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Crystal Forms of Ketorolac

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Four crystal forms of ketorolac have been obtained by recrystallization in organic solvents under variable conditions. Different ketorolac polymorphs and pseudopolymorph were characterized by X-ray powder diffraction crystallography (XRD), Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). In the dissolution studies in water at 37±0.5°C, four crystal forms showed different patterns. The solubility of Form I were the highest. The solubility decreased in rank order: Form I > Form II > Form III > Form IV. Form Iand Form III were shown to have a good physical stability at room temperature for 60 days. However, Form II is converted to Form III and Form IV is converted to Form I after 60 days storage. Therefore, these observations indicate that crystalline polymorphism for ketorolac is readily inter-convertible and the relationship may have to taken into consideration in the formulation of the drug.

Key words: Ketorolac, Crystalline polymorphism, X-ray powder crystallography, Differential scanning calorimetry, Thermogravimetric analysis

INTRODUCTION

Pharmaceutical solids can exist in different crystal forms, such as crystalline, amorphous, or glass, and also in solvated or hydrated states (Borka, 1991; Haleblian *et al.*, 1969; Haleblian, 1975; Kuhnert-Brandstaetter, 1973; Lachman *et al.*, 1986; Sohn, 1995). In general, polymorphism defines 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, melting properties, vapor pressure, solubility, dissolution rate, tabletting and mechanical properties (Kuhnert-Brandstaetter, 1973; Haleblian, 1975), and, ultimately, bioavailability (Sohn, 1995; Sohn *et al.*, 2002).

A stoichiometric adduct, commonly referred to as a solvate, is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called a hydrate. Identification of possible hydrate compounds is important since their aqueous solubilities can be significantly less than their anhydrous forms. Conversion of an anhydrous compound to a hydrate within the dosage form may reduce the dissolution rate and extent of drug absorption (Shefter *et al.*, 1963; Sohn, 1991; Sohn *et al.*, 1993; Sohn *et al.*, 1996). However, crystalline polymorphism for ketorolac has not been systematically studied in the literature. Therefore, the aim of this study was to investigate the existence of different crystal forms of ketorolac, nonsteroidal anti-inflammatory agent.

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MATERIALS AND METHODS

Materials

Ketorolac was donated from Pacific Co. Ltd., Seoul, Korea. Other chemicals and solvents were of analytical regent or special grade.

Preparation of crystal forms of ketorolac

Form I is the ketorolac standard and donated one, which is identical to solid phase of recrystallization from methanol. Form II was obtained by dissolving in 1,4-dioxane (150 mg/mL) at 25°C. The un-dissolved drug was filtered off and the resultant solution was then cooled at 5°C. The obtained crystals were separated by filtering under reduced pressure and dried over silica gel in a desiccator at 25°C.

Form III was prepared by dissolving in 1,4-dioxane (150

mg/mL) at 25°C. The un-dissolved drug was filtered off and the resultant solution was then cooled at -10°C. The obtained crystals were separated by filtering under reduced pressure and dried as described for Form II. Form IV was obtained by dissolving in 1,4-dioxane (150 mg/mL) at 25°C. The undissolved drug was filtered off and the resultant solution was then cooled at -72°C. The obtained crystals were separated by filtering under reduced pressure and dried as described for Form II.

Identification and characterization

X-ray powder diffraction (XRD) patterns were obtained with a Rigaku DMA S-IIIA with Cu Ka radiation over the interval 5-30°/2θ. The measurement conditions were as follows. Target, Cu; filter, Ni; voltage, 30 kV; current, 20 mA. Differntial scanning calorimetry (DSC) curves of the different crystalline forms were recorded on a Mettler Toledo, DSC 12E thermal analyzer. The thermal behavior was studied by heating the crystal forms in a covered sample pan over the temperature range 35-300°C at a heating rate of 10°C/min.

Thermogravimetric analysis (TGA) was carried out on thermogravimetric system (Seiko I SSC-5000) by recording mass loss of solvate over the temperature range 35-300°C at a heating rate of 10°C/min.

Dissolution test

The dissolution tests were according to the Korean Pharmacopeia paddle method using a rotational speed of 100 rpm at 37±0.5°C. A fixed amount (10 mg, <100 mesh) of ketorolac crystal forms was placed into 1 L distilled water (pH 6.7) and at an appropriate intervals, and an aliquot (1 mL) was withdrawn with a syringe and filtered through a 0.45 μm membrane filter (Millipore). In this study, 1 mL water at same temperature was replaced in the dissolution vessel. The concentration was spectrophotometrically determined at 322 nm using a Hewlett Packard HP 8452A diode-array spectrophotometer.

Stability

Samples of ketorolac crystal forms were stored in saturated salt solutions of two relative humidities (75%, 0%) in desiccators at 20±0.5°C for 60 days.

RESULTS AND DISCUSSION

Characterization of crystal forms of ketorolac

The XRD patterns of the four crystal forms of ketorolac are shown in Fig. 1. The XRD patterns of the four crystal forms are quite different, indicating that the four crystalline forms are indeed different. The XRD patterns were consistent with the fact that the four DSC patterns (Fig. 2) were also different. DSC profiles obtained for Form I, Form II, and Form III showed sharp endotherm peaks corresponding to the melting of ketorolac at 158°C, 157°C,

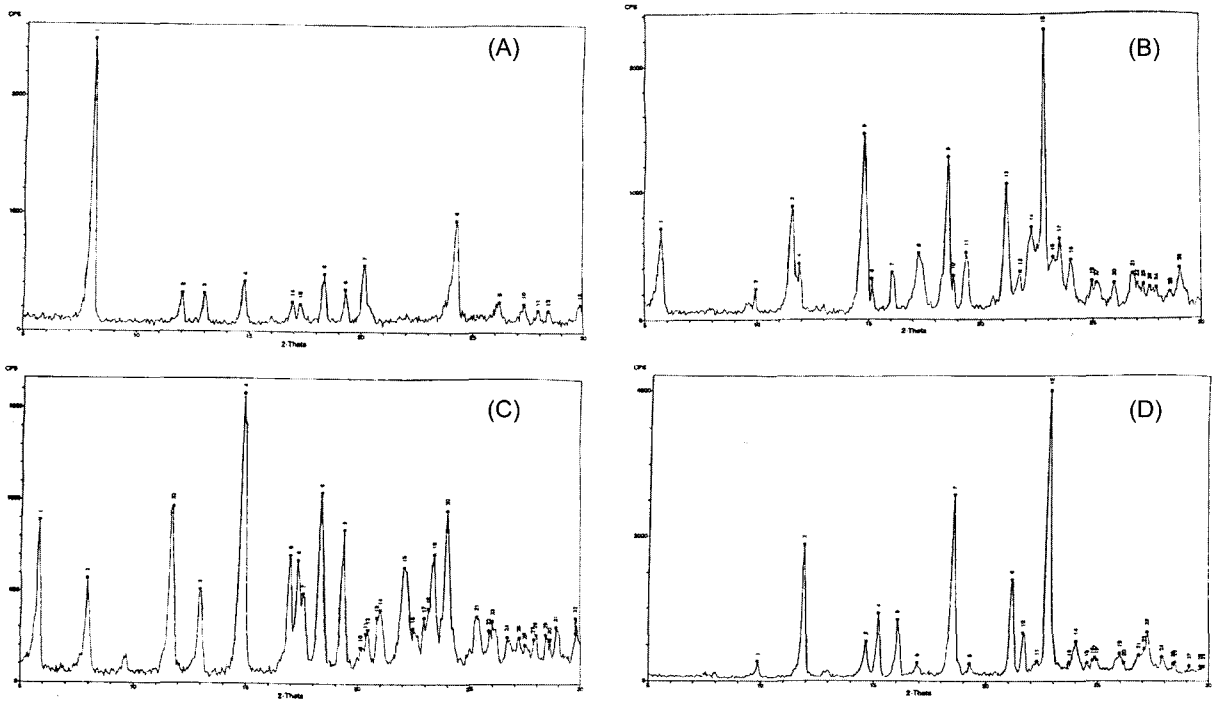

Fig. 1. X-ray diffraction patterns for ketorolac crystalline forms. Panel A, the pattern for Form I; Panel B, the pattern for Form II; Panel C, the pattern for Form III; Panel D, the pattern for Form IV.

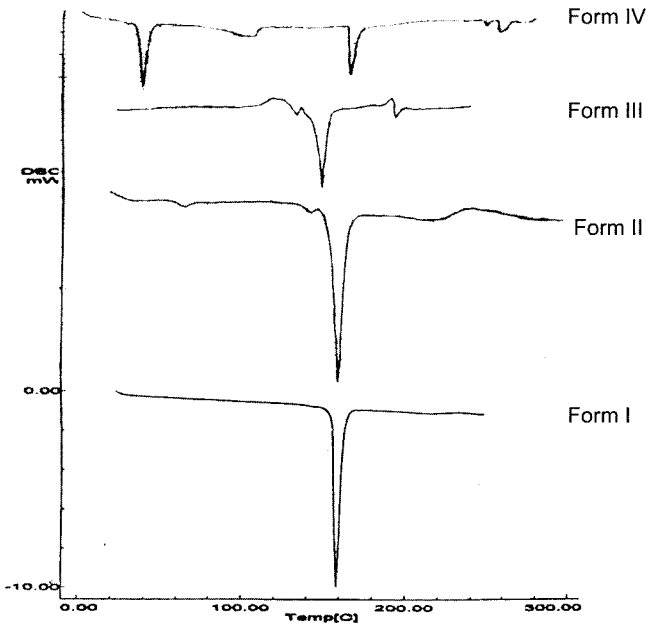

Fig. 2. DSC curves of four crystal forms of ketorolac

and 153°C, respectively. The heats of fusion for Form I, Form II, and Form III were 26.8 cal/g, 160.8 cal/g, and 23.8 cal/g, respectively. Form IV had two endothermic peaks at 61°C and 191°C and their heats of fusion were 9.3 cal/g and 6.7 cal/g.

Fig. 3 showed TGA curves of the four crystal forms of ketorolac. According to the analysis, Form I, II and III are not apparently solvates. In contrast, however, Form IV showed the weight loss of a desolvation at 55-67°C. Considering the fact that dioxane was used as a solvent in the preparation of the crytal, an 1:1 molar ratio of ketorolac to dioxane was calculated, and therefore Form IV is likely to be a pseudopolymorph.

Dissolution behavior of crystal forms of ketorolac

Fig. 4 shows dissolution profiles of ketorolac crystal forms in distilled water at 37±0.5°C. The solubility of Form I was the highest. The solubility decreased in rank order: Form I > Form II > Form III > Form IV. The solubility of Form IV was 64% of Form I after 5 h.

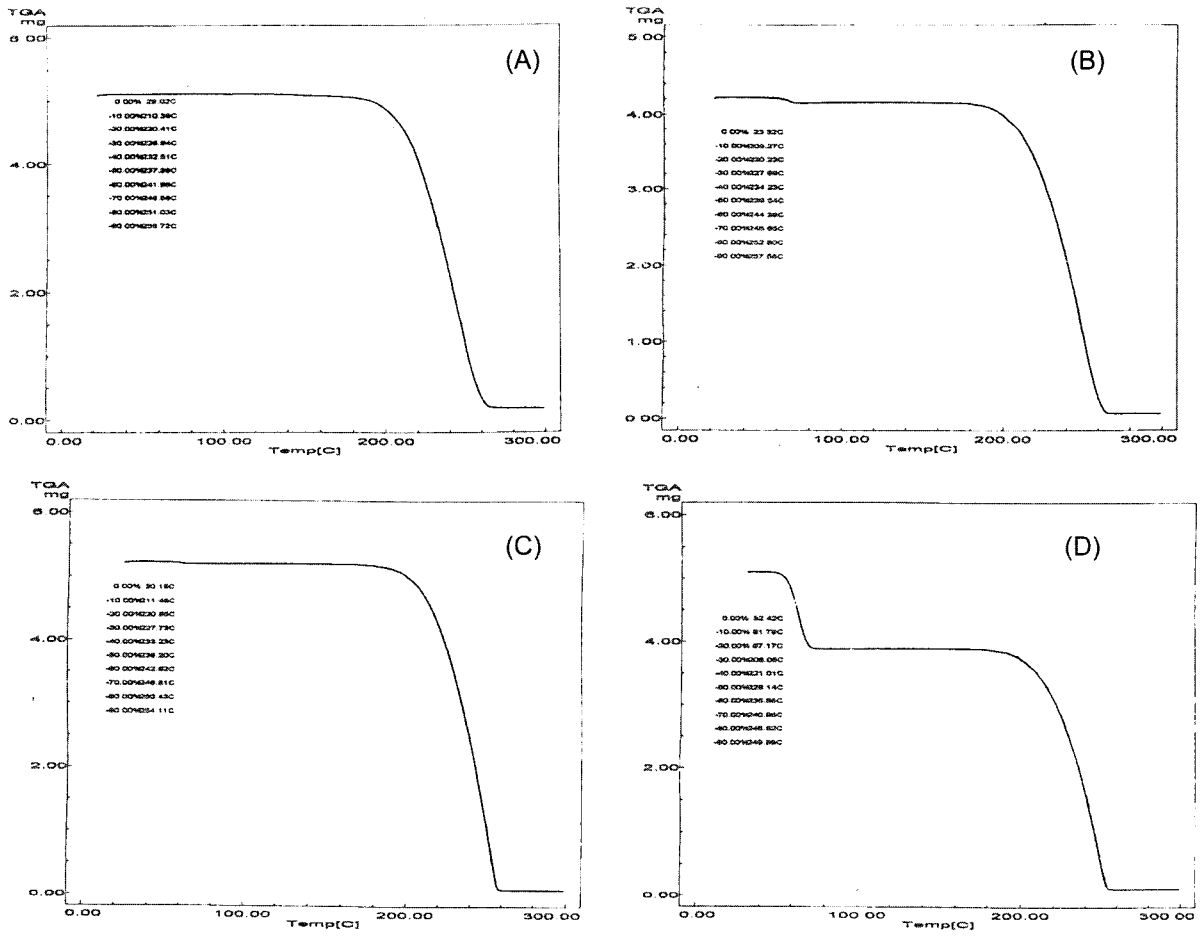

Fig. 3. TGA curves for ketorolac crystalline forms. Panel A, the curve for Form I; Panel B, the curve for Form II; Panel C, the curve for Form III; Panel D, the curve for Form IV.

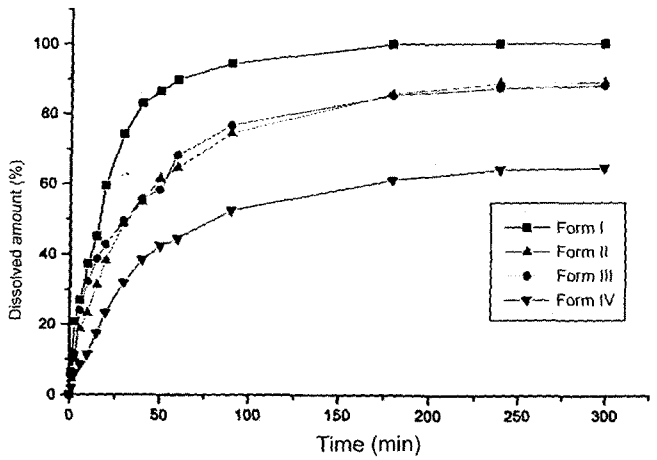

Fig. 4. Dissolution profiles of different crystalline forms for ketorolac

Transition behavior of crystal forms of ketorolac

After 60days storage at 75% and 0% RH, DSC and XRD analyses showed that Form I and Form III were quite stable. In contrast, however, Form II and Form IV were thermodynamically unstable. In addition, after 60 days storage, DSC and XRD analyses showed that Form II is transformed to Form III and Form IV is transformed to Form I. The pharmaceutical impact on the inter-conversion of the crystalline forms for ketorolac has not been studied extensively in the literature. However, in this study, Form II was found to be transformed to Form III, a less soluble form and Form III was quite stable during the storage. Therefore, these observations indicate that an extensive storage of ketorolac may lead to a formation of the less soluble form. The potential alteration in the overall solubility for ketorolac has to be taken into consideration for the formulation of the non-steroidal anti-inflammatory agent.

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