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Crystal Form of Cephradine

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Four crystal forms of cephradine were isolated by recrystallization and characterized by powder X-ray diffractometry, differential scanning calorimetry, and thermogravimetric analysis. The dissolution patterns of four crystal forms of cephradine were studied in water at 37±0.5°C, 90 rpm for 120 min. The amount dissolved at 120 min was highest for Form I (100%), followed by Form 3 (98.9%), Form 4 (77.83%), and Form 2 (75.55%). After storage for two months at 0% RH (silica gel, 20°C), 52% RH (saturated solution of $Na_2Cr_2O_7 \cdot 2H_2O$/20°C), and 95% RH (saturated solution of Na_2HPO_4/20°C), none of the crystal forms showed transformation.

Key words: Cephradine, Crystal form, Polymorphism, Solubility, Transformation

INTRODUCTION

Pharmaceutical solids can exist in different crystal forms, such as crystalline, amorphous, or glass, and also in solvated or hydrated states (Haleblian and McCrone, 1969; Haleblian, 1975; Hüttenrauch, 1998). Polymorphism is defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Polymorphs share the same chemical composition but have different crystal structures. Because of their structural differences, polymorphs may have different physicochemical properties. For example, polymorphs can have different density, habit, melting properties, vapor pressure, solubility, dissolution rate, tableting and mechanical properties (Higuchi *et al.*, 1963; Haleblian and McCrone, 1969; Haleblian, 1975; Grünenberg, 1997; Hüttenrauch, 1998). Identification of possible hydrate compounds is also important since their aqueous solubilities can be significantly less than their anhydrous forms (Shefter and Higuchi, 1963; Kuhnert-Brandstätter, 1973; Sohn, 2004). Conversion of an anhydrous compound to a hydrate within the dosage form may reduce the dissolution rate and extent of drug absorption.

If the rate of absorption of the active ingredient in an oral preparation is dissolution-rate dependent, the use of a compound exhibiting polymorphism may lead to good or bad consequences. The successful utilization of a polymorph of significantly greater thermodynamic activity (*i.e.*, solubility) than the stable modification may provide, in some instances, therapeutic blood levels from otherwise inactive drugs. On the other hand, when the existence of multiple crystalline modifications goes unrecognized in a particular formulation, this may possibly result in unacceptable dose-to-dose variations in drug availability to the patient.

Evaluation of the solubility of a drug substance is of extreme importance in the drug development process, since it must become dissolved in a fluid medium for it to have its intended therapeutic effect. Cephradine belongs to the first generation cephalosporin antibiotics. Cephradine has a low solubility for the most of the solvents. Therefore, the aim of this study was to investigate the existence of crystal forms of cephradine and the effect of these different polymorphs on the solubility and dissolution rate.

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MATERIALS AND METHODS

Materials

Cephradine was provided by Yu Han Pharmaceutical Co. Ltd., Korea. Other extra pure chemicals were purchased from a reagent commercial company.

Preparation of crystal forms

Form 1

Form 1 was provided by Yu Han Pharmaceutical Co. Ltd.

Form 2

A suspension of Form 1 (200 mg) in ethylene glycol and acetonitrile (2:5) was heated to 40°C for 30 min. The resulting solution was vigorously stirred with acetonitrile. The resulting solid was filtered and dried for one week in a desiccator to give Form 2.

Form 3

A suspension of Form 1 (200 mg) in ethylene glycol and acetonitrile (3:5) was heated to 40°C for 30 min. The resulting solution was vigorously stirred with acetonitrile. The resulting solid was filtered and dried for one week in the desiccators to give Form 3.

Form 4

A suspension of Form 1 (200 mg) in methyl alchol (50 mL) was heated to 40°C for 30 min. The hot solution was filtered to remove most nuclei and then left undisturbed for two weeks at room temperature. The resulting solid was filtered and dried for one week in the desiccator to give Form 4.

Powder X-ray diffraction

Powder X-ray diffraction patterns under ambient conditions were collected on Rigaku DMAX-IIIA (Japan) diffractometer using graphite monochromatized CuKα radiation (λ=1.54178 Å). The 2Θ range was 5-30°, step size 0.02°, integration time 10 s/step, divergence and receiving slit set to a constant (6 mm) length of the illumination of the sample and receiving slit was 0.2 mm. The isothermal measurement conditions were; target, Cu; voltage, 30 kV, current, 10 mA. The PXRD patterns of the samples were compared with regard to peak position and relative intensity, peak shifting, and the presence of lack of peaks in certain angular regions.

Thermal analysis

The thermal analysis methods used in this study included differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) (Kuhnert-Brandstätter and Lehner, 1984; Giron, 1995). DSC patterns were recorded with a Shimadzu DSC-50 instrument (Shimadzu, Kyoto, Japan). The temperature was usually scanned from 40 to 250°C at 10°C/min. 5 mg of sample was used for each study. TG analysis was performed on all samples indicated by DSC as being possible solvates or hydrates. TGA patterns were recorded with a Shimadzu TGA-50 instrument (Shimadzu, Kyoto, Japan). The temperature was usually scanned from 20 to 300°C at 10°C/min. A 5 mg of sample was used for each study.

Dissolution

The dissolution rate was measured according to the dissolution test (paddle method) of the Korean Pharmacopoeia (Eighth Edition). The paddle was rotated at 90 rpm for 120 min. Certain amount of crystal forms (30 mg, <100 mesh) was exposed to 1000 mL of distilled water equilibrated at 37±0.5°C. A UV detection method was used to determine the concentrations of the samples (Hewlett Packard 8452A). The UV wavelength was set at 262 nm.

Transformation of crystal forms

Certain amounts (20 mg) of the crystal forms were taken and placed in weighing dishes. They were stored in a desiccator of 0% RH (silica gel, 20°C), 52% RH (saturated solution of $Na_2Cr_2O_7 \cdot 2H_2O$/20°C), and 95% RH (saturated solution of Na_2HPO_4/20°C).

The transformation behavior of polymorphs was monitored by powder X-ray diffraction (XRD) analysis, DSC and TGA.

RESULTS AND DISCUSSION

Differential scanning calorimetry curves of Form 1, Form 2, Form 3, and Form 4 are illustrated in Figs. 1-4. The DSC curve of Form 1 exhibited an exothermic peak at 194-196°C. The DSC curve of Form 2 exhibited an endothermic peak at 139.25°C. The DSC curve of Form 3 exhibited an exothermic peak at 158.53°C. The DSC curve of Form 4 exhibited an endothermic peak at 88.81°C followed by an exothermic peak at 190.58°C.

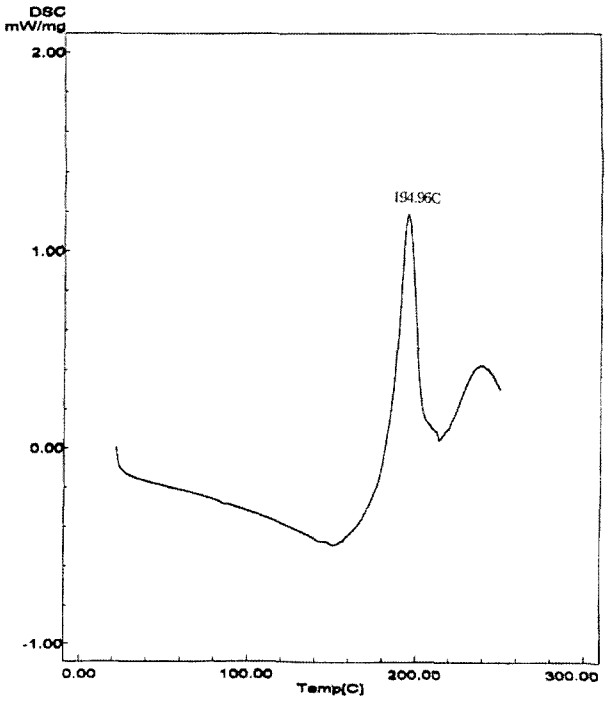

Fig. 1. DSC thermograms of Form 1

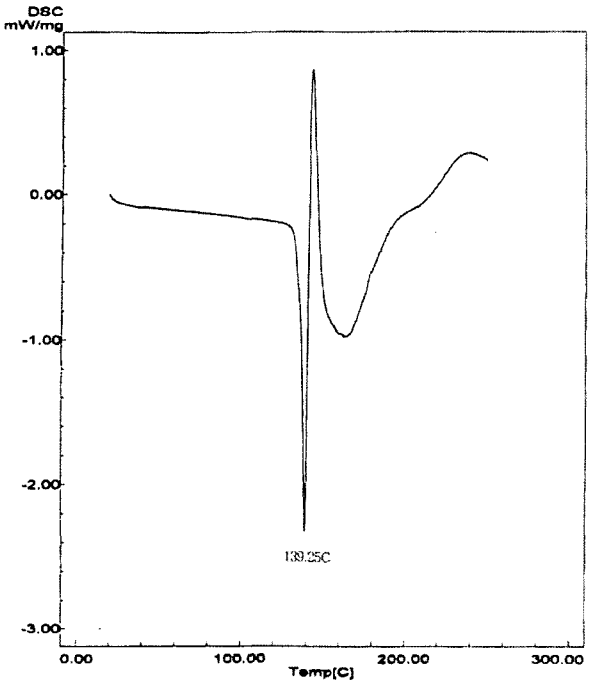

Fig. 2. DSC thermograms of Form 2

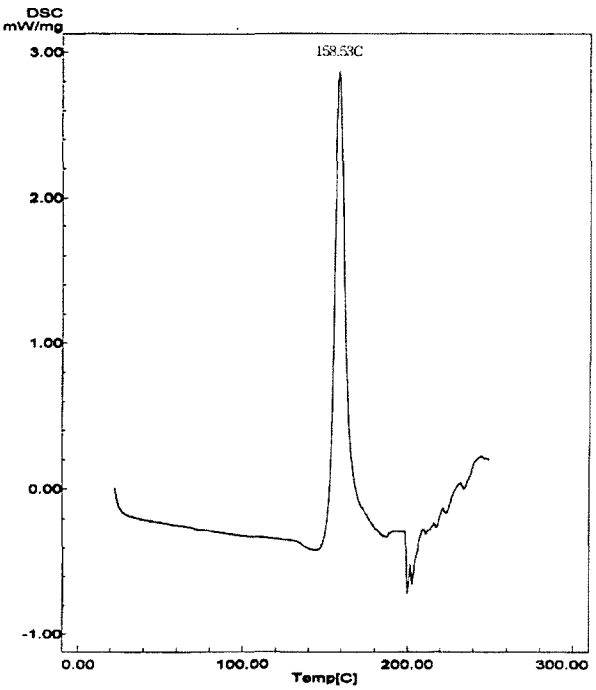

Fig. 3. DSC thermograms of Form 3

The Powder X-ray diffraction patterns of Form 1, Form 2, Form 3, and Form 4 are illustrated in Fig. 5-8, and they showed distinct differences. Tables I-IV list the 2-theta angle where the main differences in the diffraction patterns of four crystal forms can be found.

Examination of the TGA curves of Form 1, Form 2, Form 3, and Form 4 (not shown) proved that these crystal

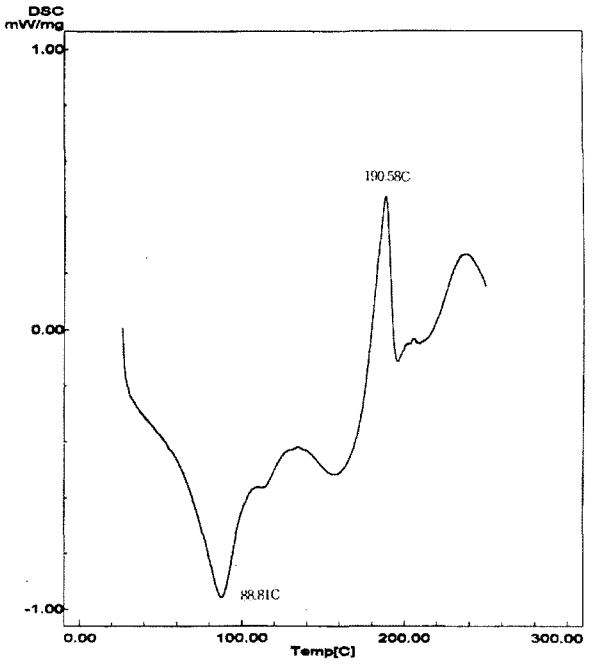

Fig. 4. DSC thermograms of Form 4

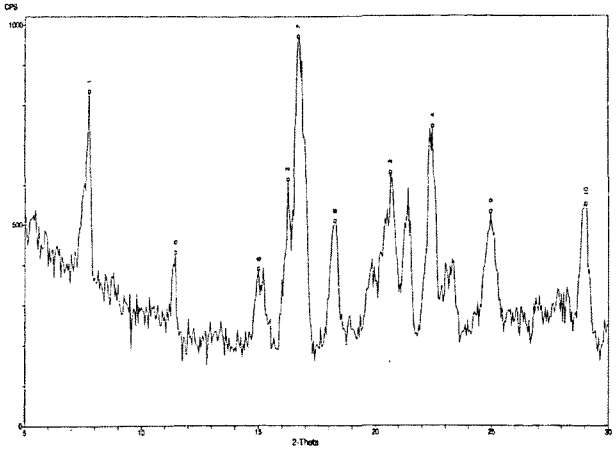

Fig. 5. Powder X-ray diffraction patterns of Form 1

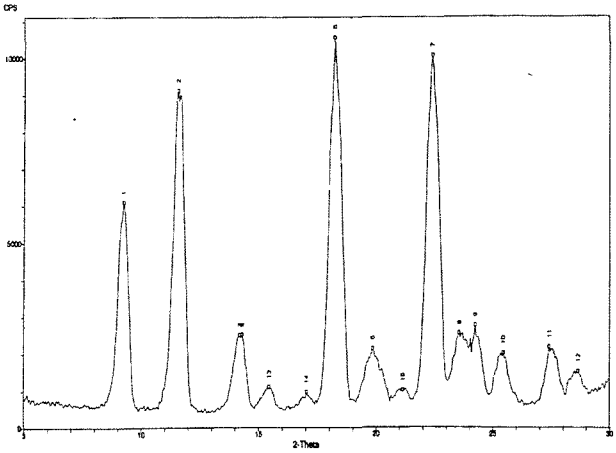

Fig. 6. Powder X-ray diffraction patterns of Form 2

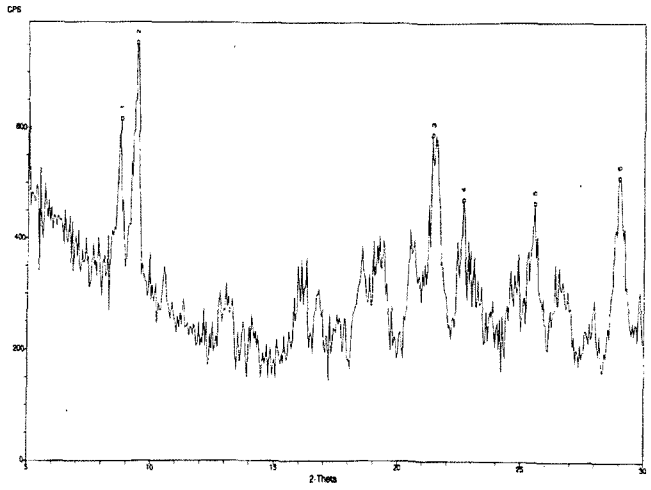

Fig. 7. Powder X-ray diffraction patterns of Form 3

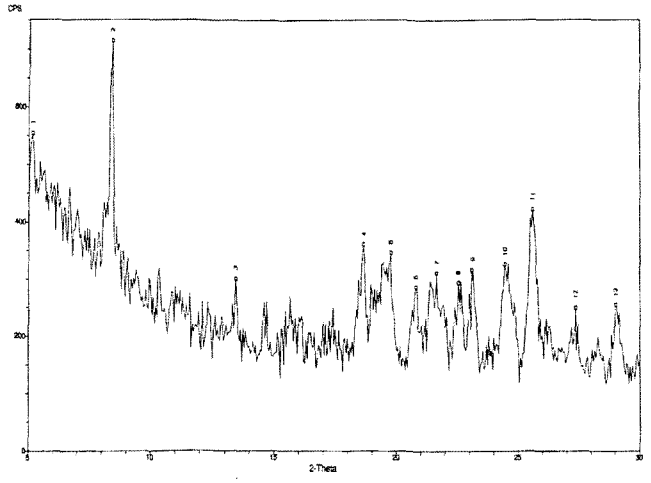

Fig. 8. Powder X-ray diffraction patterns of Form 4

Table I. Characteristic diffraction peaks of Form 1 up to 30°

2Θ	d-space	ratio
7.75	11.407	92
11.45	7.72	47
15	5.906	43
16.25	5.454	67
16.7	5.308	100
18.25	4.861	56
20.65	4.301	69
22.45	3.96	82
24.95	3.569	59
29.05	3.074	61

forms were non-solvated forms.

The dissolution patterns of four crystal forms were studied in distilled water at 37±0.5°C, 90 rpm for 120 min (Fig. 9). Four crystal forms showed differences in the dissolution profile. The amount dissolved at 120 min was highest for Form I (100%) followed by Form 3 (98.9%),

Table II. Characteristic diffraction peaks of Form 2 up to 30°

2Θ	d-space	ratio
9.25	9.56	58
11.55	7.661	86
14.2	6.237	24
14.3	6.194	24
18.25	4.861	100
19.85	4.473	20
22.4	3.969	95
23.55	3.778	24
24.25	3.67	26
25.45	3.5	19
27.4	3.255	21

Table III. Characteristic diffraction peaks of Form 3 up to 30°

2Θ	d-space	ratio
8.75	10.106	93
9.4	9.408	100
21.4	4.152	90
22.65	3.926	76
25.55	3.486	75
29	3.079	83

Table IV. Characteristic diffraction peaks of Form 4 up to 30°

2Θ	d-space	ratio
5.15	17.159	78
8.4	10.526	100
13.45	6.583	42
18.65	4.758	51
19.75	4.495	49
20.8	4.27	40
21.65	4.105	44
23.1	3.85	44
24.45	3.641	46
25.6	3.48	59

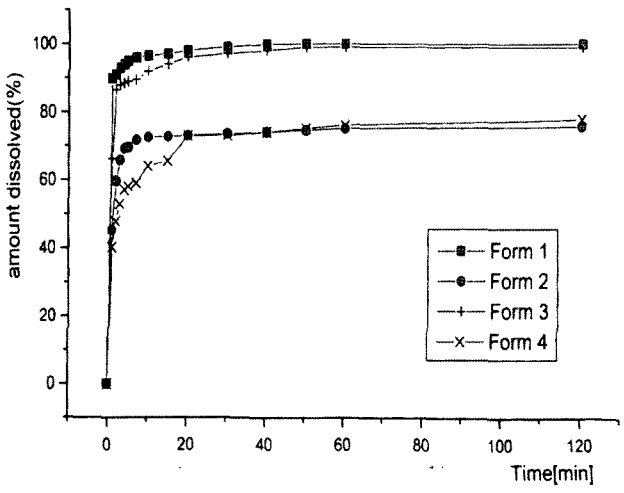

Fig. 9. Dissolution profiles of four crystal forms

Form 4 (77.83%), and Form 2 (75.55%).

The solubility of a drug substance is very important in the drug development process, because it needs to be dissolved in a fluid medium for it to have its intended therapeutic effect. Therefore, we presume that these results may be applied to improve bioavailability of cephradine.

After storage for two months at 0% RH (silica gel, 20°C), 52% RH (saturated solution of $Na_2Cr_2O_7 \cdot 2H_2O$/ 20°C), and 95% RH (saturated solution of Na_2HPO_4/ 20°C), all crystal forms showed no transformation.

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