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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.

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.

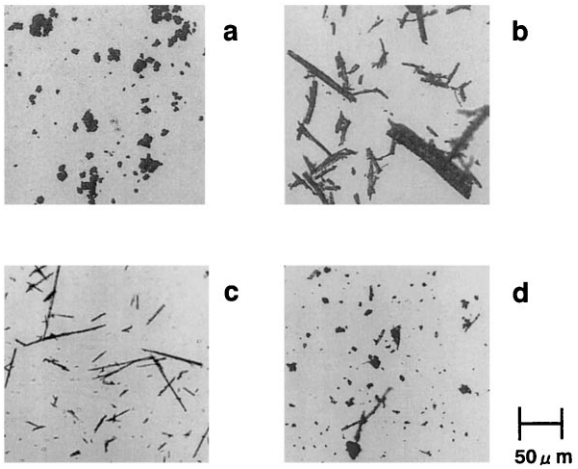

Fig. 1. Microscopic photographs of CZP samples. a: Sample A, b: Sample B, c: Sample C, d: Sample B′.

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/

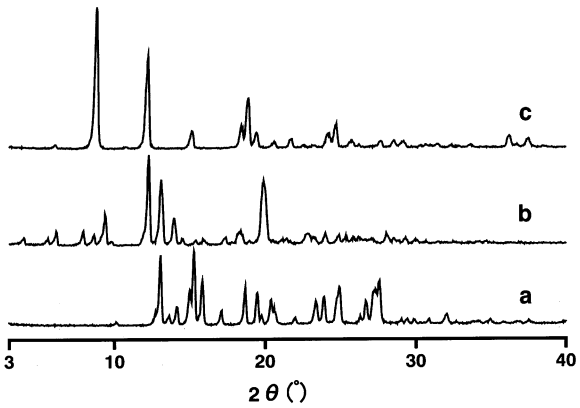

Fig. 2. Powder X-ray diffraction patterns of CZP samples. a: Sample A, b: Sample B′, c: Sample C.

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 2θ = 15.2, 15.8 and 17.0° for sample A, 2θ = 6.1, 9.4 and 19.9° for sample B′ and 2θ = 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

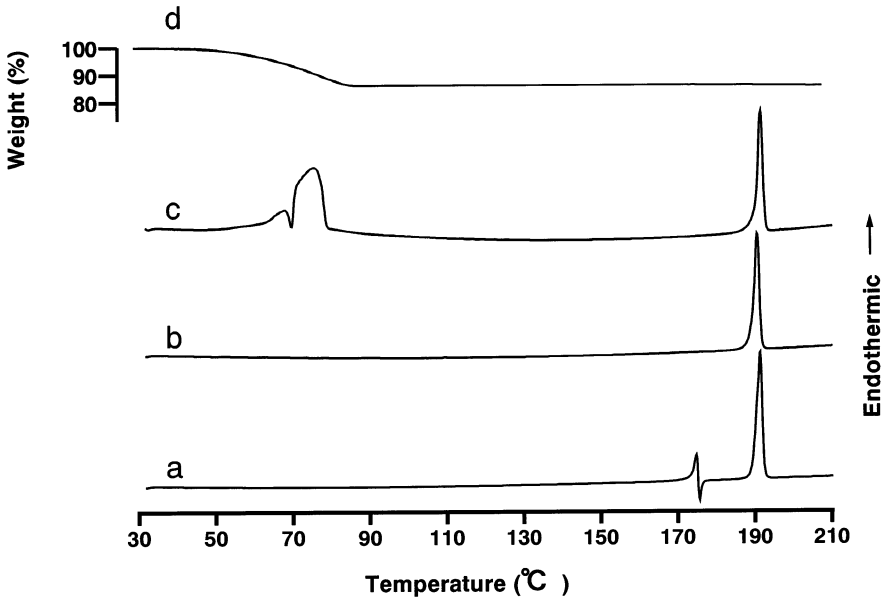

Fig. 3. DSC and TG curves of CZP samples. a: DSC curve of Sample A, b: DSC curve of Sample B′, c: DSC curve of Sample C, d: TG curve of Sample C.

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).

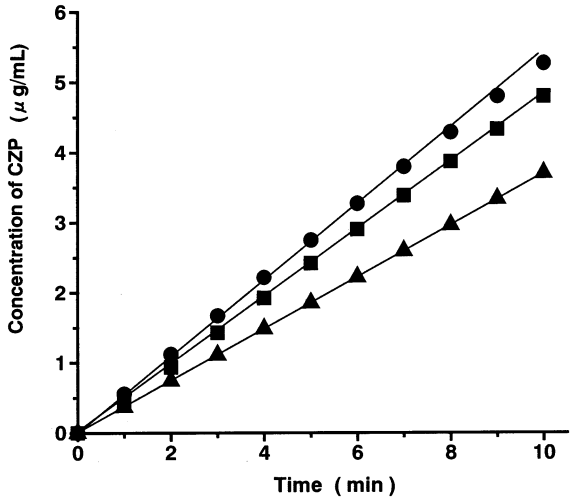

Fig. 4. Dissolution patterns of CZP polymorphs and dibydrate determined by the static disk method in JP13 1st fluid at 37°C, (0–10 min), ■: form I, ●: form III, ▲: dihydrate.

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