[Chem. Pharm. Bull. 34(2) 917—921 (1986)]

Kinetic Study on the Isothermal Transition of Benoxaprofen Polymorphs in the Solid State at High Temperature[1)]

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(Received July 22, 1985)

The kinetics of the isothermal transition between benoxaprofen polymorphic forms I and II at high temperature were investigated by means of X-ray powder diffractometry. Kinetic analysis according to the method of Hancock and Sharp indicated that the isothermal transition of form I to form II proceeds in accordance with the mechanism of random nucleation and two-dimensional growth of nuclei (Avrami–Erofeev equation). The activation energy for this transition calculated from the slope of the Arrhenius plots was 164 kJ·mol^{-1}.

Keywords——benoxaprofen; polymorphism; isothermal transition; kinetic analysis; X-ray powder diffractometry

In the previous papers,[2,3)] we reported the kinetics and mechanisms of the isothermal transitions of carbamazepine, tolbutamide, mefenamic acid and acetazolamide polymorphic forms in the solid state.

As a part of our series of kinetic studies on the isothermal transition of polymorphic forms, in the present study, the kinetics of the isothermal transition between benoxaprofen polymorphic forms I and II at high temperature were investigated by means of X-ray powder diffractometry.

Experimental

Materials——Benoxaprofen (Lot No 4FA85) was supplied by Shionogi Co., Ltd. All other chemicals were reagent-grade commercial products.

Preparation of Polymorphic Forms——Benoxaprofen polymorphic forms I and II were prepared as described previously.[4)] The particle sizes of each polymorphic form were in the range of 62—74 μm.

Identification of Polymorphic Forms——Polymorphic forms were identified by X-ray powder diffractometry (Rigaku Denki, Geigerflex 2011, monochromator, Cu-K_α radiation), differential scanning calorimetry (DSC, Perkin-Elmer, model DSC-2C) and thermogravimetry (TG, Perkin-Elmer, model TGS-2).

X-Ray powder diffraction patterns (Fig. 1) and DSC–TG curves of benoxaprofen polymorphic forms were identical with those reported previously.[4)]

Preparation of Calibration Curve——The kinetics of isothermal transition of polymorphic forms were investigated by means of X-ray powder diffractometry. In the previous paper,[2)] we reported that this technique was available for analysis of isothermal transitions of polymorphic forms.

The quantity of form I in a form I—form II binary system of benoxaprofen polymorphic forms was determined by measuring the diffraction peak intensity (height) at 5.4° (2θ) after performing the following process. Physical mixtures (100 ± 10 mg) of specified proportions of forms I and II were prepared by mixing them in a mortar for 1 h. No polymorphic transition was observed due to the mixing. Then the sample was placed flat in a glass holder having a depression 0.5 mm deep, and scanned from 3 to 8° (2θ). The conditions for measurement were as follows: voltage, 40 kV; current, 20 mA; range, 48000 cpm; time constant, 2 s; scanning speed, 0.5° (2θ)·min^{-1}; chart speed,

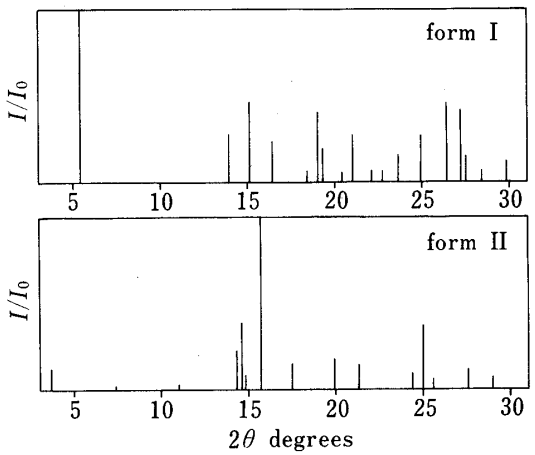

Fig. 1. X-Ray Powder Diffraction Patterns of Benoxaprofen Polymorphic Forms

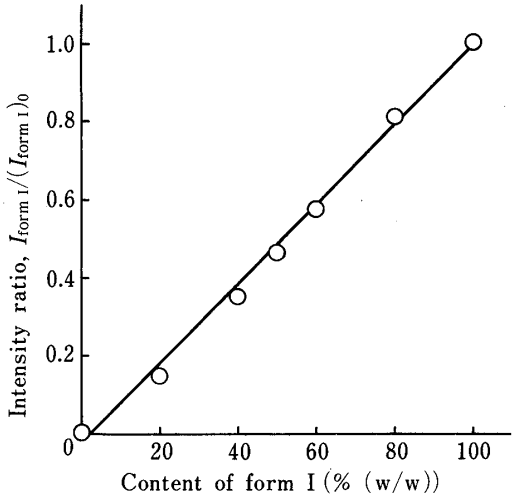

Fig. 2. Calibration Curve for Form I—Form II Mixture of Benoxaprofen Polymorphic Forms ($r=0.998$)

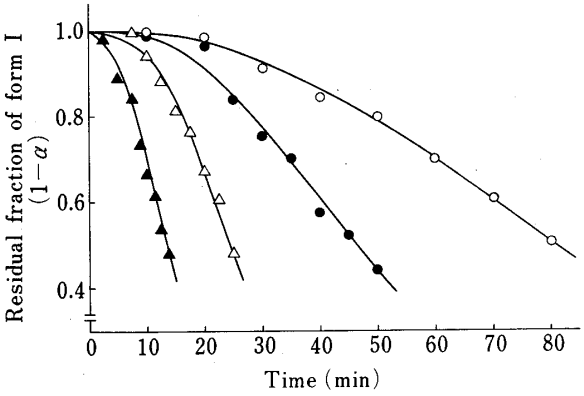

Fig. 3. Residual Fraction of Form I during the Isothermal Transition to Form II of Benoxaprofen

○, 135 °C; ●, 140 °C; △, 145 °C; ▲, 150 °C.

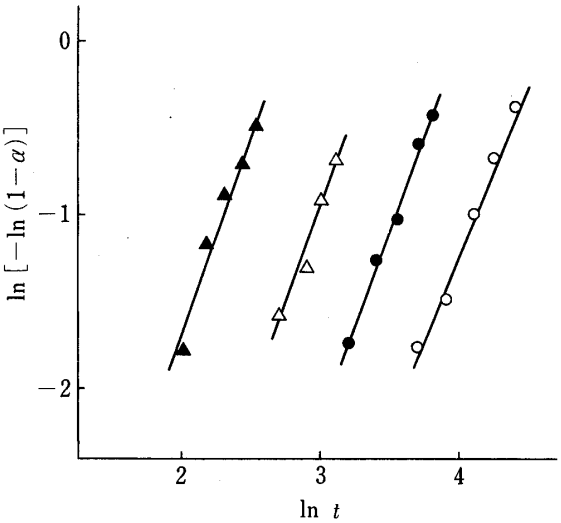

Fig. 4. Plots of $\ln[-\ln(1-\alpha)]$ *versus* $\ln t$ for the Isothermal Transition of Form I to Form II of Benoxaprofen ($\alpha=0.15$—0.5)

○, 135 °C ($m=2.05$, $r=0.992$); ●, 140 °C ($m=2.24$, $r=0.993$); △, 145 °C ($m=2.28$, $r=0.996$); ▲, 150 °C ($m=2.40$, $r=0.982$).

5 mm·min^{-1}; divergence slit, 0.5 °; scatter slit, 0.5 °; receiving slit, 0.15 mm; detector, GMC.

The replacement of the same sample in the holder was repeated at least 5 times in every case. The coefficient of variation of peak height for each sample was less than 5.9%. The obtained calibration curve for the form I—form II binary system showed a good linearity ($r=0.998$), as can be seen in Fig. 2.

Kinetic Study of Isothermal Transition——Form I (25 ± 5 mg) was weighed into aluminum pans. The sample was then kept at selected constant temperatures (135, 140, 145 and 150 °C) for a suitable time in the analyzer unit of a differential scanning calorimetry (Perkin-Elmer, model DSC-2C). Dry nitrogen gas was passed at 20 ml·min^{-1} during the heating. The same procedure was carried out 4 times. These samples were collected and were sufficiently mixed in a mortar for 1 h. The diffraction peak intensity of each sample was determined by placing them in a holder at least 5 times under the conditions described in the case of preparation of the calibration curve. The residual fraction of form I was calculated from the calibration curve.

Scanning Electron Microscopy——Changes of crystal shapes during the isothermal transition of polymorphic forms were observed with a scanning electron microscope (Nihon Denshi, JSM-T20).

Results and Discussion

The physico-chemical properties of benoxaprofen polymorphic forms I and II were reported in the previous paper[4]; forms I and II each showed one endothermic peak corresponding to the melting point at 187 and 193 °C, respectively, but no transition peak of form I to form II was found in the DSC curves. In this work, the kinetics of the isothermal transition of form I to form II at 135, 140, 145 and 150 °C were investigated by means of X-ray powder diffractometry.

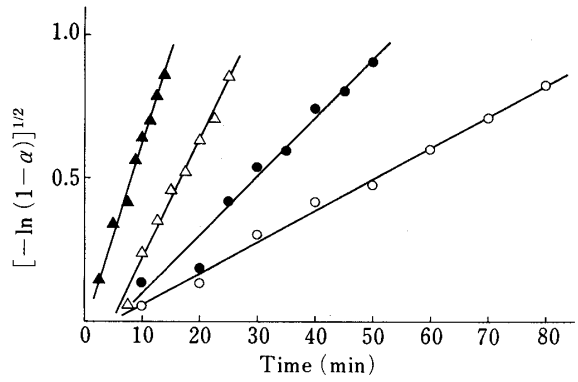

Fig. 5. Plots of $[-\ln(1-\alpha)]^{1/2}$ *versus* t for the Isothermal Transition of Form I to Form II of Benoxaprofen

○, 135 °C (r=0.997); ●, 140 °C (r=0.983); △, 145 °C (r=0.993); ▲, 150 °C (r=0.995).

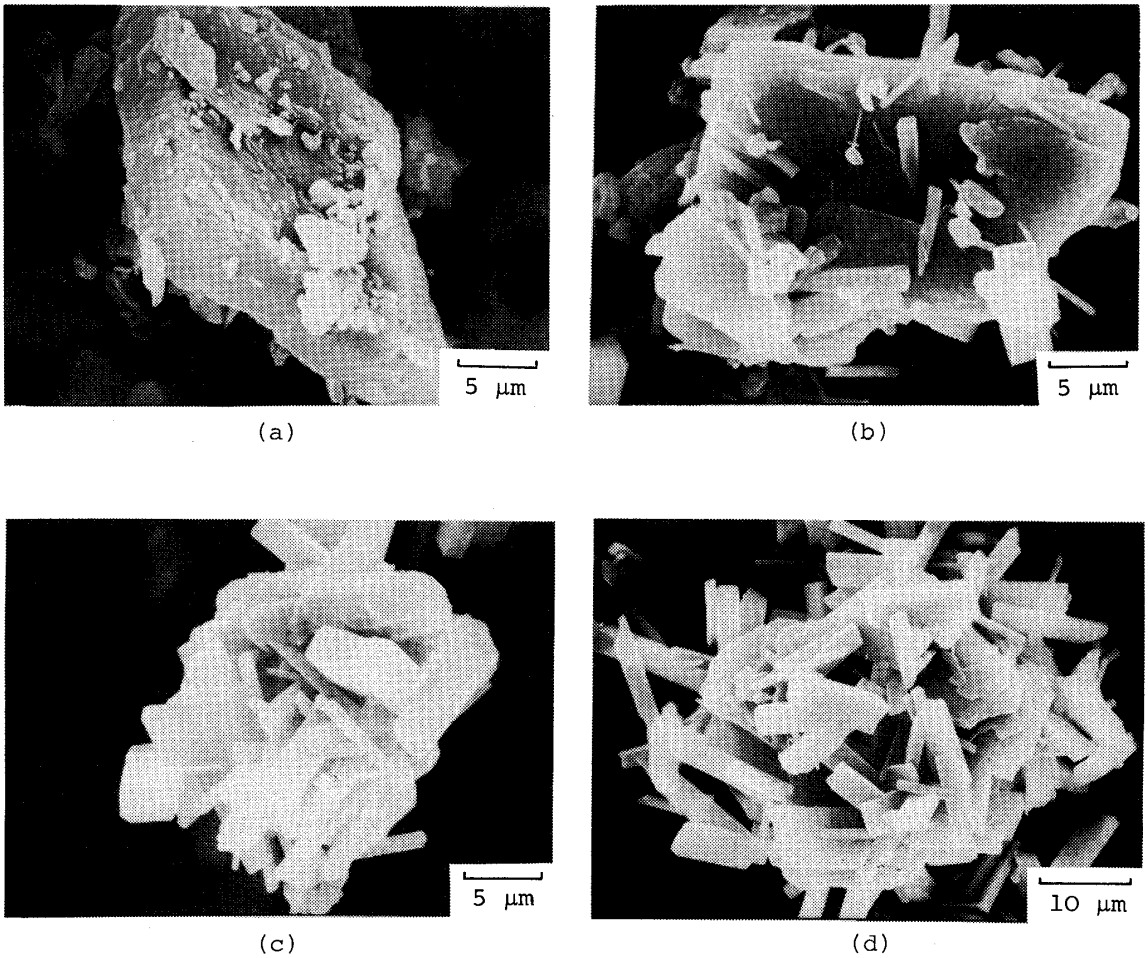

Fig. 6. Scanning Electron Microphotographs of Benoxaprofen Crystals at Various Stages during the Isothermal Transition of Form I to Form II at 150 °C

(a) form I before heating (×3500), (b) after 5 min (×3500), (c) after 10 min (×3500), (d) form II (×2000).

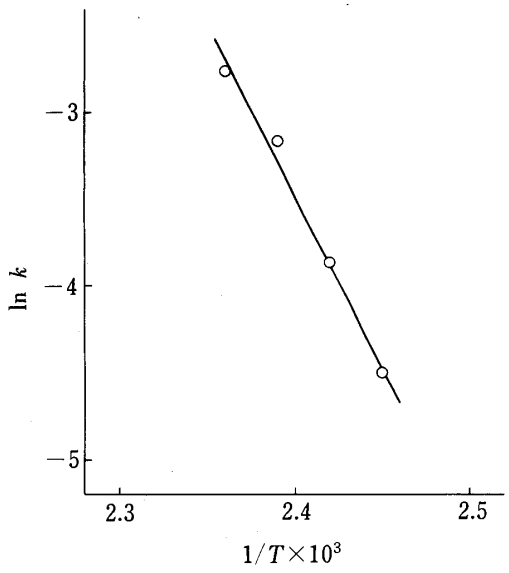

Fig. 7. Arrhenius Plots for the Isothermal Transition of Form I to Form II of Benoxaprofen ($r=0.994$)

Figure 3 shows the isothermal transition curves of form I to form II at the temperatures given above. It was confirmed that the transition rates were relatively lower at the earlier period of transition and then increased rapidly at any temperature.

The kinetic analysis of the isothermal transition of form I to form II was performed according to the method of Hancock and Sharp,[5] and the value of m for this transition was estimated, based on Eq. 1:

$$\ln[-\ln(1-\alpha)]=\ln B+m\cdot\ln t \quad (\alpha=0.15\text{—}0.5) \tag{1}$$

where m is the intrinsic value for various theoretical equations of solid-state decomposition, α is the fraction of transition and B is a constant. The relationship between the theoretical equations and the value of m is described in the previous paper.[1]

The value of m for the isothermal transition of form I to form II was calculated to be 2.24 ± 0.15 (mean$\pm$S.D., $n=4$), as shown in Fig. 4. Accordingly, this transition appears to proceeed by the mechanism of random nucleation and two-dimensional growth of nuclei (Avrami–Erofeev equation).[6,7] The plots of $[-\ln(1-\alpha)]^{1/2}$ against time at every temperature gave straight lines, as shown in Fig. 5. The transition rate constant at 150 °C calculated from the slope of the straight line was about 6 times higher than that at 135 °C.

Figure 6 shows the scanning electron microphotographs of benoxaprofen crystals during the isothermal transition of form I to form II at 150 °C. From these results, it was concluded that nuclei randomly occur within a crystal of form I, then grow into crystals of form II.

In addition, the apparent transition rate constants were obtained from the slope of the straight lines shown in Fig. 5, and the activation energy for the isothermal transition of form I to form II was calculated to be 164 kJ·mol^{-1} from the slope of the Arrhenius plots (Fig. 7).

Acknowledgement The authors are grateful to Shionogi Co., Ltd. for gift of benoxaprofen.

References and Notes

1) This paper forms Part XVI of "Studies on Drug Nonequivalence." The preceding paper, Part XV: T. Umeda, N. Ohnishi, T. Yokoyama, T. Kuroda, Y. Kita, K. Kuroda, E. Tatsumi, and Y. Matsuda, *Chem. Pharm. Bull.*, **33**, 3422 (1985).
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