CBZ displayed some intense and sharp peaks, which confirming its crystalline nature. On the contrary, the HP-β-CD and HPMC profile was characterized by a typical amorphous pattern. The physical mixture showed the characteristic peaks of CBZ and amorphous pattern of HP-β-CD, which proves there are no interactions taking place during physically mixing. In contrast, there exists almost only HP-β-CD typical amorphous pattern in the complex profile, thus indicating a complete amorphous form of the drug. These results also further highlighted the great complexing power of HP-β-CD toward the drug (Leuner and Dressman, 2000).

3.3. Dissolution study

Solubility plays an important role in the dissolution of a drug substance from a solid dosage form. For water insoluble drugs, difficulties are usually encountered in selecting a dissolution medium of acceptable volume and a composition as well as a good discriminating power (He et al., 2004). In our study, we investigated the solubility of CBZ in 1000 mL and 500 mL dissolution medium such as water, 0.1 mol/L HCl, pH 4.5 acetate buffers, pH 6.8 phosphate buffers, pH7.2 phosphate buffers, and 0.065 mol/L HCl to mimic the complicated microenvironment in whole gastrointestinal tract. The complex formulation enhanced CBZ dissolution in all dissolution media compared to the commercial formulation. When pH was changed from 1.0 to 7.2, dissolution rate changed slightly. This result could be explained that as a neutral substance, CBZ may be considered with no acidic or basic functions in a wide range of pH (Martindale, 1982). But when the volume of dissolution medium changed from 500 mL to 1000 mL, the dissolution rate changed significantly between the complex tablets and the commercial tablets. Fig. 4 shows the dissolution profile of the CBZ

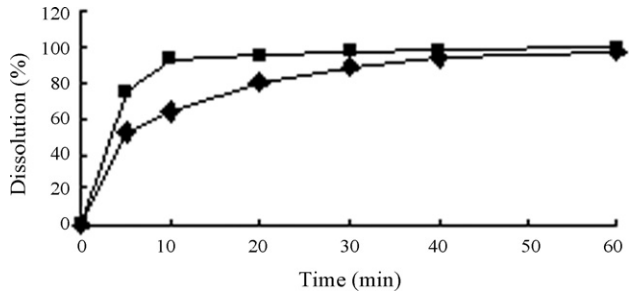

Fig. 4. Dissolution of complex tablets and commercial tablets in 1000 mL 0.065 mol/L HCl (-■- standard for complex tablets, -♦- standard for commercial tablet, mean ± S.D., $n = 6$).

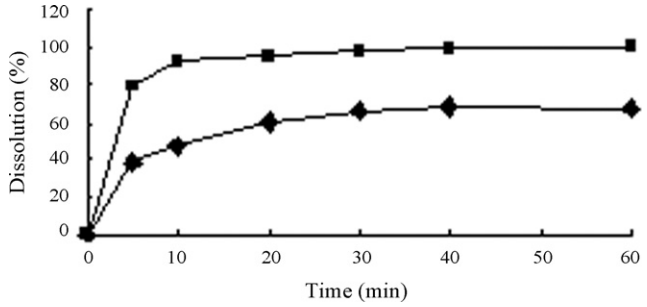

Fig. 5. Dissolution of complex tablets and commercial tablets in 500 mL 0.065 mol/L HCl (-■- standard for complexes tablets, -♦- standard for commercial tablet, mean ± S.D., $n = 6$).

from the complex tablets and the commercial tablets in 1000 mL 0.065 mol/L HCl which was specified in the Chinese Pharmacopoeia (2010), complete dissolution of two kinds of tablets was achieved in 1000 mL dissolution media, However, when 500 mL 0.065 mol/L HCl was used as dissolution medium, the complex tablets also exhibit instantaneous dissolution with 97.39% dissolved from complex tablets within 10 min, and achieved 100% dissolution after 60 min. In contrast, the dissolution rate of commercial tablets was slow and incomplete with 65–70% being dissolved after 60 min as Fig. 5 shows. Fig. 6 also shows the dissolution results of two kinds of CBZ tablets in different medium at 60 min. From the solubility study it was found that although the dissolution medium which was specified in Chinese Pharmacopoeia (2010) satisfied the sink condition, for the poorly soluble drug, we need a kind of medium which has sufficient discriminating power to evaluate the relationship between *in vitro* dissolution and *in vivo* absorption of CBZ.

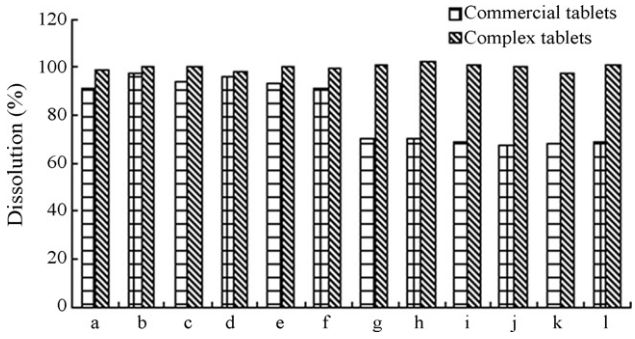

Fig. 6. Dissolution percent of carbamazepine at 60 min in different medium. (a) 1000 mL pH 7.2 phosphate buffers; (b) 1000 mL pH 6.8 phosphate buffers; (c) 1000 mL pH 4.5 acetate buffers; (d) 1000 mL 0.1 mol/L HCl; (e) 1000 mL water; (f) 1000 mL 0.065 mol/L HCl; (g) 500 mL pH 7.2 phosphate buffers; (h) 500 mL pH 6.8 phosphate buffers; (i) 500 mL pH 4.5 acetate buffers; (j) 500 mL 0.1 mol/L HCl; (k) 500 mL water; and (l) 500 mL 0.065 mol/L HCl (mean ± S.D., $n = 6$).

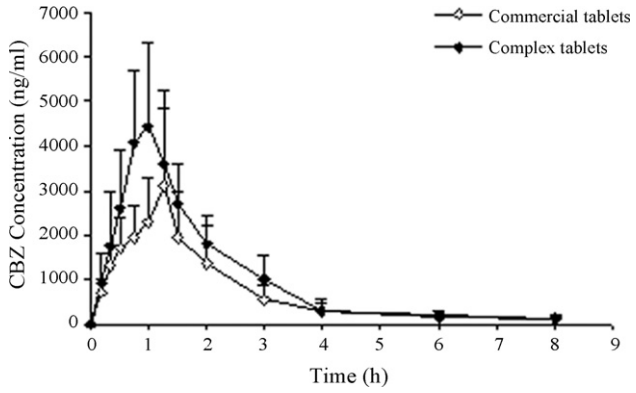

Fig. 7. Mean (±S.D.) plasma concentration–time profiles of CBZ after oral administration of complex tablets and commercial immediate-release tablets.

3.4. In vivo study

A liquid chromatography coupled with tandem mass spectrometry (UPLC/MS/MS) method was developed to determine CBZ in beagle dog plasma, with a lower limit of quantification (LLOQ) being 50 ng/mL and a good linearity in the concentration range from 50 to 7200 ng/mL with acceptable intra- and inter-day precision. Under the present chromatographic conditions, the retention times were about 1.01 min for CBZ and 0.85 min for the IS. The total run time was 2 min. This is also the advantage of the current method. The intra-day precision was found to be below 6.5%. The inter-day accuracy as determined from QC sampling was within ±1.4%. The extraction recoveries of CBZ were 76.6%, 76.5%, and 67.0% at concentration of 100.0, 1200.0, 5400.0 ng/mL, respectively.

In order to investigate the *in vivo* absorption profile, bioavailability of complex tablets and the commercial tablets being the same dosage were investigated in beagle dogs. Fig. 7 shows the mean plasma concentration–time profile of CBZ from complex tablets and commercial tablets and the pharmacokinetic parameters are summarized in Table 4. The mean peak plasma concentration (C_{max}) for complex tablets was 4951.04 ± 1585.21 ng/mL, T_{max} was 0.88 ± 0.14 h, and $AUC_{0-\infty}$ was 8597.85 ± 2786.18 ng h/mL. The mean elimination half time ($t_{1/2}$) was 1.52 ± 0.60 h. For commercial tablets, the mean peak plasma concentration (C_{max}) was 3577.99 ± 1444.90 ng/mL, T_{max} was 1.25 ± 0.16 h, and $AUC_{0-\infty}$ was 6000.65 ± 2227.61 ng h/mL. In addition, the mean elimination half time ($t_{1/2}$) was 1.52 ± 0.60 h. Analysis of variance applied to $\ln AUC_{0-\infty}$ and $\ln C_{max}$ data are shown in Table 5. The results showed that there is a significant difference in C_{max} and $AUC_{0-\infty}$ between complex tablets and commercial tablets ($P < 0.05$). In addition, no significant difference was observed in T_{max} ($P > 0.05$). The bioavailability of the complex tablets is 1.5-fold compared with that of immediate-release commercial tablets. The pharmacokinetic parameters were in good agreement with dissolution data using 500 mL dissolution volume. Besides, this result also confirmed that increased dissolution rate *in vitro* lead to a faster absorption rate *in vivo*. Moreover, the complex tablets showed not

Table 4
Pharmacokinetic parameters (mean ± S.D.) after oral administration of the following formulation: the complex tablets and commercial immediate-release tablets.

Pharmacokinetic parameters	Complex tablets	Commercial tablets
C_{max} (ng/mL)	4951.04 ± 1585.21	3577.99 ± 1444.90
T_{max} (h)	0.88 ± 0.14	1.25 ± 0.16
K_e (h^{-1})	0.50 ± 0.15	0.39 ± 0.20
$t_{1/2}$ (h)	1.52 ± 0.60	2.71 ± 2.43
$AUC_{0-\infty}$ (ng h/mL)	8597.85 ± 2786.18	6000.65 ± 2227.61
F (%)	152.70 ± 23.30	–

Table 5
ANOVA of $\ln AUC_{0-\infty}$ (ng h/mL) and $\ln C_{max}$ after oral administration of the following formulation: the complex tablets and commercial immediate-release tablets.

Source of variation	Degree of freedom	Sum of squares	Mean square	*F*	*P*
Treatments	1				
$AUC_{0-\infty}$		0.410	0.410	133.442	0.000
C_{max}		0.339	0.339	16.335	0.016
Total	11				
$AUC_{0-\infty}$		1.613			
C_{max}		1.509			

only the faster absorption rate but also a significantly greater extent of drug absorption than the commercial tablets.

According to the literature, CBZ shows slow, irregular absorption and unpredictable fluctuations in the plasma (Barakat et al., 2008), the variability of therapeutic efficiency can be attributed to many reasons, such as inter-individual sensibility, chronobiologic effect, and the rates of dissolution. But when complex tablets were given, the fluctuation of the plasma concentration has not been observed and the same phenomenon was detected by Koester et al. (2003). We calculated the percent coefficient of variation (CV %) for plasma concentration at each sampling time, the average inter-subject plasma concentration variability CV % was 39.7%, 49.9% after administration of test and reference tablets, respectively. the same observation was also reported by Barakat et al. (2008). The lower inter-subject variability for complex tablets may due to the presence of HP-β-CD combined with HPMC, a good carrier for improvement of the water-solubility toward drug, thereby resulting in a decreased fluctuation in plasma levels. It could be concluded that HP-β-CD combined HPMC can successfully improve the bioavailability of CBZ as well as enhance CBZ dissolution and absorption.

4. Conclusion

CBZ solubility was increased to up to 95 times by integrated complexation with 0.1% HPMC and HP-β-CD. The presence of HPMC greatly increased the complexing efficiency of CBZ with HP-β-CD. X-ray diffractometry and DSC revealed an interaction between CBZ and HP-β-CD in the complex. The tablets of complex prepared by direct compression technique demonstrated an increased dissolution profile *in vitro* with 97.63% dissolved with 10 min. The *in vivo* study of the complex tablets illustrated a greater and faster absorption, together with a lower inter-subject variability. The results suggest that complexation with HP-β-CD combined with the addition of 0.1% HPMC is effective for the improvement of CBZ bioavailability and modulation *in vivo* release from tablets.

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Appendix A.

$$Ks = \frac{slope}{D_0 * (1 - slope)} \quad (1)$$

D_0, solubility of CBZ without cyclodextrin; *slope*, slope of phase-solubility diagram.

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