A Kinetic Study of the Crystallization Process of Noncrystalline Indomethacin under Isothermal Conditions[1]

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The crystallization process of noncrystalline indomethacin (IMC) obtained by the grinding and by the fusion method was analyzed by a kinetic method. The noncrystalline samples of IMC were the α form ground for 10 h at 4 °C (GNCα), the γ form ground for 10 h at 4 °C (GNCγ) and the fused solid (NC). Ten kinetic models were employed, and crystallinity was determined by X-ray diffractometry. Data obtained were used to determine the thermodynamic parameters and crystallization mechanism.

Under isothermal conditions GNCα crystallized in both the α and γ forms simultaneously. The GNCγ and NC crystallized in the γ form, and the results of the Hancock–Sharp method suggested that both crystallizations occurred by a two-dimensional phase boundary reaction; the activation energies (E) were estimated to be 24.1 and 27.2 kcal/mol. The crystallization rate of GNCγ was about 60 times faster than that of NC, and therefore NC was a very stable noncrystalline solid. These results suggest that there are several kinds of noncrystalline solids.

Keywords——indomethacin; noncrystalline solid; crystallization; isothermal kinetics; stability; X-ray diffraction analysis; thermal behavior

Introduction

Recently, drug polymorphism and noncrystalline pharmaceutical preparations in the form of bulk powders have attracted the interest of many investigators, because the physical state of preparations affects the bioavailability controlling the dissolution rate.[2] A metastable form or noncrystalline solid is transformed to a stable form, because these two solid forms have higher enthalpy than the stable form.[3-6] Therefore, the stability of the metastable form and the noncrystalline solid is a very important factor for drug design. We have reported on the physicochemical properties of cephalexin[7] and chloramphenicol palmitate[8] during grinding. The effect of the temperature on noncrystalline indomethacin (IMC) obtained from the α or γ form by grinding in an agate centrifugal ball mill at 4 °C was investigated.[9]

Imaizumi *et al.*[10] reported on the crystallization of the glassy solid IMC obtained by the fusion method under various relative humidities. Fukuoka *et al.*[11] examined the stability and the crystallization of glassy solid IMC at room temperature. In the present study, we investigated the stability of noncrystalline IMC obtained by grinding and by the fusion method under isothermal condition. In order to clarify the stability and the crystallization mechanism of noncrystalline IMC, we analyzed the crystallization processes on the basis of several solid-state kinetic models.

Experimental

Materials——Crystalline Forms: Highly purified α and γ forms of IMC were obtained as described in a previous paper.[12]

Noncrystalline IMC (NC): NC (glassy solid) was obtained by cooling at about $-20\,°C$ after fusing the bulk powder of IMC at 165 C for 5 min. It was then pulverized in an agate mortar and pestle as described in a previous paper.[10]

Ground Noncrystalline Solid (GNC): The GNCα and the GNCγ of IMC were obtained by grinding in an agate centrifugal ball mill (200 rpm) at 4 C from the α and γ forms of IMC, respectively, as described in a previous study.[9]

X-Ray Diffraction Analysis——The X-ray diffraction profiles of ground samples were measured with a type JDX 7E X-ray diffractometer (Nihon Denshi Co., Ltd.) at room temperature. The measurement conditions were as follows; target, Cu; filter, Ni; voltage, 30 kV; current, 6 mA; receiving slit, 0.2 mm; time constant, 2 s; counting range, 6×10^4 cpm; scanning speed; 1 /min.

Nuclear Magnetic Resonance (NMR) Spectra——The NMR spectra were measured with an FX-100 NMR spectrometer (Nihon Denshi Co., Ltd.). Solutions of about 2—5% of the ground products in $CDCl_3$ were prepared and the spectra were measured using tetramethylsilane as an internal reference. It was confirmed that no NMR-detectable decomposition of the ground products occurred due to mechanical stress during grinding.

Determination of the Rate of Crystallization of IMC under Isothermal Conditions——Samples in glass holder were stored in P_2O_5 desiccators at 20, 25, 30, 40, $45 \pm 0.5\,°C$, and the X-ray diffraction profiles of the samples were measured at suitable time intervals. Standard samples with various degrees of crystallinity were obtained by physically mixing the α or γ form and glassy solid IMC. The degree of crystallinity of the α or γ form was taken as 100% solid and the glassy solid was considered to have 0% crystallinity. The X-ray diffraction peaks of the standard sample and that of LiF (external standard) were measured, and plots were made of the ratio of the peak areas at $2\theta = 8.5°$ due to the α form and at $2\theta = 38.7°$ due to LiF *versus* the content of the α form. Also, the ratio of the peak areas at $2\theta = 11.6°$ due to the γ form and at $2\theta = 38.7°$ due to LiF *versus* the content of the γ form was determined. Each plot gave a straight line, and the fractional crystallization of a sample could be obtained by using calibration plots. Each value is the average of 3 measurements.

Results and Discussion

X-Ray Diffraction Profiles of Noncrystalline IMC

The α and γ forms (metastable and stable forms) of IMC were converted to a noncrystalline solid during grinding at 4 °C, as described in the previous study.[9] Figure 1 shows the X-ray diffraction profiles of the polymorphs and the noncrystalline solids of IMC obtained by grinding and by the fusion method. The X-ray diffraction profiles of the α form ground at 4 °C for 10 h (GNCα), the γ form ground at 4 °C for 10 h (GNCγ) and NC, all showed a halo pattern with two very broad peaks at 2θ about 10° and about 18°. These two halo peaks can be attributed to the heterogeneous structure in the solid and reflect distances of about 4.43 and 2.49 Å. Therefore, it seems that the peaks are attributable to the indole ring (4.43 Å) and the benzene ring (2.49 Å) in the IMC molecule.

Crystallization Kinetics of Noncrystalline IMC under Isothermal Conditions

The stability of noncrystalline IMC under isothermal conditions at 0% relative humidity was investigated. Figure 2 shows the crystallization process of GNCα. The crystallization product of GNCα contained crystals of both the α and γ forms. After GNCα had been stored for 10000 min the percentage of α and the γ forms were almost constant at about 25% and 65%, respectively, at all temperatures. This finding may be explained by Ostwald's step law.[13] In the first step, the α form was crystallized and after the nuclei of γ form appeared, the γ form was crystallized. The complex crystallization process will be discussed further elsewhere.

Figure 3 shows the crystallization process of GNCγ under isothermal conditions. After the induction period the GNCγ transformed into the γ form. The induction period of GNCγ decreased and the crystallization rate increased with increasing temperature, and the 50% crystallization time of the GNCγ at 20 °C was about 10 times longer than that at 35 °C.

Figure 4 shows the crystallization process of NC under isothermal conditions. The γ form crystallized from the NC after an induction period. The induction period of NC decreased and the crystallization rate increased with increasing temperature. The time for 50% crystallization of NC at 25 °C was about 60 times longer than that of GNCγ at the same temperature. These findings suggest that during the induction periods of NC and GNCγ the nuclei of the γ

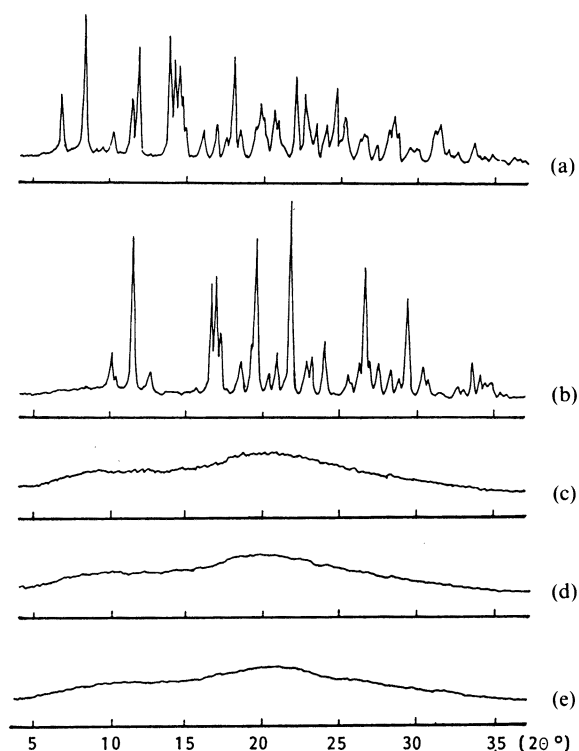Fig. 1. X-Ray Diffraction Profiles of Poly-
morphs of IMC and Noncrystalline IMC

(a) Intact α form, (b) intact γ form, (c) GNCα, (d)
GNCγ, (e) NC.

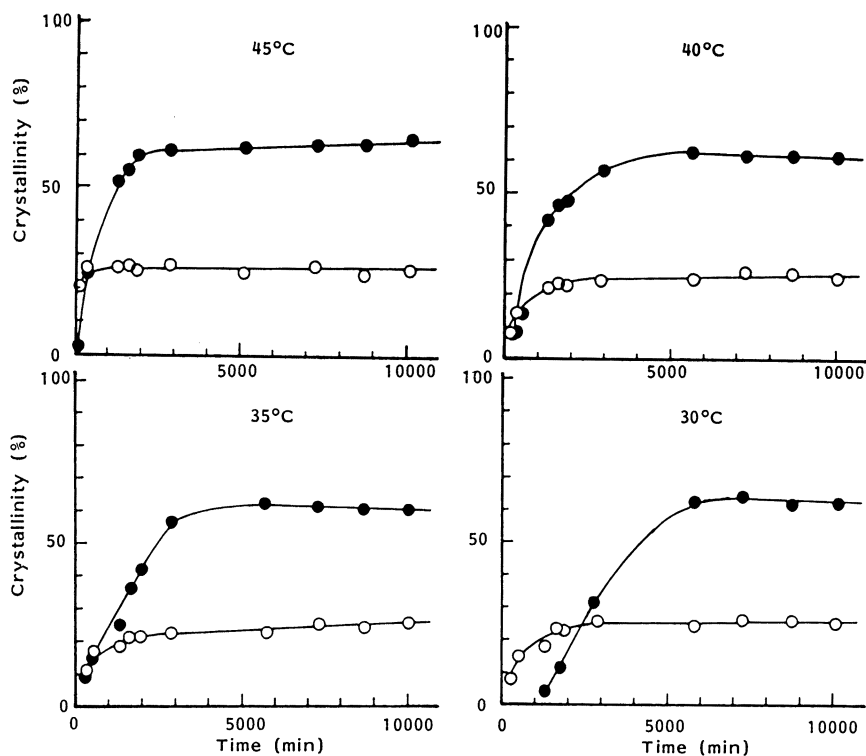
Fig. 2. Crystallization Process of GNCα under Isothermal Conditions

○, α form content; ●, γ form content.

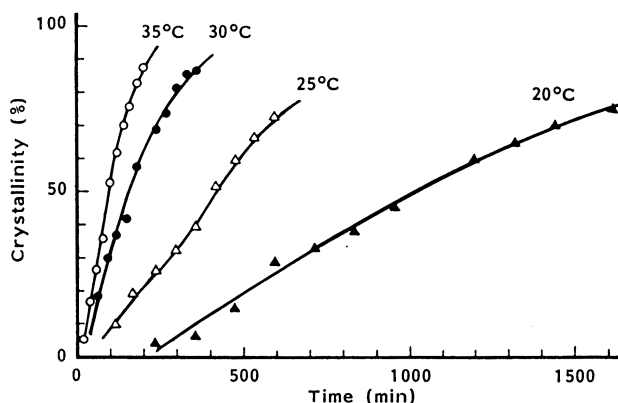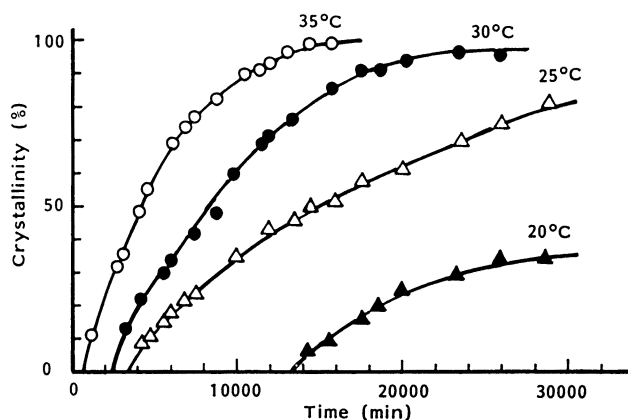Fig. 3. Crystallization Process of GNCγ under Isothermal Conditions

Fig. 4. Crystallization Process of NC under Isothermal Conditions

TABLE I. Kinetic Equation for the Most Common Mechanisms of Solid-State Decomposition and Values of Hancock–Sharp Constant

Symbol	$g(x)$	$m^{a)}$	Mechanism
R_1	x	1.24	Zero-order mechanism (Polany–Winger equation)
R_2	$2(1-(1-x)^{1/2})$	1.11	Two-dimensional phase boundary mechanism (one-half order)
R_3	$3(1-(1-x)^{1/3})$	1.07	Three-dimensional phase boundary mechanism (two-thirds order)
F_1	$-\ln(1-x)$	1.00	First-order mechanism
A_2	$(-\ln(1-x))^{1/2}$	2.00	Two-dimensional growth of nuclei (Avrami equation)
A_3	$(-\ln(1-x))^{1/3}$	3.00	Three-dimensional growth of nuclei (Avrami equation)
D_1	x^2	0.62	One-dimensional diffusion
D_2	$(1-x)\ln(1-x)+x$	0.57	Two-dimensional diffusion
D_3	$(1-(1-x)^{1/3})^2$	0.54	Three-dimensional diffusion (Jander equation)
D_4	$(1-2x/3)-(1-x)^{2/3}$	0.57	Three-dimensional diffusion (Ginstiling–Brounshtein equation)

a) $\ln[-\ln(1-x)]=\ln B+m\ln t$ $(x=0.15—0.50)$.

form appear and grow in the solid.

The crystallization process of NC and GNCγ under isothermal conditions were analyzed by the Hancock–Sharp method[14] (Table I) and the results are shown in Figs 5 and 6. The Hancock–Sharp constant (m) of GNCγ was calculated to be 1.18 ± 0.09 (mean $\pm$ S.D., $n=4$)
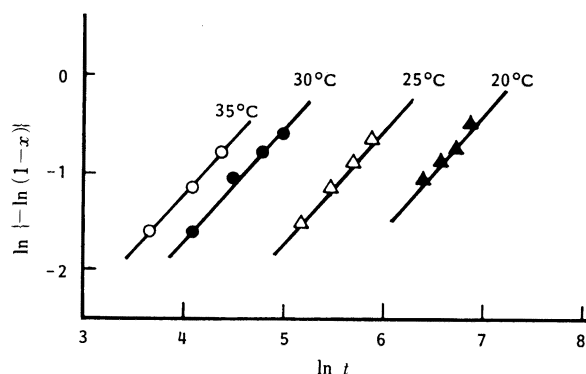
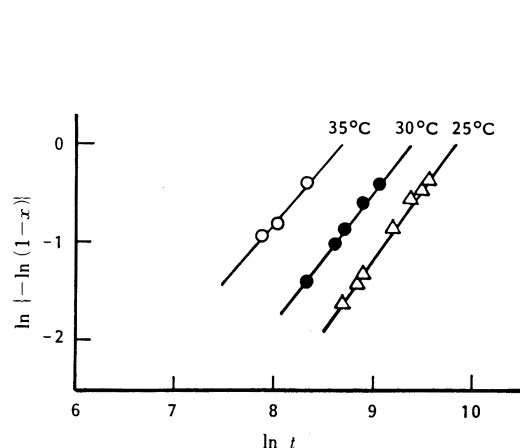Fig. 5. Hancock–Sharp Plots for Isothermal Crystallization of GNCγ of IMC (x=0.15–0.50)

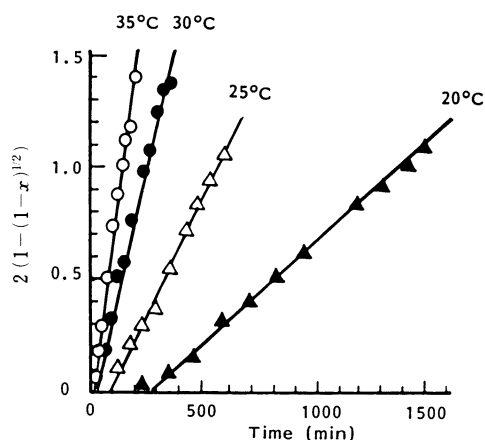Fig. 6. Hancock–Sharp Plots for Isothermal Crystallization of NC of IMC (x=0.15–0.50)

Fig. 7. Most Linear Plots of g(x) *versus* t for Isothermal Crystallization of GNCγ of IMC
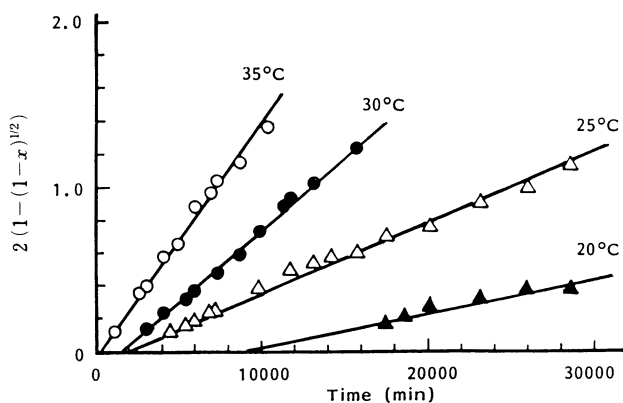

Fig. 8. Most Linear Plots of g(x) *versus* t for Isothermal Crystallization of NC of IMC

by the least-squares method. This suggests that the crystallization of GNCγ follows the mechanism of the two-dimensional phase boundary model (R_2). The value of m for the crystallization of NC was calculated to be 1.37 ± 0.09 (mean $\pm$ S.D., $n=3$). The m value suggests that the crystallization of NC follows a zero-order mechanism, but the plot (Fig. 4) of

TABLE II. Induction Period (I.P.) and 50% Crystallization Time (C.T.) of GNCγ and NC

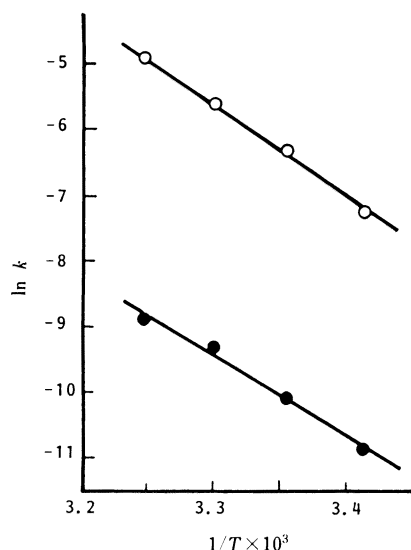| Temp.	GNCγ (min)		NC (min)	
	I.P.	50% C.T.	I.P.	50% C.T.
20 °C	200	1020	910	—
25 °C	70	410	210	1540
30 °C	40	155	170	850
35 °C	20	95	40	420

Fig. 9. Arrhenius Plots for Isothermal Crystallizations of GNCγ and NC of IMC

○, GNCγ-10; ●, NC.

TABLE III. Thermal Dynamic Parameters of Isothermal Crystallization of Various Noncrystalline Solids of IMC

Sample	Transformed form	$m^{a)}$	Most linear model	Frequency factor (min^{-1})	Activation energy (kcal/mol)
GNCγ	γ form	$1.18 \pm 0.09^{b)}$	R_2	1.413×10^{17}	27.2 (0.999$^{c)}$)
NC	γ form	1.37 ± 0.09	R_2	2.022×10^{13}	24.1 (0.994)

a) Hancock–Sharp constant.   b) S.D.   c) Correlation coefficient.

the crystallization process of the NC did not fit this mechanism, and we concluded that the best-fit mechanism is the R_2 equation for NC.

From the results of the Hancock–Sharp method, Figs. 7 and 8 show the plots of the R_2 equation for GNCγ and NC. Each plot of GNCγ and NC at four different temperatures is linear. These results and the induction periods for GNCγ and NC suggest that in the first step the nuclei of γ form appear during the induction period (Table II). In the second step the plate crystals grow from the nuclei in the noncrystalline solid, therefore the mechanism follows the R_2 equation.

The activation energy (E) and the frequency factor (A) for the crystallization of GNCγ and NC were calculated from Arrhenius plots (Fig. 9) and are summarized in Table III. Imaizumi et al.[10] reported that the crystallization process of NC of IMC followed the first-order model and the value of E was 22 kcal/mol. They used different model equation for

calculation but the value of E was very close to ours. The E of GNCγ was slightly larger than that of NC but the mechanism of both noncrystalline solids followed the R_2 equation. The value of A for GNCγ was much larger than that of NC. Therefore, GNCγ was a more unstable solid than NC.

Conclusion

The X-ray diffraction profiles of noncrystalline samples of IMC (GNCα, GNCγ and NC) showed a halo pattern. The GNCγ and NC transformed into the γ form after an induction period, but GNCα transformed into the α form without the induction period. Thereofre it seems that GNCα contains nuclei of α form in the noncrystalline solid. The γ form grew in GNCγ or NC after the induction period because the GNCγ or NC contains no nuclei. The crystallization processes of GNCγ and NC followed the two-dimensional phase boundary model. The E of GNCγ was slightly smaller than that of NC, but the A was much larger than that of NC. These results suggest that the stability difference between NC and GNC depends on the nucleation rate in the noncrystalline solid. The crystallization pathways reflect the structure of the noncrystalline solids. There may be several kinds of noncrystalline IMC.

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