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Application of thermally stimulated current measurement to the polymorphic characterization of drug substances

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Abstract

The thermal stimulated current measurement was used as an innovative analytical equipment to evaluate the polymorphic properties of terfenadine and Compound A, being developed by Takeda Pharmaceutical Company, Limited. At first, terfenadine, which is known to have polymorphs, was used as a model sample for thermally stimulated current (TSC) analyses. The TSC curves of amorphous and two polymorphs were distinctly different from each other. Therefore, it was considered that TSC measurement could be a useful technique to evaluate the crystalline properties of drug substances.

The polymorphs of compound A were difficult to distinguish the characteristics of polymorphs from conventional powder X-ray diffractometry and also differential scanning calorimetry. Forms A and B of compound A were clearly differentiated by the thermal stimulated current properties that were adequate to characterize each form.

Thus, it was shown that TSC was extremely useful and powerful tool for identification of complicated polymorphs, which were not distinguished by conventional methods.

Keywords: Thermally stimulated current; Differential scanning calorimetry; Polymorph

1. Introduction

The polymorphs are defined substances that are chemically identical but can differ in physicochemical properties. The polymorphism is common phenomena among pharmaceuticals. Great numbers of polymorphs are found in recent drug substances [1,2]. A research for the polymorphism of drug candidates has become more important, since the polymorphs have different physicochemical properties, such as solubility and stability [3–5]. Especially, solubility often affects seriously on the bioavailability of the drugs seriously because the increase in the number of insoluble drug substances are developed nowadays [6].

Polymorphic characterization of investigational drugs is generally carried out by solid-state spectroscopy such as powder X-ray diffractometry (XRD), differential scanning calorimetry (DSC), solid-state NMR and infrared spectroscopy, etc. [7–11]. Recently, the appearance of complicated polymorphs for drug substances is increasing, and it becomes more difficult to confirm their different properties by the conventional analytical methods. However, it is necessary to develop the new analytical methods to characterize and/or determine crystalline forms, because there are limited analytical methods for the characterization of solid pharmaceuticals.

The thermally stimulated current (TSC) technique is widely used for characterizing the property of polymers and mainly applied to the characterization of amorphous states by measuring molecular relaxations [12,13]. However, there were few papers applying it to pharmaceutical materials.

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The aim of this study is to apply the thermally stimulated current technique for the evaluation for polymorphs of solid pharmaceuticals as one of innovative analytical methods.

2. Experimental

2.1. Materials

Terfenadine was a commercially available product and was obtained from Kyoto Pharmaceutical Industries (Kyoto, Japan). Forms I and II of terfenadine were prepared by the recrystallization from *n*-butanol and ethyl acetate, respectively [14]. Amorphous terfenadine was prepared by grinding, using a CMT model TI 100 vibration mill (Tokyo, Japan). Compound A was prepared by the Medicinal Chemistry Research Laboratories, Takeda Pharmaceutical Company Limited. All other chemicals were of analytical grade.

2.2. Powder X-ray diffractometry

Powder X-ray diffraction patterns were obtained using a RINT2100 Ultima+ type diffractometer (Rigaku Corporation, Tokyo, Japan) using Cu Kα radiation at a wavelength of 1.5418 Å at 50 kV and 40 mA. Samples were mounted on a silicon plate, and the instrument was operated in the continuous scan mode over the 2θ range of 3–35°. High resolution X-ray diffraction analyses were performed with a TTR-2 type diffractometer (Rigaku Corporation, Tokyo, Japan) using Cu Kα radiation at a wavelength of 1.5418 Å at 50 kV and 300 mA. Samples were put into a quartz capillary, and the instrument was operated in the FT scan mode while the capillary was rotated over the 2θ range of 3–40°.

2.3. Differential scanning calorimetry

Model DSC6200R (SII NanoTechnology Inc., Tokyo, Japan) was used under a nitrogen gas flow. The gas flow rate was 50 mL/min. A DSC apparatus was calibrated with indium as the standard. An accurately weighed amount (5 mg) of the sample was transferred to aluminum pans and the sides of the cover were crimped. Samples were run at a heating rate of 5 °C/min.

2.4. XRD-DSC simultaneous measurement

A simultaneous XRD-DSC measurement was performed using a TTR2 type diffractometer attached to a Thermo-Plus DSC8230 (Rigaku Corporation, Tokyo, Japan) [15]. The gas flow rate was 50 mL/min. The DSC apparatus was calibrated with indium as the standard. An accurately weighed amount (5 mg) of the sample was transferred to aluminum open pans for XRD-DSC analyses. Samples were run at a heating rate of 5 °C/min with the XRD scanning rate of $20^\circ\ \mathrm{min}^{-1}$.

2.5. Thermally stimulated current measurement

A TS-POLAR thermal stimulated current spectrometer (Rigaku Corporation, Tokyo, Japan) was used in this study. An accurately weighed amount (20 mg) of sample was compressed at 400 N to make 0.65 mm thick disk. An insulation film of PTFE (NAFRON® #9001, 50 μm, NITTO DENKO Corporation, Osaka, Japan) was inserted between the sample disk and the electrode to block static current. Polarization was caused at 85 °C by applying a DC electric field at 1×10^5 V/m. After the molecular dipoles were oriented, the sample was rapidly cooled to 0 °C to trap the polarized dipoles. Samples were run at a heating rate of 5 °C/min while monitoring the current caused by relaxation of the polarized dipoles.

3. Results and discussion

3.1. Terfenadine

The powder X-ray diffraction patterns of polymorphs and amorphous of terfenadine are shown in Fig. 1. The polymorphic forms of terfenadine gave different diffraction patterns and no diffraction peak was observed for amorphous terfenadine. Fig. 2 shows DSC curves for polymorphic forms of terfenadine. These melting temperatures were well consistent with reported melting temperatures. The polymorphic system of terfenadine polymorphs was monotropic because a higher melting point of form I showed a higher heat of fusion [16]. So, it is confirmed that prepared polymorphs of terfenadine were consistent with the reported characteristics of terfenadine and used for the measurement of TSC.

Fig. 3 shows the TSC curves of terfenadine. The form I of terfenadine showed a single thermal stimulated current peak at about 120 °C. However, form II of terfenadine showed a doublet peaks at around 90 °C and 115 °C. The amorphous compound showed a unique spectrum in that a negative peak was observed at about 25 °C as well as two positive peaks at around 60 °C and 80 °C. These results showed

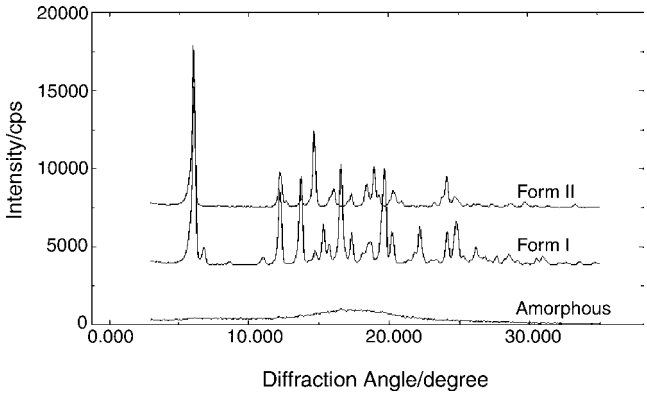

Fig. 1. X-ray powder diffraction patterns of terfenadine polymorphs and amorphous.

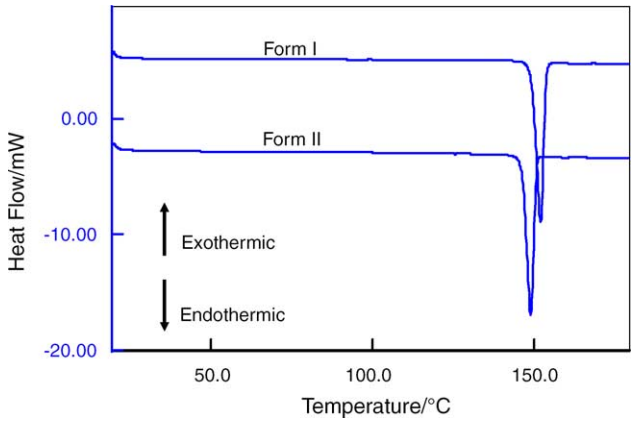

Fig. 2. DSC curves of terfenadine polymorphs.

that each substance showed characteristic relaxation according to temperature, although the mechanism of each depolarization has not yet been assigned. It was clarified that TSC measurement was applicable to the characterization for amorphous as well as crystalline properties of the drug substances.

3.2. Compound A

The conventional powder X-ray diffraction patterns of polymorphic forms of compound A are shown in Fig. 4. The polymorphic forms of forms A and B gave very similar diffraction patterns, although these patterns were different from crystal habit and preferred orientation. Fig. 5 shows the DSC curves of polymorphic forms of compound A. The thermodynamic parameters of polymorphs, such as melting points and heat of fusion, were not discernible. There was no endothermal and/or exothermal change during the heating process with some heating rates (0.5–20 °C/min) on DSC. The differences between forms A and B were only detected by the high resolution powder X-ray diffraction analysis. The characteristic diffraction peaks of each form were

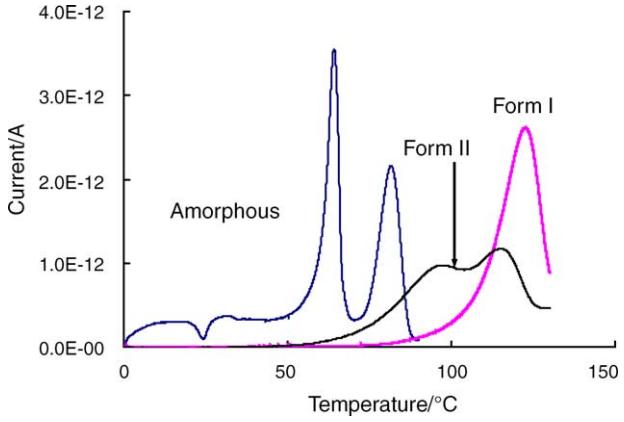

Fig. 3. TSC spectra of terfenadine polymorphs and amorphous.

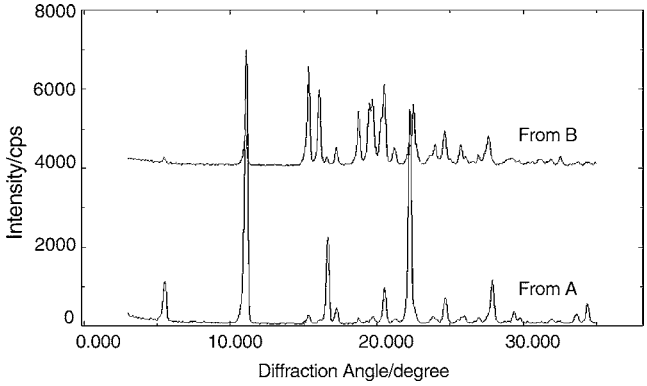

Fig. 4. X-ray powder diffraction patterns of compound A polymorphs.

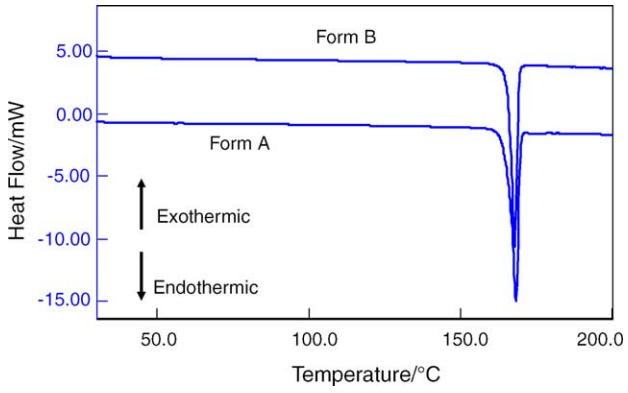

Fig. 5. DSC curves of compound A polymorphs.

indicated using arrows. The characteristic diffraction peaks of each form were almost located within 0.2° each other, so, it might be difficult to evaluate the crystalline form of compound A by the conventional XRD analysis (Fig. 6).

In order to clarify the results described in the above, i.e., XRD-DSC simultaneous measurement was performed for form A of compound A. Fig. 7 shows the simultaneous measurements of DSC curves and powder X-ray diffraction

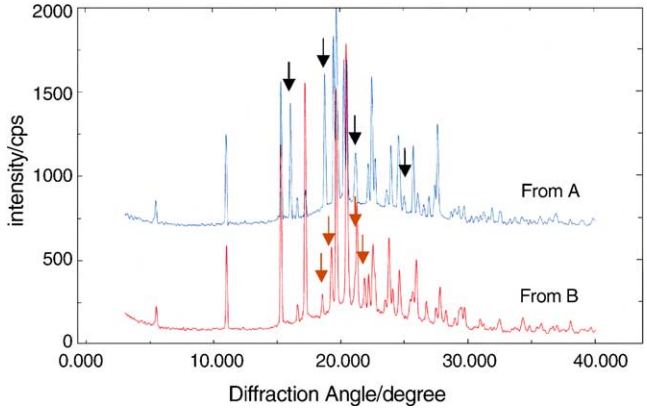

Fig. 6. High resolution X-ray powder diffraction patterns of compound A polymorphs.

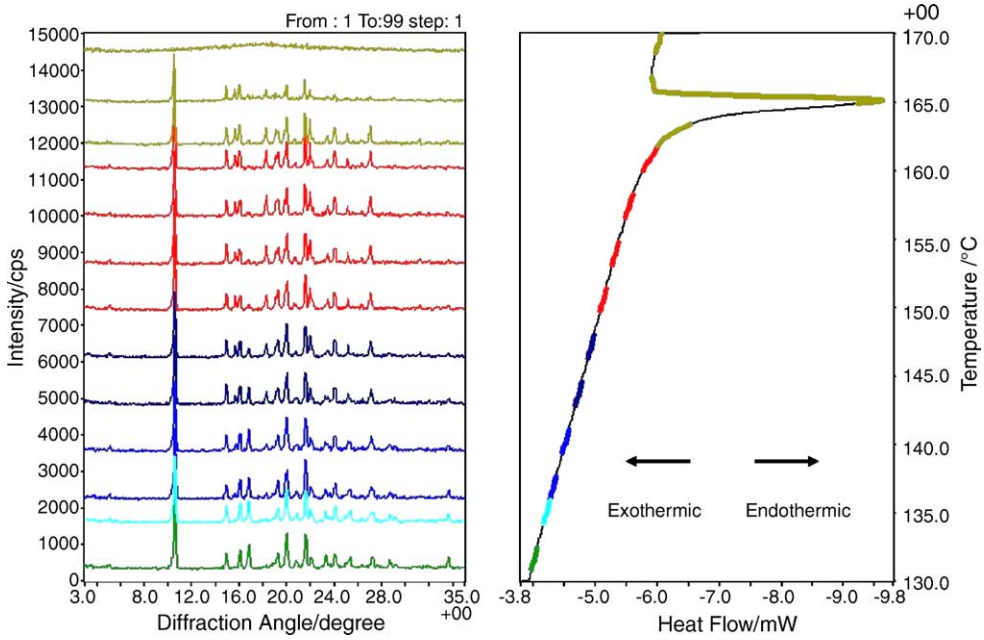

Fig. 7. XRD patterns and DSC curve of Form A of compound A in simultaneous analyses.

patterns. The form A is gradually transformed to form B at from 135 °C without thermal change. It was presumed that undetectable slight thermodynamic change was progressed gradually. The silent transformation of form A was the reason why the melting peak temperature and heat of fusion of form A by DSC were seemingly the same as those of form B. This phenomenon is very unique and uncommon in pharmaceuticals.

TSC measurement was applied to characterize the properties of forms A and B for compound A. As shown in Fig. 8, form A showed a single thermal stimulated current peak at about 50 °C, however, form B showed a single peak at about 85 °C. The imperceptible change that could not be detected by DSC could have been clearly differentiated by the depolarization current based relaxation of polymorphs.

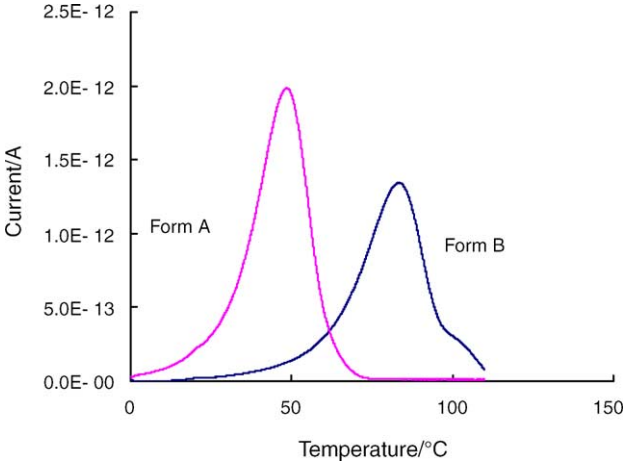

Fig. 8. TSC spectra of compound A polymorphs.

4. Conclusions

It was clarified that TSC method could have been successfully identified complicated polymorphs, which were not distinguished by conventional analytical methods. The TSC technique is applicable to for characterization of the polymorphic properties of drug substances.

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