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Physicochemical properties and bioavailability of carbamazepine polymorphs and dihydrate

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Abstract

The dissolution behaviors of carbamazepine (CZP) polymorphs and pseudopolymorphs (form I, form III and dihydrate) and the bioavailabilities (BA) of each form in dogs after oral administration were investigated. Bioavailability tests were carried out at a dose of either 40 mg/body or 200 mg/body. The results of dissolution tests in JP13 first fluid (pH 1.2) at 37°C indicated that the initial dissolution rate was in the order of form III > form I > dihydrate, while form III was transformed to dihydrate more rapidly than form I, resulting in decrease of the dissolution rate. The solubilities of both anhydrates (form I and form III), calculated from the initial dissolution rate of each anhydrate, were 1.5–1.6 times that of the dihydrate. At the dose of 40 mg/body, there were no significant differences in the area under the curve (AUC) between forms; their AUCs were nearly equal to that of CZP solution using polyethyleneglycol 400. These findings suggested that most crystalline powder of each form administered at the low dose was rapidly dissolved in gastrointestinal (GI) fluid. On the other hand, for the dose of 200 mg/body, significant differences in plasma concentration–time curves of CZP among polymorphic forms and dihydrate were observed. The order of AUC values was form I > form III > dihydrate. The inconsistency between the order of initial dissolution rates and that of AUC values at the high dose may have been due to rapid transformation from form III to dihydrate in GI fluids. © 2000 Published by Elsevier Science B.V. All rights reserved.

Keywords: Carbamazepine; Polymorph; Dihydrate; Dissolution rate; Transformation; Bioavailability

1. Introduction

For drugs which have several polymorphs or pseudopolymorphs, differences in bioavailability (BA) between forms have been reported (York, 1983; Rajendra and David, 1995). Carbamazepine (CZP), which has at least four polymorphic forms and a dihydrate (Kaneniwa et al., 1984; Krahn and Mielck, 1987), is a widely prescribed anticonvulsant antiepileptic drug. Meyer et al. (1992) compared the BAs of three lots of a generic 200 mg CZP tablet to that of one lot of the innovator product in healthy volunteers and found significant differences in the rate and extent of absorption between the generic products and the

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innovator product, as well as among the generic lots. The mean maximum CZP plasma concentrations for two of the generic lots were only 61–74% of that of the innovator product, while that for the third lot was 142% of that of the innovator product. However, it has not been clear what causes the differences in bioavailability among CZP tablets. Some factors contribute to these differences, i.e. differences in crystalline form and/or particle size of CZP raw material.

Behme and Brooke (1991) reported that CZP form I (USP grade material) and form III, which melt at 176 and 189°C, respectively, were enantiotropic and had a transition temperature at 71°C.

Kaneniwa et al. (1984) demonstrated that when form I and form III were stored under water vapor condition at 37°C for 2 weeks, both crystal forms were transformed to dihydrate. Kaneniwa et al. (1987) carried out a dissolution study of the two anhydrates (form I and form III) and dihydrate in water using the rotating disk method. The dissolution study revealed that initial dissolution rates of both anhydrates were higher than that of the dihydrate and the anhydrates transformed to the dihydrate rapidly. However, in their study, the initial dissolution rate of form I was higher than that of form III, even though their experiment was performed in the temperature range in which form I was more stable than form III according to the theory of thermodynamic stability.

The bioavailabilities of one anhydrate (crystal form was not shown) and dihydrate were investigated by Kahela et al. (1983). In a comparison of the anhydrate and dihydrate at a dose of 200 mg/body in humans after oral administration, there was no marked difference between the plasma concentration–time curves of the two crystal forms. Whereas in the bioavailability test of generic 200 mg CZP tablets studied by Meyer et al. (1992) described above, the notable differences between the area under the curve (AUC) values of tablets were observed. Various studies of physicochemical properties of form I, form III and the dihydrate have been reported; however, there are some discrepancies among findings of these studies, and the relationship between physicochemical properties of CZP polymorphic forms and dihydrate and the BA of CZP is not completely understood.

In the present study, the dissolution properties of form I, form III and dihydrate and the behaviors of transformation from form I or form III to the dibydrate during dissolution tests were investigated and bioavailability tests in dogs were performed in order to determine the effects of physicochemical properties of form I, form III and dihydrate on the plasma level of CZP. The bioavailability tests in this study were carried out at a dose of either 40 mg/body or 200 mg/body, since the absorption of drugs with poor solubility such as CZP were affected by the dose administered.

2. Materials

Carbamazepine was obtained from Wako Pure Chemical Industries (Japan; sample A). Other crystalline forms were obtained according to the method described by McMahon et al. (1996). Sample B was prepared by heating sample A at 170°C for 2 h. Sample C was prepared by suspending sample A in distilled water for 24 h at room temperature, then dried on filter at room temperature for 30 min. Sample B was ground using an agate centrifugal ball mill (Model Pulverisette 5, Fritsch) for 5 min (sample B′), since the particle size of sample B was significantly greater than those of samples A and C (Fig. 1). The mean particle size (d) was determined using the microscopic technique (Microscope; E8-21-1, Nikon; Real-time image analyzer; Luzex- F, Nireco) as Heywood diameter, and the specific surface area (S) was determined by the air permeability method (Powder specific surface area meter; Model SS-100, Shimadzu) (Table 1).

3. Methods

3.1. Identification of crystalline forms of samples

3.1.1. Powder X-ray diffractometry

The powder X-ray diffraction patterns were

determined with an X-ray diffractometer (Model RAD3-C, Rigaku). The conditions of measurement were as follows: Target; Cu, filter; Ni, voltage; 40 kV, current; 30 mA, scanning speed; 4°/min, scanning angle; 3 ~ 40°.

3.1.2. Differential scanning calorimetry (DSC)

DSC curves were obtained with a differential scanning calorimeter (Model DSC-7, Perkin-Elmer). Differential scanning calorimetry was performed under the following conditions: Sample weight; about 2 mg, sample cell; an aluminium open cell with a cell cover, nitrogen flow rate; 20 ml/min, heating rate; 10°C/min.

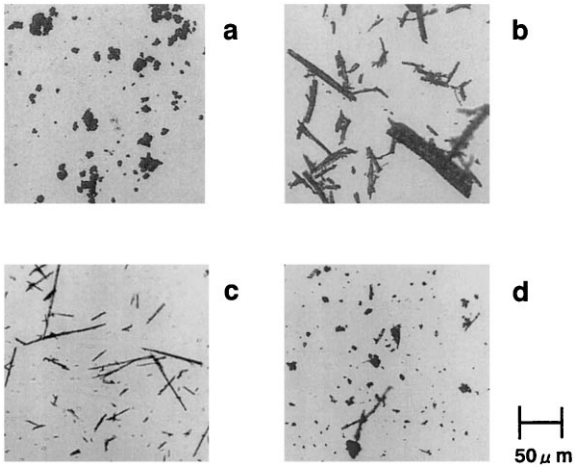

Fig. 1. Microscopic photographs of CZP samples. a: Sample A, b: Sample B, c: Sample C, d: Sample B′.

Table 1
Mean particle diameter and specific surface area of samples

	Mean particle diameter (d) (μm)	Specific surface area (S) (cm^2/g)
Sample A	13.9	1.27×103
Sample B	108.0	2.43×102
Sample B′	19.5	1.10×103
Sample C	13.4	1.24×103

3.1.3. Thermogravimetric analysis (TG)

TG curve was obtained with a thermogravimetric analyzer (Model TGA-7, Perkin-Elmer). Thermogravimetry was performed under the following conditions: Sample weight; about 8 mg, sample cell; a platinum open cell, nitrogen flow rate; 70 ml/min, heating rate; 10°C/min.

3.2. Physicochemical properties

3.2.1. Dissolution studies by the static disk method

The intrinsic dissolution rates of samples A, B′ and C were determined by the static disk method described in the previous report (Ito et al., 1997). It was confirmed by powder X-ray diffraction analysis that no polymorphic transition took place during disk preparation for any sample.

Four hundred milliliters of JP13 first fluid (pH 1.2) at 37°C was used as the dissolution medium, which was stirred at 150 rpm with a paddle. At definite time intervals, the solution was passed through G-3 glass filter and delivered to the cell using pump attached to the apparatus. The concentration of CZP in the solution was determined by measurement of the absorbance at 285nm (Ultraviolet spectrophotometer; Model W-1600, Shimadzu). The sampling solution was returned to the original solution by the circulation system.

3.2.2. Dissolution studies by the dispersion method

The dissolution behaviors of CZP samples in the JP13 first fluid at 37°C were investigated by the dispersion method. Approximately 50 mg of each sample was added to 30 ml of JP13 first fluid maintained at 37°C and the suspension was stirred at 650 rpm with a stirrer (Model RCN-7R, Eyela) and sampled periodically. After filtration (pore size 0.45 μm, Gelman Sciences) of sampling solution, the concentration of CZP was determined by high performance liquid chromatography (HPLC). High performance liquid chromatography analysis was performed using a Shimadzu HPLC chromatograph composed of an LC10-AT and SPD-lOAV. The conditions of HPLC method were as follows: Mobile phase; acetonitrile/0.1 M ammonium acetate = 270/

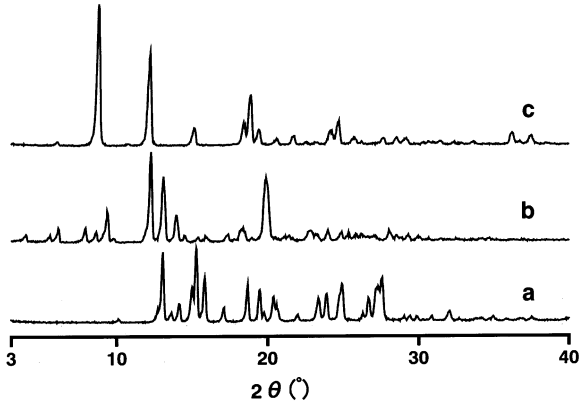

Fig. 2. Powder X-ray diffraction patterns of CZP samples. a: Sample A, b: Sample B′, c: Sample C.

730(v/v), flow rate; 10 ml/min, column; Capcelpack UG120 (4.6mm × 15cm, Shiseido) at 40°C, detection wavelength; 285 nm, injection volume; 50 μl.

3.2.3. Hygroscopicity studies

Accurately weighed amounts of either sample A or sample B′ were stored at 40°C and 98% relative humidity (RH). The 98% RH condition was prepared using saturated solution of ammonium phosphate in a desiccator. Weight changes of samples were monitored after 7, 14 and 28 days.

3.3. Bioavailability tests

3.3.1. Animal experiments

Bioavailability studies were performed using a cross-over technique in four male beagle dogs which were fasted for at least 16 h before administration. The weights of dogs ranged from 9.2 to 10.7 kg. Each sample was administered orally as a capsule with 40 ml of water. In addition, CZP solution using polyethyleneglycol 400 (PEG400) was administered orally. Blood was taken prior to administration and at 15, 30, 45 min and at 1, 2, 3, 5, 8 and 12 h after dosing. Plasma was separated by centrifugation (4°C, 3000 rpm, 10 min) and stored in a freezer at −20°C until analyzed.

3.3.2. Preparation of capsules and solution

Capsules: Each sample was mixed with lactose at a weight ratio of 1:2 (CZP: lactose) and the mixture was placed in the hard gelatin capsule. Forty milligram and 100 mg of CZP, as anhydrate, were contained in #3 and #1 capsules, respectively. Solution: 40 mg or 200 mg of sample A were dissolved in 30 ml of PEG 400.

3.3.3. Determination of CZPconcentration in plasma

Fifty microliters of internal standard (nitrazepam 5 μg/ml) methanol solution and 6 ml of ethyl acetate were added to 0.5 ml of the plasma, and the mixture was shaken for 10 min. After centrifugation (25°C, 3000 rpm, 10 min), 5ml of the ethyl acetate layer was taken and evaporated, and the residue was dissolved in 200 μl of 50%(v/v) acetonitrile aqueous solution. The concentration of CZP was determined by HPLC. Apparatus and conditions of HPLC were the same as described in Section 3.3.2.

4. Results and Discussion

4.1. Identification of prepared samples

Powder X-ray diffraction patterns of the commercial bulk (sample A), sample B′ and sample C are shown in Fig. 2. Characteristic diffraction peaks were observed at $2\theta = 15.2$, 15.8 and 17.0° for sample A, $2\theta =$ 6.1, 9.4 and 19.9° for sample B′ and $2\theta = 8.9$, 18.9 and 19.4° for sample C. The diffraction patterns of sample A, sample B′ and sample C agreed with those of form I, form III and dihydrate, respectively, given in the previous reports (Kaneniwa et al., 1984; Umeda et al., 1984).

Differential scanning calorimetry curves of sample A, sample B′ and sample C and TG curve of sample C are illustrated in Fig. 3. The DSC curve of sample A exhibited an endotherm at 174°C followed by an exotherm at 176°C and a sharp endotherm at 190°C. The DSC curve of sample B′ exhibited only one sharp endotherm at 190°C. On the DSC curve of sample C, a broad endotherm at 50–75°C and a sharp endotherm at

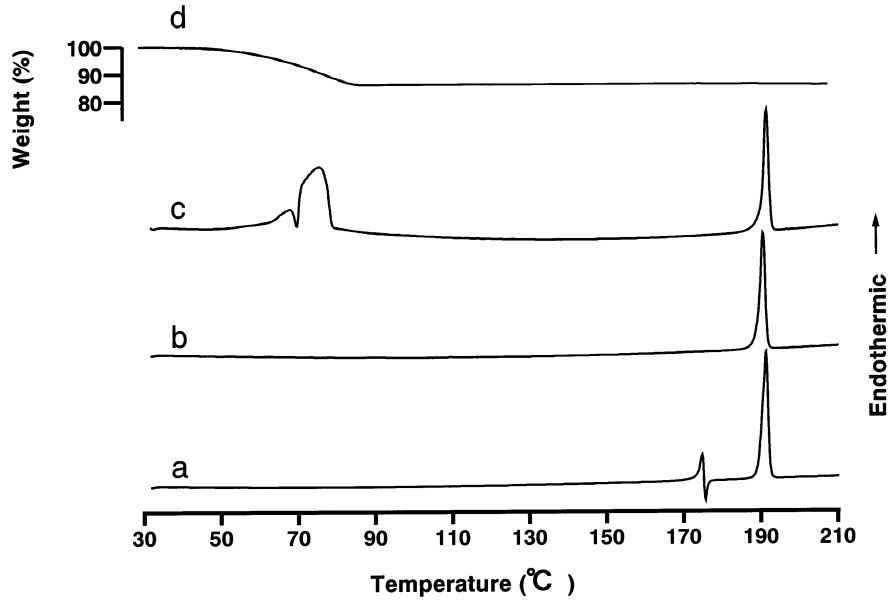

Fig. 3. DSC and TG curves of CZP samples. a: DSC curve of Sample A, b: DSC curve of Sample B′, c: DSC curve of Sample C, d: TG curve of Sample C.

190°C were observed. On the TG curve of sample C, the weight loss corresponding to the DSC endotherm at 50–75°C was 13.1%, which was nearly equal to the stoichiometric value calculated for the dihydrate of CZP (13.2%). The results of thermal analysis were also consistent with those of form I, form III and dihydrate, respectively, given in the previous reports (Kaneniwa et al., 1984, Matsuda et al., 1984).

These findings showed that sample A, B′ and C were form I, form III and dihydrate, respectively.

4.2. Physicochemical properties

4.2.1. Dissolution studies by the static disk method

Dissolution patterns of form I, form III and dihydrate in JP13 first fluid (pH 1.2) from 0 to 10 min are shown in Fig. 4. Good linearities between time and concentration were found for each form. In the sink condition, the concentration of drug, C, at time t was expressed by Eq. (1) (Nogami et al., 1966).

$$C = \frac{S}{V} kC_s t \quad (1)$$

where S is the surface area of the disk, V is the volume of test solution, k is the intrinsic dissolution rate constant, and C_s is solubility. The dissolution rate from the unit surface area, i.e., intrinsic dissolution rate (IDR), is defined by Eq. (2).

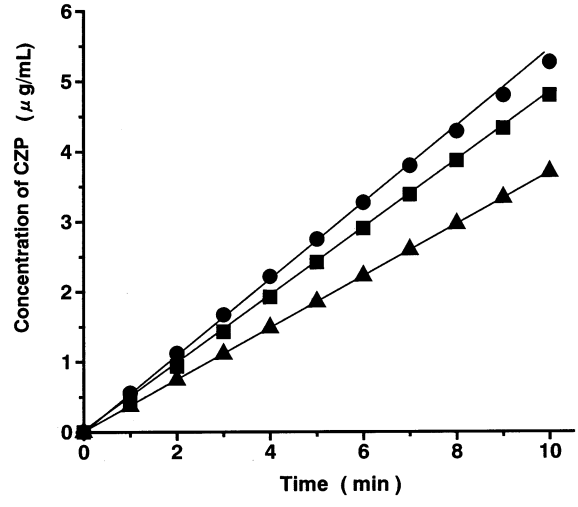

Fig. 4. Dissolution patterns of CZP polymorphs and dibydrate determined by the static disk method in JP13 1st fluid at 37°C, (0–10 min), ■: form I, ●: form III, ▲: dihydrate.

Table 2
Intrinsic dissolution rates (IDR) and solubilities of CZP polymorphs and dihydrate in JP13 1st fluid at 37°C

	IDR (μg/cm²/min)	solubility (μg/ml)
Form I	61.8	460.2[a]
Form III	67.4	501.9[a]
Dihydrate	41.8	311.1[b]

[a] Estimated value.
[b] Determined by dispersion method.

$$\mathrm{IDR} = \frac{C}{t}\frac{V}{S} = kC_s \quad (2)$$

Intrinsic dissolution rates of form I, form III and dihydrate, which were calculated from the slope of each form in Fig. 4, surface area (S) and volume of test solution (V), were 61.8, 67.4 and 41.8 μg/cm²/min (Table 2), respectively. Kaplan (1972) noted that compounds with IDR below 0.1 mg/cm²/min usually exhibited problems with dissolution rate-limited absorption. According to Kaplan's classification, form I, form III and dihydrate belonged to the category of dissolution rate-limited drugs.

The intrinsic dissolution rate constants (k) of form I, form III and dihydrate must be equal, since k depends on the diffusion coefficient and thickness of the diffusion layer.

The intrinsic dissolution rate constant (k) was calculated by substitution of both the obtained solubility (described below) and IDR of dihydrate. The value of k obtained was 0.134 cm/min. Solubilities of form I and form III, which were metastable forms in aqueous medium, could be calculated using k and IDR of form I and form III, respectively. The observed solubility of dihydrate and the estimated solubilities of form I and form III are listed in Table 2. Comparing with the solubility of dihydrate, those of anhydrates were 1.5–1.6 times higher. The solubility of form III was higher than that of form I, while the difference in solubilities between the two anhydrates was relatively small. Kaneniwa et al. (1987) reported the difference in solubilities between anhydrates and hydrate, but the order of solubility of form I and form III was inconsistent with that observed in the present study. Behme and Brooke (1991) reported that form I and form III were enantiotropic and that form I was stable below 71°C. Therefore, the finding that the solubility of form I was less than that of form III appears to be reasonable.

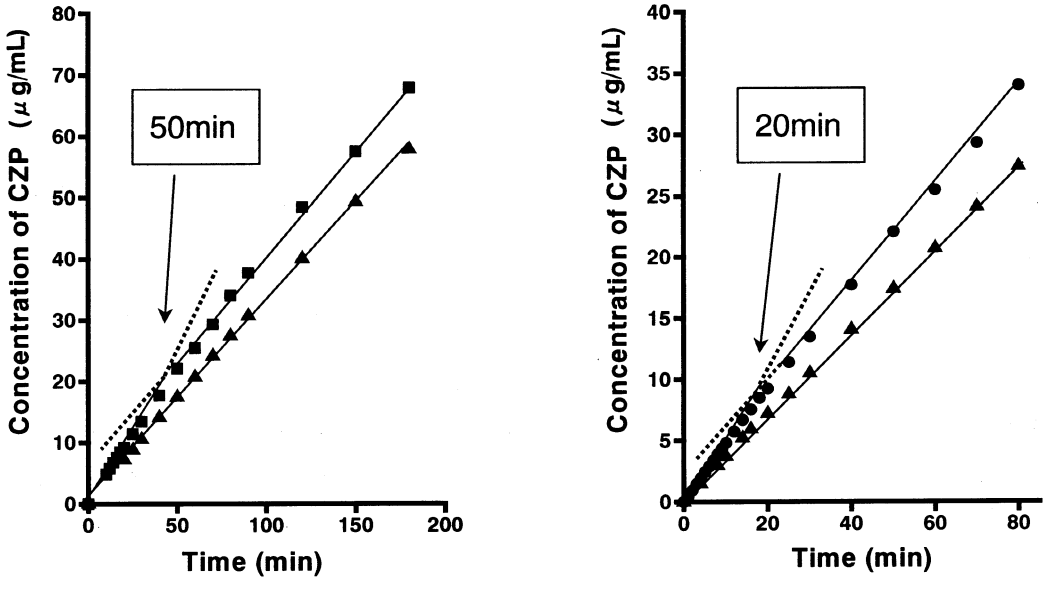

Fig. 5. Dissolution patterns of CZP polymorphs and dihydrate determined by the static disk method in JP13 1st fluid at 37°C, ■: form I, ●: form III, ▲: dihydrate.

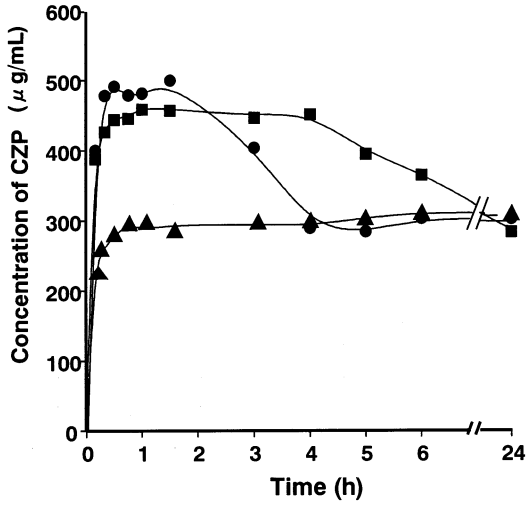

Fig. 6. Dissolution patterns of CZP polymorphs and dibydrate in JP13 1st fluid at 37°C, ■: form I, ●: form III, ▲: dihydrate.

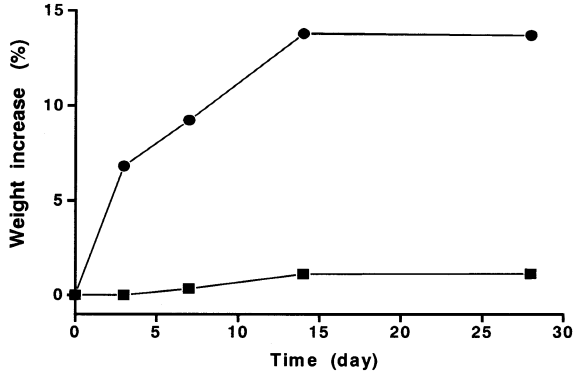

Fig. 7. Hygroscopicity study of polymorphs at 40°C and 98% RH, ■: form I, ●: form III.

The dissolution curves of the individual form for prolonged time periods are shown in Fig. 5. Decreases in dissolution rates of form I and form III were observed after 50 and 20 min, respectively. Differential scanning calorimetry measurement of the surface of the disk after the dissolution test confirmed that both form I and form III were thoroughly transformed to dihydrate. The changes in dissolution rates of anhydrates were due to transformation to hydrate, and the rate of transformation from form III to dihydrate was higher than that from form I. However, the slopes of anhydrates after transformation to hydrate did not completely agree with that of dihydrate (Fig. 5). The inconsistency in dissolution rates of dihydrate and anhydrates after transformation may have been due to changes in the surface area of anhydrate disks accompanied by dissolution of anhydrate and transformation to dihydrate.

4.2.2. Dissolution studies by the dispersion method

The dissolution behaviors of the individual form determined by the dispersion method in JP13 first fluid at 37°C are demonstrated in Fig. 6. Form m exhibited a rapid increase in CZP concentration and the maximum value at the initial stage, then the concentration gradually decreased with precipitation of dihydrate crystals. On the other hand, form I maintained high constant concentration over 4 h. These observations suggested that the transformation from form III to dihydrate was faster than that of form I, which was compatible with the results obtained by using the static disk method.

The maximum concentrations obtained for form I and form III, 459.3 and 499.5 μg/ml, respectively, were in good agreement with the solubilities estimated from the intrinsic dissolution rates of form I and form III (Table 2).

4.2.3. Hygroscopicity studies

The weight increase of form I and form m stored at 40°C and 98% RH for 28 days are exhibited in Fig. 7. Form III exhibited a gradual increase in weight due to water vapor adsorption, and after 2 weeks the water content of form III reached 13.7%, corresponding to the stoichiometric value of the dihydrate (13.2%). On the other hand, the weight increase of form I after 28 days was only 1.9%. The crystalline forms of both form I and form III stored for 28 days were confirmed by powder X-ray diffractometry. For form III, the powder X-ray diffraction pattern was consistent with the pattern of the dihydrate, while for form I the pattern was the same as that before the test (Fig. 8). The results of hygroscopicity studies revealed that form III transformed to dihydrate faster than did form I.

A comparison of crystal data and molecular arrangement between form I and form III was performed by Roberts and Rowe (1996). Both form I and form III formed centrosymmetric dimers via intermolecular hydrogen bonding between the carboxamide groups, however, the crystal systems differed; form I and form III were monoclinic and triclinic, respectively. Form I was more stacked than form III, in which significant hexagonal voids were included in the lattice due to three dimers forming a triangular structure. Consequently, the density of form III(1.24 g/cm^3) was less than that of form I (1.34 g/cm^3). The significant hexagonal void in form III might facilitate the invasion of water molecules into the crystal lattice of form III and accelerate the transformation to dihydrate.

4.3. Bioavailability tests

Since the clinical dose of CZP in humans is increased up to la/day based on clinical efficacy, BA tests in dogs were carried out at a dose of either 40 mg/body or 200 mg/body. Plasma concentration-time curves of form I, form III and dihydrate after oral administration at doses of 40 mg/body and 200 mg/body in dogs are demonstrated in Fig. 9 and Fig. 10, respectively. Pharmacokinetic parameters are shown in Table 3.

With the low dose, the plasma concentration-time curves of the three forms were nearly equal, and there was no significant differences in C_{max}, T_{max}, or AUC among the forms. The BA of each form was more than 80% of the AUC for PEG solution; this BA value was corresponding to relative BA. On the other hand, with the high dose, marked differences in plasma concentration–time curves were found among the three forms. The plasma concentration level of form I was the highest among three forms, while those of form III and dihydrate were similar. The C_{max} of form I was approximately twice those of form III and dihydrate. The AUC of the forms were in the order of form I > form III > dihydrate. The relative BAs of form I and dihydrate were 68.7 and 33.1%, respectively. However, this finding that

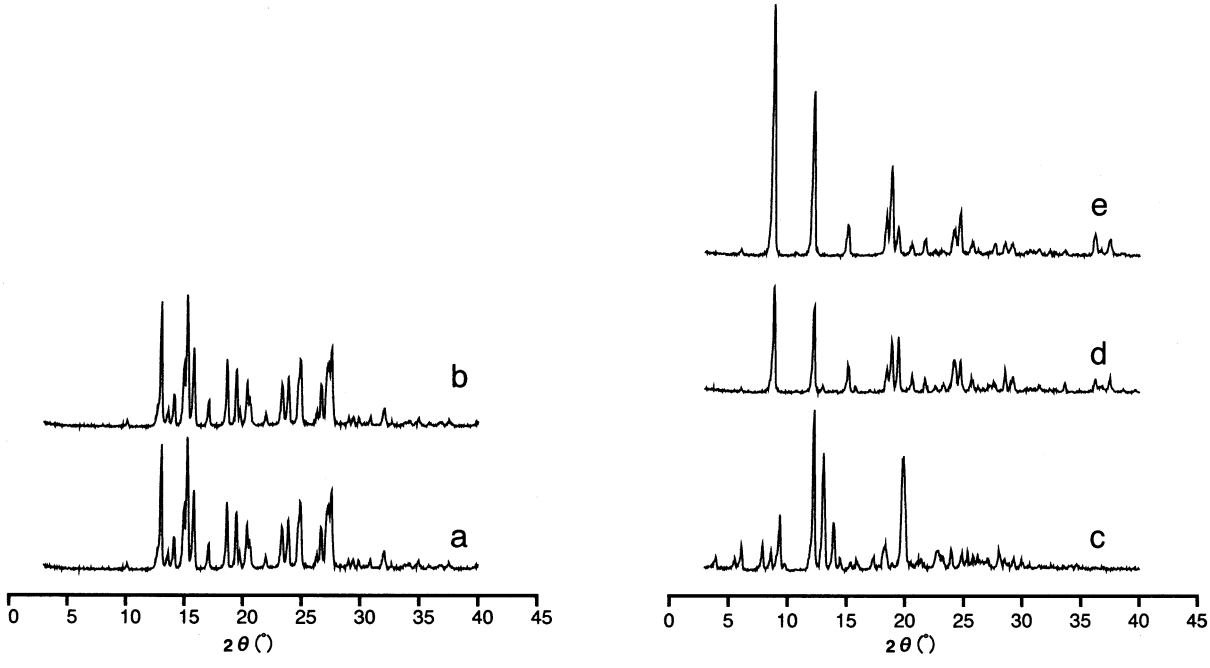

Fig. 8. Powder X-ray diffraction patterns of CZP polymorphs stored at 40°C and 98% RH for 4 weeks. a: Intact form I, b: form I stored at 40°C and 98% RH for 4 weeks, c: intact form III, d: form III stored at 40°C and 98% RH for 4 weeks, e: dihydrate.

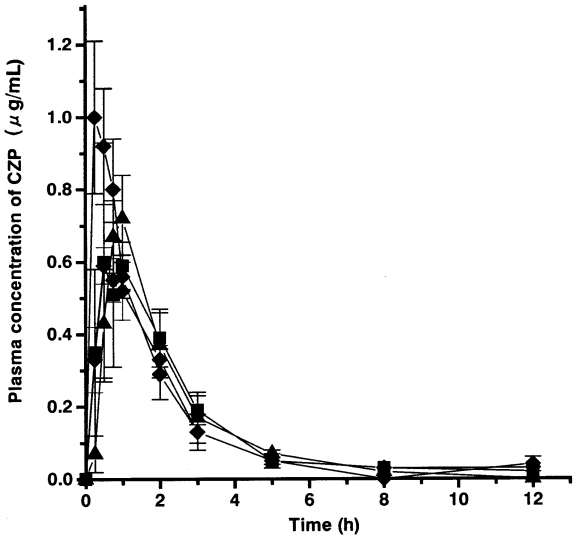

Fig. 9. Plasma concentration–time curves of CZP polymorphs and dihydrate after oral administration to dogs ($n=4$; mean ± S.E.). Dose: 40 mg/body, ◆: solution, ■: form I, ●: form III, ▲: dihydrate.

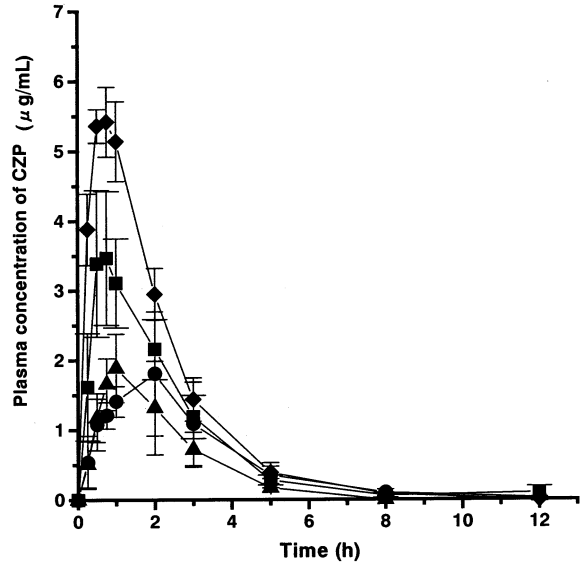

Fig. 10. Plasma concentration–time curves of CZP polymorphs and dihydrate after oral administration to dogs ($n=4$; mean ± S.E.). Dose: 200 mg/body, ◆: solution, ■: form I, ●: form III, ▲: dihydrate.

Table 3
Pharmacokinetic parameters of CZP polymorphs and dihydrate after oral administration in dogs ($n=4$; mean ± S.E.)*

	C_{max} (μg/ml)	T_{max} (h)	AUC (μg.h /ml)	Relative BA (%)
Dose:40 mg/body				
Solution	1.06 ± 0.17^{a}	0.4 ± 0.1^{a}	1.76 ± 0.20^{a}	100.0a
Form I	0.71 ± 0.16^{a}	0.8 ± 0.2^{a}	1.53 ± 0.07^{a}	86.9a
Form III	0.70 ± 0.05^{a}	0.7 ± 0.1^{a}	1.46 ± 0.18^{a}	82.9a
Dihydrate	0.80 ± 0.06^{a}	0.9 ± 0.1^{a}	1.59 ± 0.18^{a}	90.3a
Dose: 200 mg/body				
Solution	5.59 ± 0.45^{a}	0.6 ± 0.1^{a}	13.25 ± 1.20^{a}	100.0a
Form I	4.29 ± 0.41^{b}	1.1 ± 0.4^{a}	9.10 ± 1.00^{b}	68.7 b
Form III	2.36 ± 0.65^{c}	1.3 ± 0.4^{a}	$6.33 \pm 2.39^{b, c}$	47.8 b'C
Dihydrate	1.90 ± 0.38^{c}	0.8 ± 0.1^{a}	4.39 ± 1.30^{c}	33.1c

* Different superscripts indicate significant differences among the means ($P<0.05$) and same superscripts indicate no significant difference.

form I had higher BA than form III, was inconsistent with the thermodynamic stability.

The similarity in BA of the three crystal forms when administered at a dose of 40 mg/body could be explained by the dissolution behavior of each form; most of the administered samples dissolved in the gastrointestinal tract. This consideration was also supported by the high relative BAs for each form as compared with that for PEG solution. On the other hand, with the high dose (200 mg/body), the dissolution property of each form might have affected the plasma concentration of CZP, since most of the administered powder could not dissolve in the GI tract due to low solubility and excess dose. The finding of lowest solubility of dihydrate among the three forms

could account for the finding of lowest AUC of dihydrate. The differences in BA and thermodynamic stability between form I and form m should be attributed to the more rapid transformation from form III to dibydrate than that from form I. This consideration for the relationship between BAs of form I and form III was supported by the similar plasma concentration–time profiles of form m and dihydrate as administered orally at high dose. The S.E.s of C_{max} and AUC for form III were larger than those for the other forms. The scatter of form III parameters was due to variability in effects on transformation from form III to dihydrate of motility, pH and volume of the individual GI tract.

In this study, results of evaluation of BA for form I, form III and dihydrate CZP in dogs differed between doses administered (40 mg/body and 200 mg/body). Assessment of BA for water-insoluble compounds with polymorphism or pseudopolymorphism should be performed with various doses.

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