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Evaluation of the physical stability and local crystallization of amorphous terfenadine using XRD–DSC and micro-TA

Etsuo Yonemochi *, Takafumi Hoshino, Yasuo Yoshihashi, Katsuhide Terada

Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan

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Abstract

It is very difficult to follow rapid changes in polymorphic transformation and crystallization and to estimate the species recrystallized from the amorphous form. The aim of this study was to clarify the structural changes of amorphous terfenadine and to evaluate the polymorphs crystallized from amorphous samples using XRD–DSC and an atomic force microscope with a thermal probe (micro-TA). Amorphous samples were prepared by grinding or rapid cooling of the melt. The rapid structural transitions of samples were followed by the XRD–DSC system. On the DSC trace of the quenched terfenadine, two exotherms were observed, while only one exothermic peak was observed in the DSC scan of a ground sample. From the in situ data obtained by the XRD–DSC system, the stable form of terfenadine was recrystallized during heating of the ground amorphous sample, whereas the metastable form was recrystallized from the quenched amorphous sample and the crystallized polymorph changed to the stable form. Obtained data suggested that recrystallized species could be related to the homogeneity of samples. When the stored sample surface was scanned by atomic force microscopy (AFM), heterogeneous crystallization was observed. By using micro-TA, melting temperatures at various points were measured, and polymorph forms I and II were crystallized in each region. The percentages of the crystallized form I stored at 120 and 135 °C were 47 and 79%, respectively. This result suggested that increasing the storage temperature increased the crystallization of form I, the stable form, confirming the temperature dependency of the crystallized form. The crystallization behavior of amorphous drug was affected by the annealing temperature. Micro-TA would be useful for detecting the inhomogeneities in polymorphs crystallized from amorphous drug.

Keywords: XRD–DSC; Terfenadine; Amorphous drug; Crystallization; Microthermal analysis

1. Introduction

The large number of drugs characterized by low oral bioavailability has resulted in a continued focus of research activities in the area of increasing drug absorption. Often times the limitation in bioavailability lies in poor solubility or a low dissolution rate; therefore, formulation approaches that can address these issues will result in increased bioavailability. One of the possible approaches to increase the solubility and dissolution rate is the use of solid dispersions [1,2]. In these dispersions, the drug can be present in a partially crystalline and amorphous state. Often the amorphous state of the drug is preferred in solid dispersions, since it shows a greater solubility and dissolution rate in comparison to the crystalline state. Despite these benefits of the amorphous state with respect to enhanced dissolution rate, it corresponds to a high energy state and is physically metastable, especially when stored relatively close to the glass transition temperature [3–5]. Another problem faced when running research programs on polymorphism of drugs is the simultaneous presence of several crystalline forms generated in crystallization processes from melts. Solidification gives rise to metastable forms accompanying the thermodynamic stable one. On studying polymorphism of drugs, one expects to find complex mixtures of close energy crystalline forms, often containing solids with different crystallinity. Therefore, to get reliable data,

* Corresponding author. Tel.: +81 47 472 1494; fax: +81 47 472 1344.
E-mail address: yone@phar.toho-u.ac.jp (E. Yonemochi).

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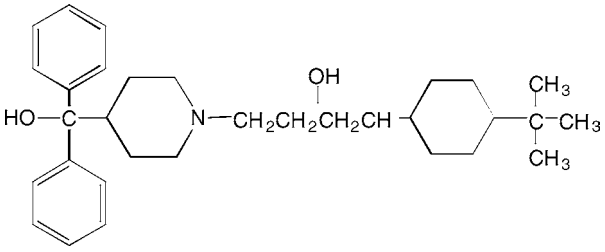

Fig. 1. Chemical structure of terfenadine.

accurate experiments and sensitive methods are required [6,7].

Thermal analysis, especially differential thermal analysis (DTA), thermogravimetry (TG), and differential scanning calorimetry (DSC), is commonly used to evaluate the physicochemical properties of a new chemical entity (NCE) for a drug [8]. When NCE is formulated for a new dosage form, polymorphic transition, crystallization, and glass transition are important information for keeping the desirable physical state. Because of the lack of structural information, it is very difficult for thermal analysis to follow rapid changes in polymorphic transformation and crystallization and to determine which species recrystallises from the amorphous form. In situ analysis is known as a useful method to follow the complicated phase transition of various materials. The simultaneous measurement system of XRD and DSC (XRD–DSC) and atomic force microscopy (AFM) are useful methods that allow for the observation of structural changes and thermal analysis on a microscopic scale compared with the conventional analysis techniques [9–16].

Terfenadine is known as an antiallergic drug (Fig. 1), and it has two polymorphs, stable form I and metastable form II [17]. It is also known that terfenadine crystals are changed to an amorphous state by grinding. The aim of this study was to clarify the structural changes of amorphous terfenadine using XRD–DSC evaluate the species recrystallized from amorphous samples, and determine the ratio of crystallized polymorphs using micro-TA.

2. Materials and methods

Terfenadine was of JPXIII grade, supplied by Wako Pure Chemical Industries Ltd. (Osaka, Japan). Form I (stable form) was crystallized from *n*-butanol solution, and form II (metastable form) was crystallized from ethyl acetate solution. Other chemicals were of special reagent grade.

2.1. Preparation of amorphous samples

Quenched glass of terfenadine was prepared as follows. Crystalline terfenadine was melted by heating at 155 °C, after which the melt was rapidly cooled to an appropriate temperature using liquid nitrogen. Ground samples were obtained by grinding for 60 min using a TI100 vibration mill (TI-100, CMT, Tokyo).

2.2. Powder X-ray diffraction measurement

The powder X-ray diffraction pattern was obtained from a RAD-type diffractometer (Rigaku, Tokyo Japan) using a scintillation counter. The X-ray source was Cu Kα, and the diffracted beam was monochromated by a bent graphite monochromator. Measurement conditions were as follows: filter, Ni; voltage, 35 kV; current, 10 mA; receiving slit, 0.3 mm. Sample powder was packed in a glass plate.

2.3. DSC measurement

The temperatures of polymorphic transition, crystallization, and glass transition of samples were measured by DSC (Perkin-Elmer DSC-7). The DSC apparatus was calibrated with indium as the standard. Accurately weighed amounts (5 mg) of samples were transferred to aluminum sample pans, and the sides of the cover were crimped. Samples were run at a scanning rate of 5 °C/min.

2.4. Simultaneous XRD–DSC measurement

XRD–DSC measurement in situ was done using a Rigaku XRD-DSCII system (Rigaku, Tokyo Japan). Samples weighing 5 mg were placed in open aluminum sample pans whose size was 7 mm × 7 mm × 0.25 mm. The inside of the DSC unit was purged by nitrogen gas at a flow rate of 50 ml/min. The heating rate of the DSC run was 5 °C/min, and X-ray diffraction was measured simultaneously. For the Cu Kα radiation, a graphite monochromator was used for XRD measurements. The line shape X-ray source used was a RIGAKU/RINT-Ultima system, and it was operated at 50 KV and 40 mA.

2.5. Micro-TA measurement

A microthermal analyzer (micro-TA 2990, TA-Instruments) was used. Samples were placed on the sample/temperature stage and stored at the desired temperatures. Standard topography was obtained in contact mode with the probe held isothermally at 40 °C. The scan rate was 5 μm/s over a range of 50 μm × 50 μm. Before measurement, the thermal probe was calibrated using four substances, which are listed in Table 1. Local thermal analysis was performed using heating speeds of 0.33 °C/s.

Table 1
Samples used for temperature calibration

Sample	Melting temperature (°C)
Biphenyl	68.93
Phenacetin	135.20
Diphenylacetic acid	147.19
PET	260.00

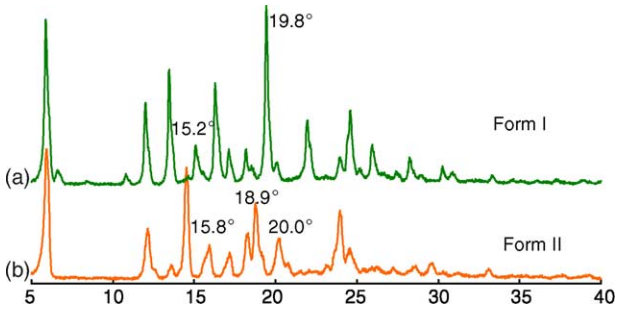

Fig. 2. X-ray powder diffraction patterns of terfenadine forms I and II.

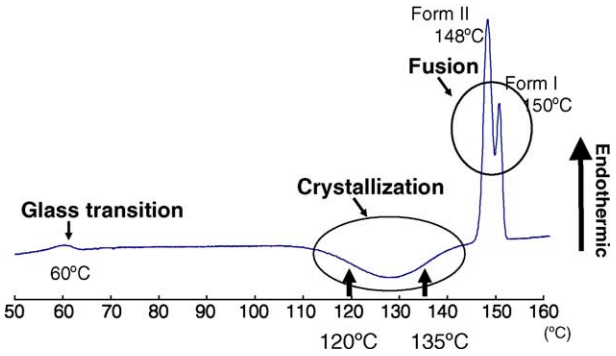

Fig. 3. DSC trace of terfenadine glass.

3. Results and discussion

3.1. Crystallization study of monotropic drug

Fig. 2 shows the XRD patterns of terfenadine polymorphs. Form I has the characteristic diffraction peaks at 15.2 and 19.8, while form II shows peaks at 15.8, 18.9, and 20.0. Terfenadine crystals were transformed to the amorphous form by grinding or by cooling the melt. Fig. 3 illustrates the DSC trace of quenched glass. Glass transition, recrystallization, and two fusions were observed at 60, 120, 148, and 150 °C, respectively. There was no polymorphic transformation on the DSC curve; therefore, transformation behavior of terfenadine would be monotropic. Fig. 4 shows the simultaneous XRD–DSC data of quenched glass of terfenadine. The metastable form II was crystallized around 100 °C, and the stable form I was also detected at 147 °C. Figs. 5 and 6 show the XRD–DSC data of the ground amorphous samples originally prepared from forms I and II. During the heating of the ground samples, both polymorphic forms were crystallized from ground form I, whereas only metastable form II was crystallized from ground form II. This result suggested that the existence of seed species could be related to crystallization behavior. The seed species originated from form I induced the crystallization of forms I and II; however, the seeds prepared from form II did not affect the crystallization of form I but only form II in the amorphous sample. The difference in crystallization behavior of ground samples could be closely associated to the homogeneity of the samples and the existence of the seed.

3.2. Change in the surface topography of amorphous samples during storage

From the results of the DSC curve of terfenadine glass, both polymorphs crystallized at between ∼110 and ∼140 °C; however, it was very difficult to evaluate the recrystallized species. We stored the amorphous samples at different

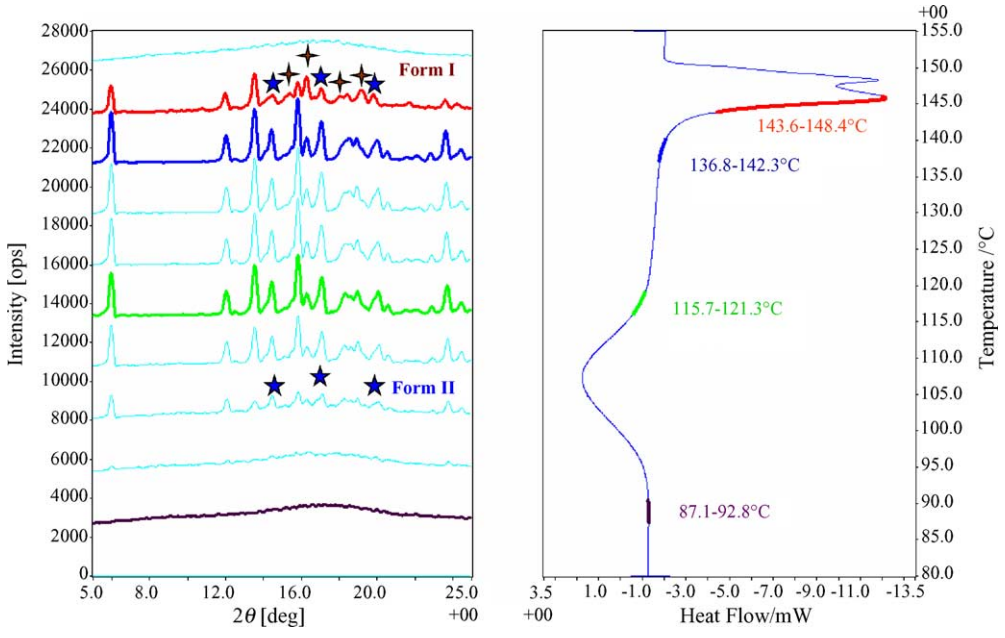

Fig. 4. XRD–DSC data of quenched glass.

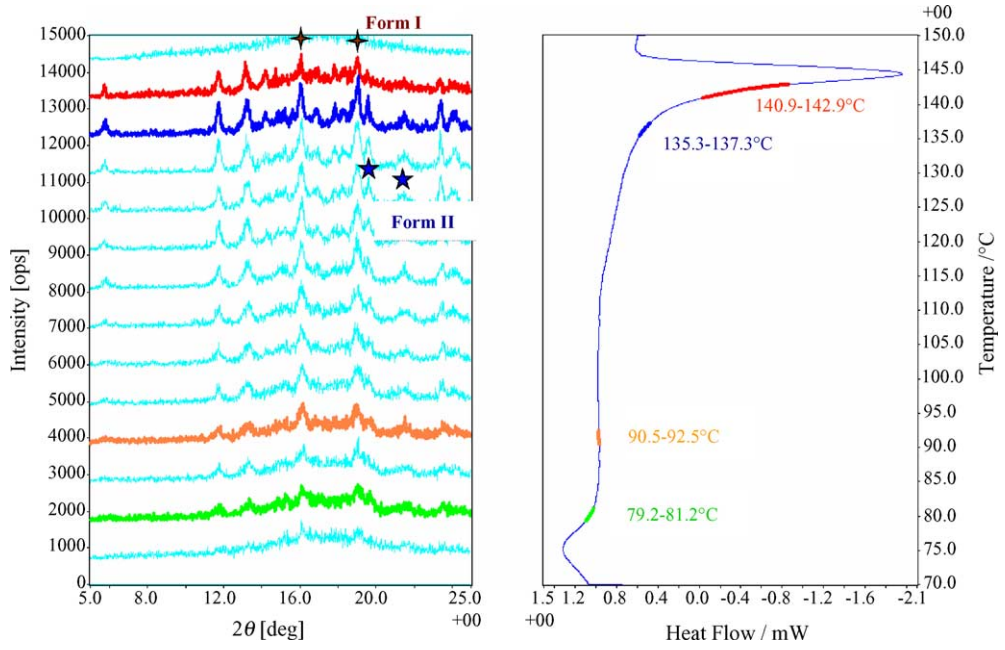

Fig. 5. XRD–DSC data of ground form I.

temperatures (120 and 135 °C) and surface analysis was performed using AFM. Representative AFM topographical images of the terfenadine glass and a stored sample (at 135 °C for 50 min) are shown in Fig. 7 (scan rate: 5 mm/s, resolution: 125 nm). The image of the surface for glass showed a smooth surface (Fig. 7a). However, when the stored sample surface was scanned by AFM, an irregular surface morphology was observed, suggesting that heterogeneous crystallization had occurred.

3.3. Effect of storage temperature on the polymorphic composition of the stored samples

By using local thermal analysis, the melting temperature at various points was measured. As shown in Fig. 8, we selected the crystallized points ①, ② and ③. Then, micro-TMA at each point was performed at a heating rate of 0.33 °C/s. Fig. 9 shows the micro-TMA curves of points ①, ② and ③. The difference of the melting points was clearly observed,

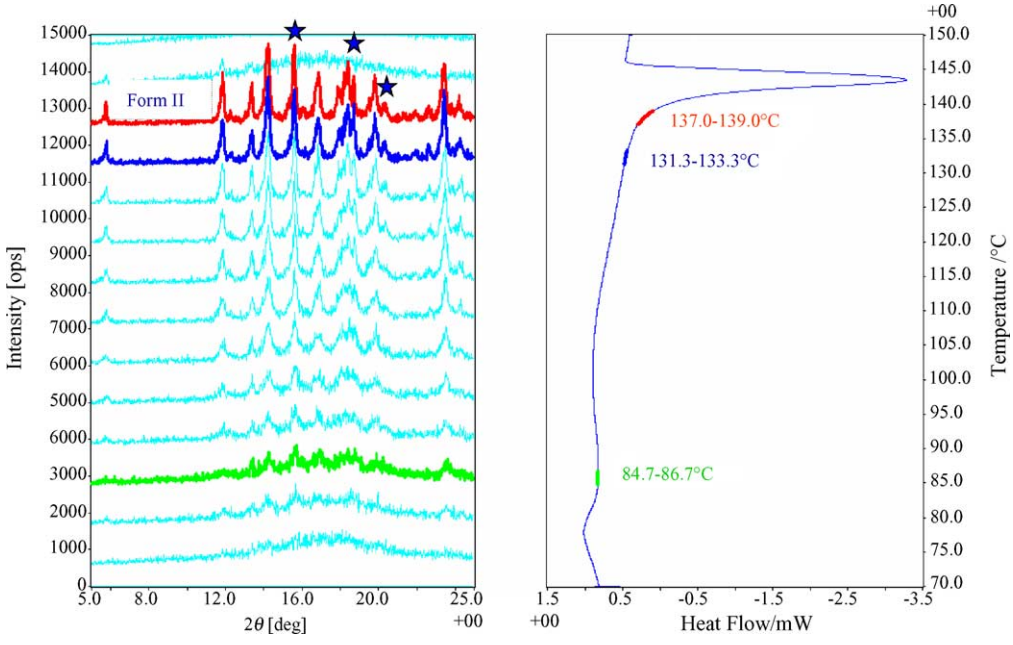

Fig. 6. XRD–DSC data of ground form II.

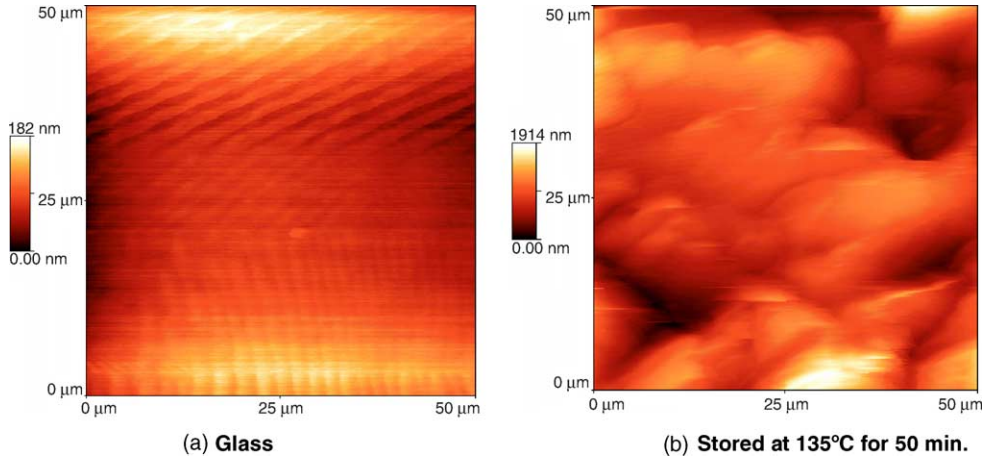

Fig. 7. AFM images of terfenadine sample.

and the crystallization of forms I and II of polymorphs was confirmed at each region. We evaluated more than 100 regions on the sample surface using micro-TMA. Then, obtained melting points were plotted along the temperature line. From the results of samples stored at 120 °C (Fig. 10),

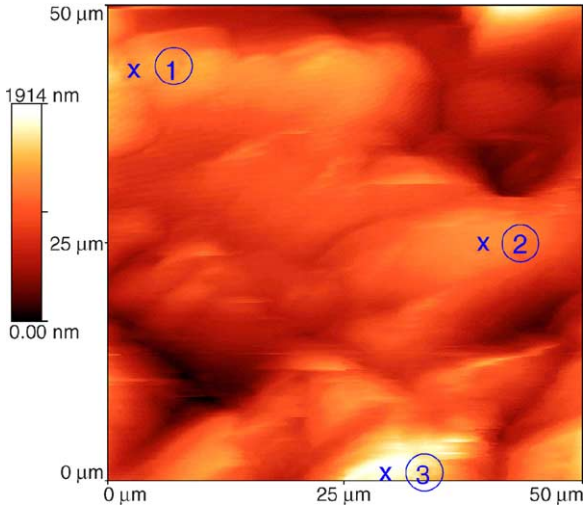

Fig. 8. AFM image of sample stored at 135 °C for 50 min.

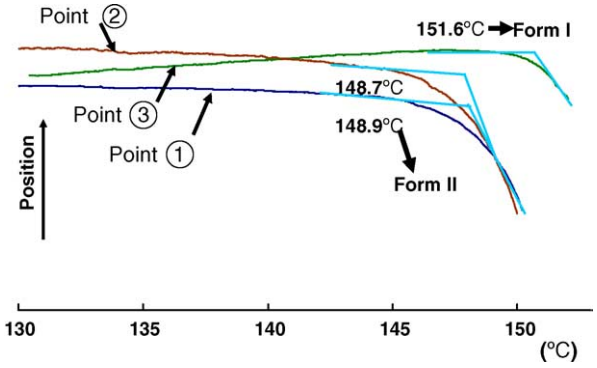

Fig. 9. Micro-TMA curves of points ①, ② and ③.

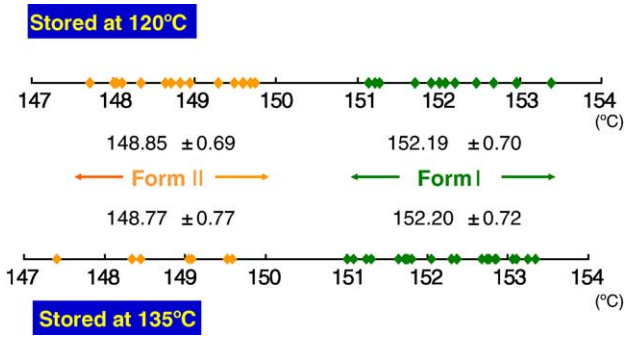

Fig. 10. Observed melting point distribution of crystallized samples.

the average and standard deviation of observed melting temperatures was calculated as 152.19 ± 0.70 °C for form I and 148.85 ± 0.69 °C for form II. These values agreed closely with the observed melting temperatures of samples stored at 135 °C. These data suggested that the experimental errors in the micro-TA method were of the order of a few per cent. Percentages of observed polymorphs in the stored samples were calculated from the number of points in Fig. 10. The percentage of recrystallized form I stored at 120 °C was 47%, while, after storage at 135 °C, recrystallized form I was increased to 79%. This result suggested that increasing the storage temperature would increase the nucleation of the stable form (form I).

4. Conclusion

Obtained data suggested that recrystallized species could be related to the homogeneity of samples. It was possible to follow the recrystallization and polymorphic change of terfenadine and probucol. The recrystallization behavior of amorphous drug was affected by the annealing temperature. Micro-TA would be useful for detecting the inhomogeneities in polymorphs crystallized from amorphous drug.

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