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Research paper

Analysis of the stabilization process of indomethacin crystals via π–π and CH–π interactions measured by Raman spectroscopy and X-ray diffraction

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ABSTRACT

In this study, formations of π–π and CH–π interactions in the crystallization of amorphous indomethacin (IMC) were investigated by simultaneous Raman spectroscopy and X-ray diffraction (XRD) measurements. The activation energy obtained from the change in the peak at 1616 cm^{-1} corresponded to the energy obtained from the XRD diffraction peak at 21.6°. We suggest that the stable IMC crystal forms by carboxyl-carboxyl interactions, which is followed by CH–π and π–π interactions supporting stabilization in the indole and chlorophenyl rings.

1. Introduction

There are a number of poorly soluble drugs. In pharmaceutical sciences, increasing the water solubility of drugs is one of the most important methods of improving bioavailability. Amorphous solids of poorly soluble drugs have been widely used to increase solubility; however, the physical stability is simultaneously reduced. The physical stability of the amorphous state is determined by several factors such as perturbations in temperature [1], humidity [2–4], pressure [5–7], and the preparation methods [8,9]. The mechanisms of instability and the effects of the perturbations on crystallization are complicated, and also depend on the chemicals used.

Indomethacin (IMC) is poorly soluble in water, and is used as a model drug to investigate the stability of amorphous solids [4,10–12]. The amorphous solids of IMC are mainly prepared by two methods, melt-quenching and milling [9,11,12]. In previous studies, crystallization of the amorphous solids of IMC was investigated by differential scanning calorimetry (DSC) and terahertz spectroscopy [9]. The amorphous solids showed individual DSC profiles and a total heat of fusion depending on the history of preparations. According to the results of the previous work, the milled amorphous solid was less stable than the melt-quenched amorphous solid [9]. In this study, the milled amorphous solid of IMC was used to investigate the mechanisms of its instable state.

X-ray diffraction is commonly used to determine crystalline polymorphs of organic and inorganic compounds, however XRD has a lower limit of detection of crystalline size [8,13]. Alternatively, the combination of XRD with Raman spectroscopy and DSC has been suggested for this purpose, and Taylor and Zografi reported that Raman spectroscopy is a precise technique to investigate the crystalline polymorphs and the amorphous state of IMC [14,15]. According to previous reports, Raman spectra in the range of 1500–1800 cm^{-1} included C=O stretching and was adequate to determine the crystallinity. On the other hand, Hédoux and Descamps reported that low-frequency Raman spectroscopy was more sensitive for detecting crystals in the micro- and nano-domains [8,11]. They applied low-frequency Raman spectroscopy to investigate changes in the long-range order interaction in the crystallization process of milled indomethacin. However, the peaks of the low-frequency Raman spectra are still unassigned to vibrational modes. Despite reports that micro- and nano-domains in solids are not detectable by XRD, a certain definition of the limit of detection has not been reported. The limit may depend on the compound. In this study, we prepared a system collecting Raman spectra concurrently with XRD to provide a link between micro- or nano-domains and the macro-domains in crystal solids.

Although, the previous reports focused only on the change in the Raman signal due to C=O stretching with the crystallization, there are other signals in the Raman spectra of IMC, such as vibrations of indole and aromatic rings. Cox et al. reported that face-to-face π–π interaction and edge-to-face CH–π interaction supported

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the stable crystalline structure [16]. The π systems of the indole and chlorophenyl rings have a two-dimensional structure which contributes strongly to form X-ray diffraction planes. The stable γ-form of IMC crystals is poorly soluble in water, which is mainly supported by the π–π and CH–π interactions. Hence, the stability and solubility in water can be evaluated by the interactions in the π systems. The objectives of this study were to make assignments to the Raman signals regarding crystal stability and to examine the formation of stable IMC crystal structure by investigating the π–π and CH–π interactions using XRD and Raman spectroscopy.

2. Material and methods

2.1. Materials

Indomethacin ($C_{19}H_{16}ClNO_4$, Lot: JOQOB-SD, IMC) was purchased from Tokyo Chemical Industry (Tokyo, Japan). The chemical structure was shown in Fig. 1. For preparing the amorphous solid of IMC, crystalline bulk powder (5 g) was fed into an agate jar (500 mL) with 10 agate balls (ϕ 20 mm), and milled via a planetary ball mill (P-6, Fritsch, Idar-Oberstein, Germany) at 14.1 G for 4 h.

2.2. Methods

2.2.1. Differential scanning calorimetry (DSC) measurements

The DSC profile of the amorphous IMC was determined using a differential scanning calorimeter (DSC-8230, Rigaku) at a constant heating rate of 0.5 K/min. Approximately 5 mg of sample and reference (Al_2O_3) were used.

2.2.2. Simultaneous measurements using X-ray diffraction (XRD) and Raman spectroscopy

The simultaneous measurement system was composed of an X-ray diffractometer (Ultima III, Rigaku, Tokyo, Japan), temperature controlling unit (DSC unit, Rigaku), and Raman probe spectroscopic system. XRD patterns were measured with Cu Kα radiation applied at 40 kV and 40 mA of voltage and current, respectively. Each pattern was collected in the diffraction angle range of 5–35° in 2θ and scanned at 15° min^{-1}. Raman spectra were collected using an electric cooled spectrometer (Raman-HR-TEC, StellarNet, Carlson circle tampa, FL) and a diode laser of 350 mW output for excitation at 785 nm (I0785MM0350MF, Innovative Photonic Solutions, Monmouth Junction, NJ). Fig. 2 shows a schematic illustration of the measurement system. The excitation laser was delivered to the optical fiber coupler (Fig. 2d) connected to the single optical hollow fiber (Fig. 2e). The hollow fiber emitted no Raman light; thus, the optical system at the measuring point was simply set up to be compact without an additional filter and a number of fibers [17,18]. In this system, the compact design was required because stability in temperature is one of the most critical points to control crystalline structure.

The sample powder was mounted on the measuring point shown in Fig. 2k using a square aluminum pan, which size was

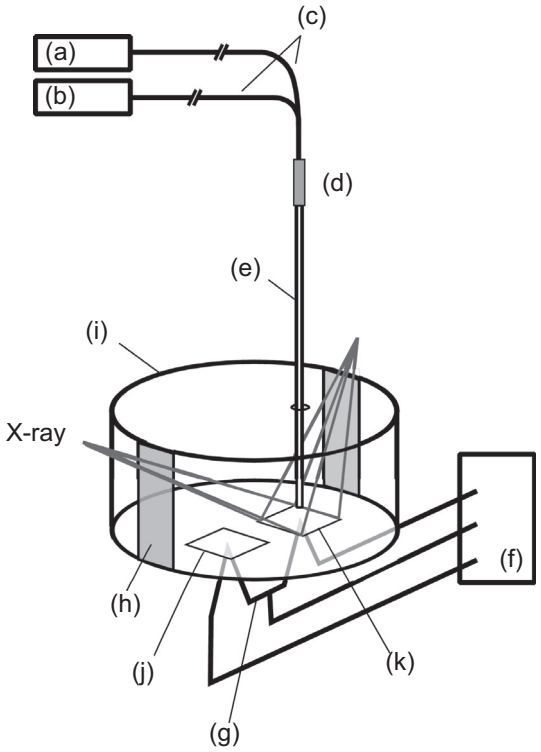

Fig. 2. Schematic illustration of the simultaneous measurement system using XRD and Raman spectroscopy. (a) Diode laser source at 785 nm; (b) Raman spectrometer; (c) quartz fiber; (d) optical fiber coupler; (e) optical hollow fiber (ϕ 1 mm); (f) temperature controlling unit (DSC unit, Rigaku, Japan); (g) thermocouple; (h) X-ray window (polyimide film); (i) heat insulation; (j) reference sample; (k) target sample.

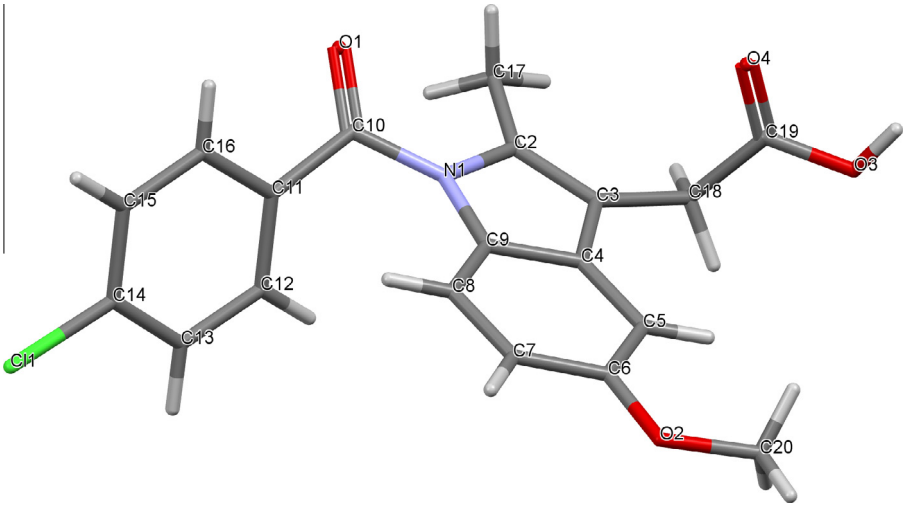

Fig. 1. Chemical structure of indomethacin (IMC).