

[Chem. Pharm. Bull.]  
33(8)3447-3455(1985)

## Physicochemical Characterization of Indomethacin Polymorphs and the Transformation Kinetics in Ethanol<sup>1)</sup>

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(Received December 12, 1984)

Methods for the preparation of polymorphs of indomethacin (IMC) were studied in order to obtain the pure polymorphs. The physicochemical properties of IMC polymorphs were measured by using X-ray diffraction analysis, infrared (IR) spectroscopy, differential thermal analysis (DTA) and differential scanning calorimetry (DSC), and two polymorphs ( $\alpha$  and  $\gamma$  forms) and one benzene solvate ( $\beta$  form) were identified.

The pure  $\alpha$  form was obtained when distilled water at room temperature was poured into IMC ethanol solution at about 80 °C, and the precipitated crystals were filtered off and dried. The pure  $\beta$  and  $\gamma$  forms were obtained by recrystallization from benzene and ethyl ether, respectively, at room temperature. The melting points of the  $\alpha$  and  $\gamma$  forms were 148 and 154 °C, respectively, and their heats of fusion were  $7.49 \pm 0.27$  and  $8.64 \pm 0.13$  kcal/mol, respectively, as determined by DSC. A mixture of  $\alpha$  and  $\gamma$  forms was obtained by the method previously reported for  $\alpha$  form preparation ("recrystallization method"), since the pure  $\alpha$  form was transformed to the  $\gamma$  form in ethanol at room temperature. The transformation of  $\alpha$  form to  $\gamma$  form in ethanol was analyzed by the kinetic method using 9 kinds of kinetic models. It was concluded that the transformation followed kinetics corresponding to two-dimensional growth of nuclei (Avrami equation), and the activation energy was calculated to be 14.2 kcal/mol from the Arrhenius plot. The solubilities of the  $\alpha$  and  $\gamma$  forms in distilled water were 0.87 and 0.69 mg/100 ml, respectively.

**Keywords**—indomethacin; polymorphism; polymorphic transformation; kinetic analysis; thermal analysis; solubility

### Introduction

The nature of the crystalline forms of a drug affects bioavailability through the effect of crystal properties on the dissolution rate. Therefore indomethacin (IMC) preparations are required to pass the dissolution test in JPX, because several polymorphs of IMC have been reported. Since Yamamoto<sup>2)</sup> first reported three polymorphic forms,  $\alpha$ ,  $\beta$  and  $\gamma$  forms, of IMC, various reports have appeared on the polymorphism and solvates of IMC obtained by recrystallization from various solvent systems.<sup>3-8)</sup> However, the results conflict with each other. In the present work, methods for the preparation of the pure polymorphs of IMC were established and the physicochemical properties of these forms were confirmed. In order to clarify the kinetic mechanism of the transformation process from the metastable  $\alpha$  form to the stable  $\gamma$  form in ethanol, the contents of  $\alpha$  and  $\gamma$  forms were determined by differential scanning calorimetry (DSC). Further, the effect of the presence of seed crystals on the transformation was studied.

### Experimental

**Materials**— $\alpha$  Form: The  $\alpha$  form of IMC was prepared by a modification of the method of Borka,<sup>3)</sup> i.e., 10 g of IMC bulk powder was dissolved in 10 ml of ethanol at 80 °C, the undissolved drug was filtered off, and 20 ml of distilled water at room temperature was added to the IMC-saturated ethanol solution at 80 °C. The precipitated

crystals were removed by filtration using a glass funnel and then dried overnight in a  $P_2O_5$  desiccator under a vacuum at room temperature.

**$\beta$  Form:** The  $\beta$  form of IMC was prepared by the method of Yamamoto<sup>2)</sup> as follows: IMC bulk powder was dissolved in benzene at about 60 °C, the undissolved drug was filtered off, and the crystals that crystallized from the filtrate on cooling were removed by filtration as soon as possible, then dried overnight in a silica gel desiccator under a vacuum at room temperature. The  $\beta$  form contained about 0.5 mol of benzene as determined by the nuclear magnetic resonance (NMR) method.

**$\gamma$  Form:** The  $\gamma$  form of IMC was prepared by recrystallization from ethyl ether at room temperature, and dried in a silica gel desiccator at room temperature. Table I shows the results of elemental analysis of the  $\alpha$ ,  $\beta$  and  $\gamma$  forms of IMC. The results of elemental analysis and the NMR spectra suggested a high degree of purity of the forms prepared by the above methods.

**X-Ray Diffraction Analysis**—The X-ray diffraction was measured at room temperature with a type JDX-7E diffractometer (Nihon Denshi Co., Ltd.). The measurement conditions were as follows; target Cu; filter Ni; voltage, 20 kV; current, 10 mA; time constant, 2 s; scanning speed, 1 °/min.

**Thermal Analysis**—The differential thermal analysis (DTA) and the DSC curves were measured with DT-20B (Shimadzu Seisakusho Co., Ltd.) and SC-20B (Shimadzu Seisakusho Co., Ltd.) instruments, respectively. The measurement conditions were as follows; sample weight, about 3 mg (DTA) or about 5 mg (DSC); gas flow, 30 ml/min; heating rate, 10 °C/min.

**Infrared (IR) Spectra**—IR spectra were recorded for mulls in Nujol on an IR-2 infrared spectrophotometer (Nihon Bunko Co., Ltd.).

**Polarizing Microscopy**—A polarizing microscope (Olympus model POS) was used.

**Measurement of the Contents of  $\alpha$  and  $\gamma$  Forms in Mixtures of the Two**—The contents of  $\alpha$  and  $\gamma$  forms of IMC were determined by measuring the heats of fusion of the  $\alpha$  and  $\gamma$  forms with a DSC instrument. Table II shows the results of measurement of known physical mixtures of  $\alpha$  and  $\gamma$  forms by using the DSC method. It appears to be possible to determine the contents of  $\alpha$  and  $\gamma$  forms with reasonable accuracy by using the DSC method.

**Measurement of Transformation of  $\alpha$  Form IMC in Ethanol**—The pure  $\alpha$  form of IMC (5 g) was placed in 50 ml of ethanol in a 100 ml light-resistant stoppered conical flask immersed in a water bath maintained at 30, 35, 40 or 45  $\pm$  0.1 °C. Samples of about 50 mg of the crystals were withdrawn at appropriate time intervals by means of a pipette, then filtered off and dried under a vacuum at room temperature. The contents of  $\alpha$  and  $\gamma$  forms were determined by using the DSC method.

**Measurement of Dissolution Curve**—A sample (500 mg) of IMC was rapidly placed in 500 ml of distilled water in a 1000 ml round-bottomed flask (JP X; Dissolution Test) maintained at 35  $\pm$  0.1 °C. The solution was stirred with a paddle at a constant rate of 200 rpm. Samples of the solution were taken by means of a glass syringe at suitable time intervals and were immediately filtered through a 0.45  $\mu$ m membrane filter (Millipore; HAWPO 01300). The filtrate was suitably diluted for spectrophotometric assay (Hitachi Seisakusho Co., Ltd., type 130) at 252 nm.

TABLE I. Elemental Analysis of Polymorphs of IMC

Sample	Calcd (%)			Found (%)		
	C	H	N	C	H	N
$\alpha$ form	63.78	4.51	3.91	63.74	4.52	3.80
$\beta$ form <sup>a)</sup>	66.57	4.83	3.53	66.47	4.76	3.60
$\gamma$ form	63.78	4.51	3.91	64.01	4.48	3.77
$\beta'$ form <sup>b)</sup>	63.78	4.51	3.91	63.94	4.45	3.78

a) 1/2 mol benzene. b)  $\beta$  form heated at 120 °C for 5 min.

TABLE II. Estimation of  $\alpha$  and  $\gamma$  Form Contents of Physical Mixtures of  $\alpha$  and  $\gamma$  Forms of IMC by the DSC Method

$\alpha$ form content of physical mixtures of $\alpha$ and $\gamma$ forms (%)	19.8	41.3	59.5	79.7
Content found by DSC method (%)	17.7	37.1	51.6	77.2

## Results and Discussion

### Physicochemical Properties of Polymorphs and Solvate of IMC

The DTA curves for polymorphs and solvate of IMC obtained by using the previously reported preparation methods are shown in Fig. 1. Two kinds of  $\alpha$  form of IMC were prepared as follows: (1) IMC ethanol solution at about 70 °C was cooled for 4 h at room temperature, and the precipitated crystals were filtered off and air-dried as reported by Yamamoto,<sup>2)</sup> and (2) IMC bulk powder was recrystallized from 30% ethanol aqueous solution by cooling at room temperature for 2 h, then air-dried as reported by Yokoyama *et al.*<sup>7)</sup> The X-ray diffraction profiles and the IR spectra of the  $\alpha$  form of IMC obtained by Yamamoto's<sup>2)</sup> and Yokoyama's<sup>7)</sup> methods agreed with their reported data,<sup>2,7)</sup> but the DTA curves (Fig. 1) had two endothermic peaks at about 150 and 160 °C. Galdecki *et al.*<sup>4)</sup> reported that the DTA curve of the  $\alpha$  form of IMC showed two endothermic peaks; the lower peak at about 150 °C was due to transformation of  $\alpha$  form to  $\gamma$  form and the higher peak at 160 °C was due to fusion. However, in the present study it was found that the ratio of the two endothermic peaks changed with increasing cooling time during recrystallization in ethanol solution. This result suggests that the  $\alpha$  form of IMC was transformed to  $\gamma$  form, and so it is necessary to separate the crystals from the mother liquid as soon as possible in order to obtain pure  $\alpha$  form. Thus, the pure  $\alpha$  form of IMC was obtained as described in the experimental section in the present study.

The  $\beta$  form of IMC was prepared by the method reported by Yamamoto,<sup>2)</sup> *i.e.*, IMC benzene solution at about 50 °C was cooled for 1 h at room temperature, and the crystals that appeared were filtered off, and air-dried. The X-ray diffraction profile and the IR spectrum of the  $\beta$  form obtained by Yamamoto's method agreed with the reported data,<sup>2,7)</sup> but the DTA curve had endo- and exothermic peaks at about 90–120 °C due to desolvation of benzene and endothermic peaks at about 150 and 160 °C due to fusion. The results of elemental analysis and the NMR method showed that the  $\beta$  form was a stoichiometric benzene solvate. It appears that the  $\beta$  form was transformed to  $\gamma$  form in benzene solution at room temperature,

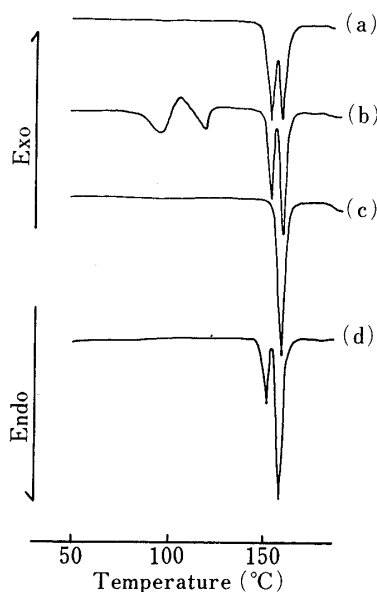


Fig. 1. DTA Curves of Polymorphs of IMC Obtained by Previously Reported Methods

(a)  $\alpha$  form,<sup>a)</sup> (b)  $\beta$  form,<sup>a)</sup> (c)  $\gamma$  form,<sup>a)</sup> (d)  $\alpha$  form.<sup>b)</sup>  
a) Method of Yamamoto,<sup>2)</sup> b) Method of Yokoyama *et al.*<sup>7)</sup>

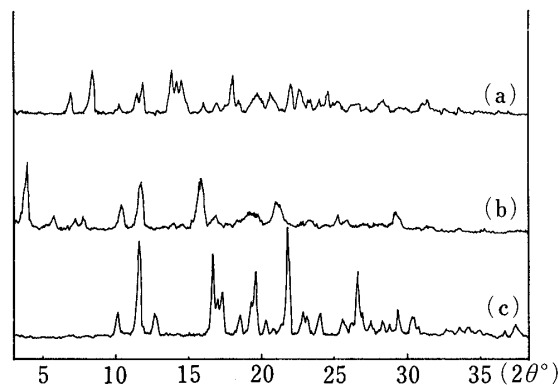


Fig. 2. X-Ray Diffraction Profiles for the Pure Polymorphs of IMC

(a) the pure  $\alpha$  form, (b) the pure  $\beta$  form, (c) the pure  $\gamma$  form.

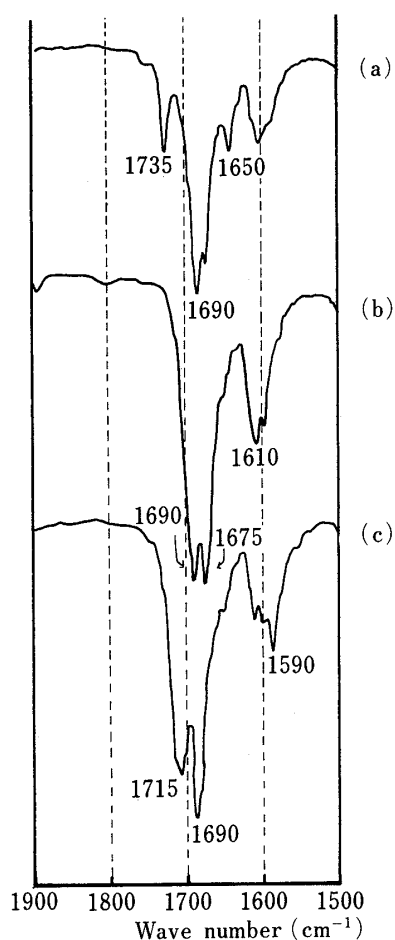


Fig. 3. IR Spectra for the Pure Polymorphs of IMC

(a) the pure  $\alpha$  form, (b) the pure  $\beta$  form, (c) the pure  $\gamma$  form.

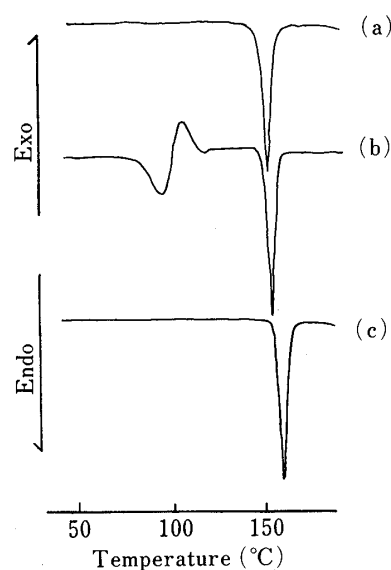


Fig. 4. DTA Curves for the Pure Polymorphs of IMC

(a) the pure  $\alpha$  form, (b) the pure  $\beta$  form, (c) the pure  $\gamma$  form.

since the endothermic peak at  $160^\circ\text{C}$  in the DTA curves of the  $\beta$  form increased with increasing cooling time during recrystallization. Therefore it is necessary to separate the crystals from the mother liquid as soon as possible in order to obtain the pure  $\beta$  form as described in the experimental section.

The pure  $\alpha$ ,  $\beta$  and  $\gamma$  forms of IMC were obtained by procedures which took account of these transformations in the mother liquid. The physicochemical properties of the pure  $\alpha$ ,  $\beta$  and  $\gamma$  forms of IMC are described below.

Figure 2 shows the X-ray diffraction profiles of the pure  $\alpha$ ,  $\beta$  and  $\gamma$  forms of IMC. The main X-ray diffraction peaks of the  $\alpha$  form were at  $2\theta = 7.0, 8.5, 11.5, 12.0$  and  $14.0^\circ$  and those of the  $\beta$  form were at  $2\theta = 3.9, 10.5$  and  $15.9^\circ$ , while those of the  $\gamma$  form were at  $2\theta = 10.2, 11.7, 12.7$  and  $17.0^\circ$ . It is impossible to assess mutual contamination among the forms of IMC from the X-ray diffraction profiles, because the X-ray diffraction peaks of all the forms overlap.

Figure 3 shows the IR spectra of the pure  $\alpha$ ,  $\beta$  and  $\gamma$  forms of IMC; the main absorption peaks are at  $1735, 1690$  and  $1650\text{ cm}^{-1}$ , at  $1690, 1675$  and  $1610\text{ cm}^{-1}$ , at  $1715, 1690$  and  $1590\text{ cm}^{-1}$  respectively.

Figure 4 shows the DTA curves of the pure  $\alpha$ ,  $\beta$  and  $\gamma$  forms of IMC. The  $\alpha$  form shows a single endothermic peak at  $148^\circ\text{C}$  due to fusion. The  $\beta$  form shows endo- and exothermic

peaks at 80–120 °C attributable to desolvation of benzene and transformation of  $\beta$  form to  $\alpha$  form, with an endothermic peak at 148 °C due to fusion of the  $\alpha$  form. It was confirmed by using X-ray diffraction analysis that the  $\beta$  form was transformed into the  $\alpha$  form by heating at 120 °C for 5 min. The pure  $\gamma$  form shows an endothermic peak at 158 °C due to fusion.

### Transformation of the $\alpha$ Form of IMC in Ethanol

The change of contents of  $\alpha$  and  $\gamma$  forms in crystals with time was determined by using the DSC method for the pure  $\alpha$  form of IMC suspended in ethanol. The DSC curves of the  $\alpha$  form suspended in ethanol at 45 °C for 3, 9 and 18 h are shown in Fig. 5. This result suggests that the  $\alpha$  form was transformed to the  $\gamma$  form in ethanol at 45 °C within 18 h.

Figure 6 shows the transformation process of the pure  $\alpha$  form of IMC to  $\gamma$  form at 30, 35, 40 and 45 °C. This result suggests that the pure  $\alpha$  form was transformed completely to  $\gamma$  form in ethanol at 30, 35, 40 and 45 °C within about 100, 60, 40 and 18 h, respectively. The heats of

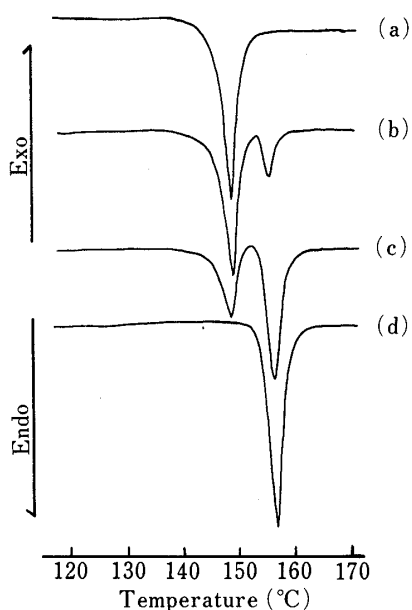


Fig. 5. Change of DSC Curves of the  $\alpha$  Form of IMC on Storage in Ethanol at 45 °C

(a) the pure  $\alpha$  form, (b) after 3 h, (c) 9 h, (d) 18 h.

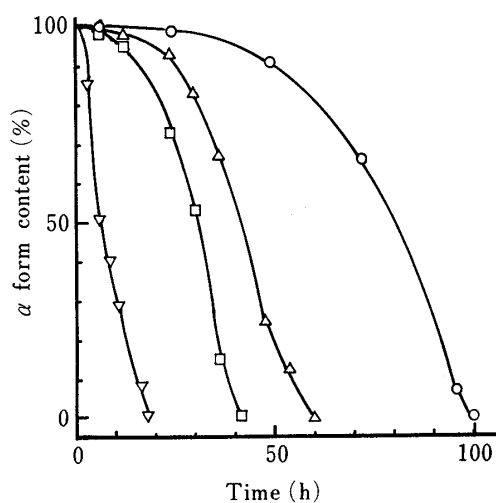


Fig. 6. Time Courses of Residual Amount of  $\alpha$  Form of IMC during the Transformation to the  $\gamma$  Form in Ethanol at Various Temperatures

○, at 30 °C; △, at 35 °C; □, at 40 °C; ▽, at 45 °C.

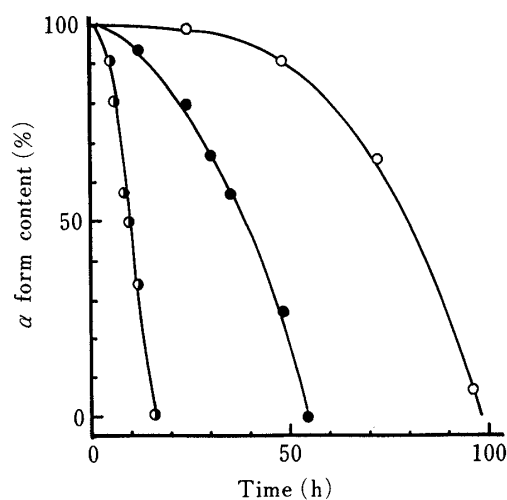


Fig. 7. Transformation of the  $\alpha$  Form of IMC in Ethanol at 30 °C

○, the pure  $\alpha$  form; ●, the  $\alpha$  form containing 1%  $\gamma$  form. ▾, the “ $\alpha$  form” obtained by the recrystallization method (10% IMC ethanol solution at 80 °C was cooled at 30 °C).

fusion of the pure  $\alpha$  and  $\gamma$  forms were  $7.49 \pm 0.27$  and  $8.64 \pm 0.13$  kcal/mol, respectively, as determined by DSC.

Figure 7 shows the transformation of polymorphs of IMC in ethanol at 30 °C. The pure  $\alpha$  form was transformed to  $\gamma$  form within about 50 h in the presence of 1%  $\gamma$  form as a seed, and this transformation time was about half that of the pure  $\alpha$  form alone. From this result, it is considered that nucleation is the rate-determining step of transformation of the  $\alpha$  form. In the method for the preparation of  $\alpha$  form by recrystallization, the metastable  $\alpha$  form was separated from the mother liquid in the first step, and the metastable  $\alpha$  form was transformed to the stable  $\gamma$  form within 18 h in the second step, following Ostwald's step law.<sup>9)</sup> This result suggests that the previously reported recrystallization method<sup>2-8)</sup> for preparing the  $\alpha$  form actually yields a mixture of  $\alpha$  and  $\gamma$  forms.

### Kinetic Mechanism of Transformation of the $\alpha$ Form of IMC to the $\gamma$ Form in Ethanol

In order to clarify the kinetic mechanism of transformation of polymorphs of IMC in ethanol, we analyzed the transformation on the basis of the solid-state kinetic models<sup>10)</sup> shown in Table III. It can be assumed that the dissolution rate of the  $\gamma$  form and the crystallization rate of the  $\gamma$  form in ethanol solution were in a pseudo-equilibrium state, since the solution had reached saturation with IMC within about 3 h (at the first sampling time). It is also assumed that the  $\alpha$  form was directly transformed to the  $\gamma$  form in ethanol.

TABLE III. Kinetic Equations for the Most Common Mechanisms of Solid-State Decomposition

Symbol	$g(x)$	Mechanism
$R_2$	$2(1-(1-x)^{1/2})$	One-half order mechanism
$R_3$	$3(1-(1-x)^{1/3})$	Two-thirds order mechanism
$F_1$	$-\ln(1-x)$	First-order mechanism
$A_2$	$(-\ln(1-x))^{1/2}$	Two-dimensional growth of nuclei
$A_3$	$(-\ln(1-x))^{1/3}$	Three-dimensional growth of nuclei
$D_1$	$x^2$	One-dimensional diffusion
$D_2$	$(1-x)\ln(1-x)+x$	Two-dimensional diffusion
$D_3$	$(1-(1-x)^{1/3})^2$	Three-dimensional diffusion (Jander)
$D_4$	$(1-2x/3)-(1-x)^{2/3}$	Three-dimensional diffusion (Ginstling-Brounshtein)

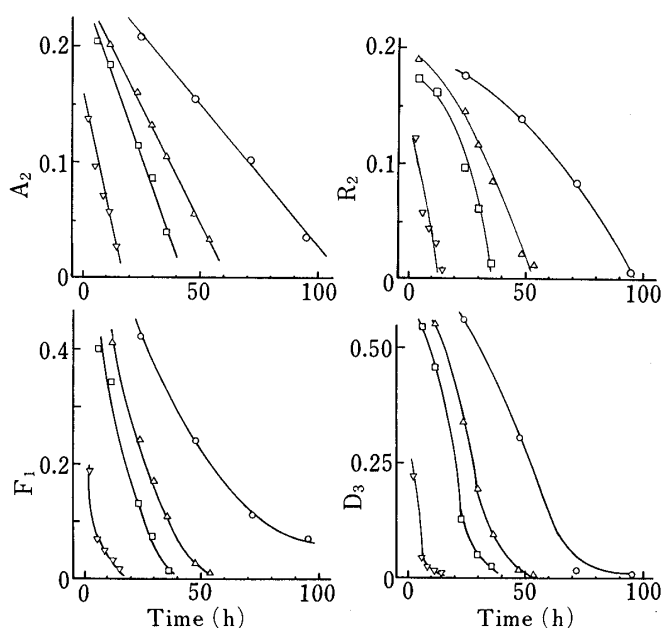


Fig. 8. Dependence of the Function  $g(x)$  on Time for Transformation from the  $\alpha$  Form of IMC to the  $\gamma$  Form in Ethanol  
 ○, at 30 °C; △, at 35 °C; □, at 40 °C; ▽, at 45 °C.

Typical plots of kinetic model function  $g(x)$  against time  $t$  of transformation of the  $\alpha$  form in ethanol are shown in Fig. 8. The most linear plot was obtained with the two-dimensional nuclear growth equation (the Avrami equation)<sup>11)</sup> by using the least-squares method. Thus, it appears that the transformation mechanism of the  $\alpha$  form in ethanol follows the Avrami equation.

Figure 9 shows that the transformation of the  $\alpha$  form of IMC in the presence of 1%  $\gamma$  form followed the same Avrami equation as that of the pure  $\alpha$  form, though the rate constant  $k$  was about twice that of the pure  $\alpha$  form. Since the transformation rate of the  $\alpha$  form was increased by adding 1%  $\gamma$  form as a seed, the rate-determining step may be the nucleation, given that there was no change in the kinetic mechanism.

In the recrystallization of the pure  $\alpha$  form, the transformation rate decreased after 5–10 h, and there was a little precipitate in the mother liquid at the initial stage; thus, the crystallization rates of the  $\alpha$  and  $\gamma$  forms from the super-saturated ethanol mother liquid

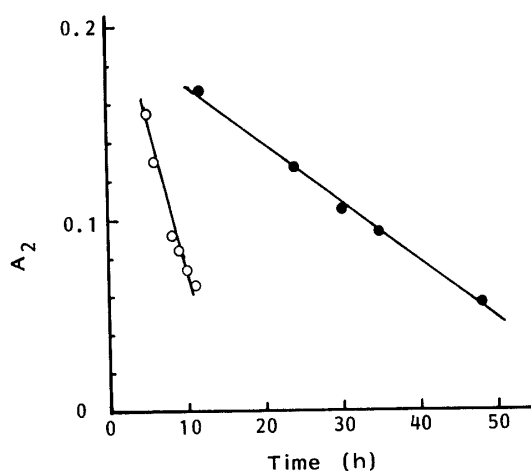


Fig. 9. Dependence of the Function  $g(x)$  on Time for Transformation of the  $\alpha$  Form of IMC in Ethanol

●, the pure  $\alpha$  form containing 1%  $\gamma$  form; ○, sample obtained by the recrystallization method (see legend to Fig. 7).

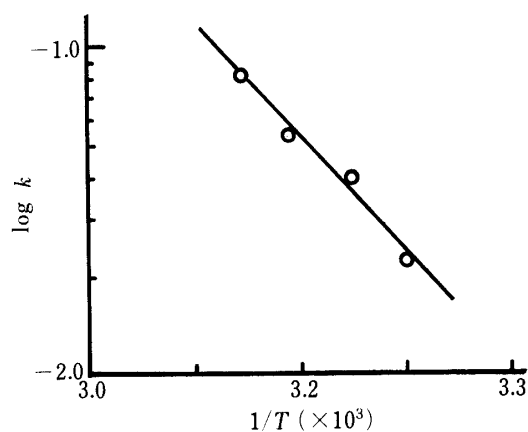


Fig. 10. Arrhenius Plot for Transformation from the  $\alpha$  Form of IMC to the  $\gamma$  Form in Ethanol

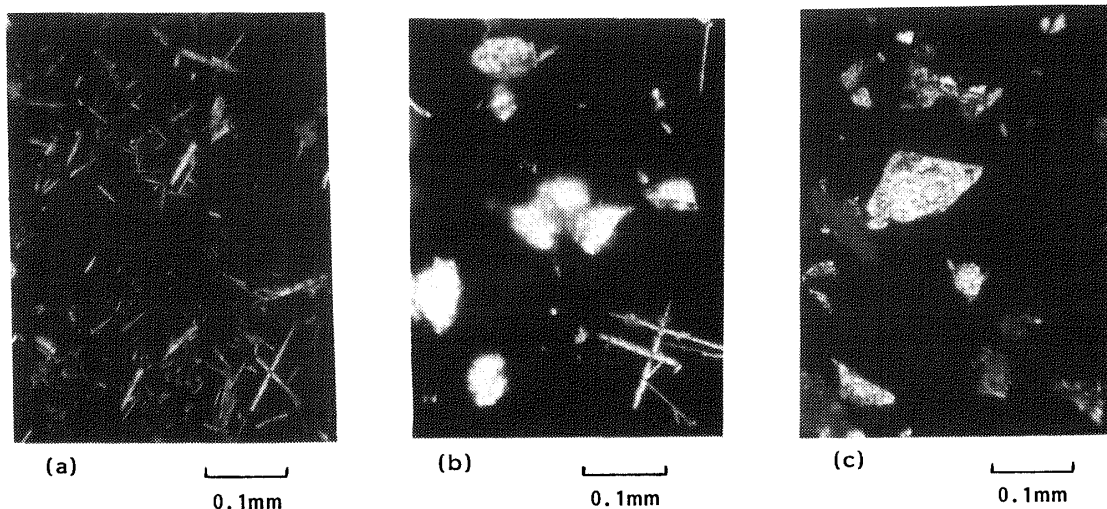


Fig. 11. Polarizing Microphotographs of Polymorphs of IMC ( $\times 100$ )

(a) the pure  $\alpha$  form, (b) the sample suspended for 54 h in ethanol at 35°C, (c) the pure  $\gamma$  form.

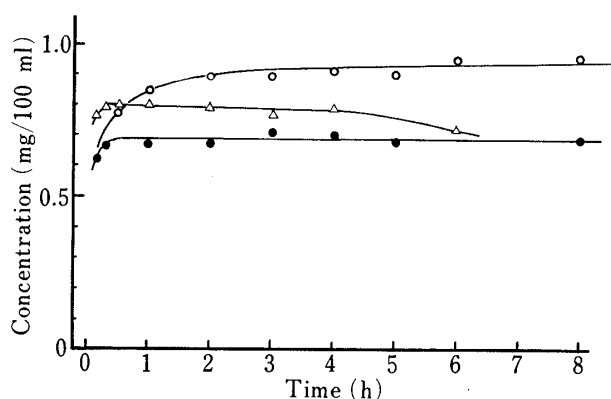


Fig. 12. Dissolution Curves for Polymorphs of IMC in Distilled Water at 35 °C

○, the pure  $\alpha$  form; ●, the pure  $\gamma$  form; △, the  $\alpha$  form obtained by Yamamoto's method.

should not be neglected. A kinetic model including the transformation rate of  $\alpha$  form to  $\gamma$  form and the crystallization rates of  $\alpha$  and  $\gamma$  forms from the mother liquid may be necessary in order to clarify fully the kinetic mechanism of the recrystallization of IMC.

The transformation rates of  $\alpha$  form to  $\gamma$  form in ethanol (the Avrami equation) at each temperature were calculated from Fig. 8 by using the least-squares method. The activation energy of the transformation of  $\alpha$  form to  $\gamma$  form in ethanol was calculated to be 14.2 kcal/mol from the slope of the Arrhenius plots (Fig. 10) by the least-squares method.

Figure 11 shows polarizing microphotographs of the polymorphs of IMC. The  $\alpha$  and  $\gamma$  forms are needle and plate crystals, respectively. Figure 11(b) shows the result for a sample which had been suspended in ethanol at 35 °C for 54 h; this sample is clearly a mixture of  $\alpha$  and  $\gamma$  forms.

### The Dissolution Curves of Polymorphs of IMC

The dissolution curves of polymorphs of IMC in distilled water at 35 °C are shown in Fig. 11. The concentration of the pure  $\alpha$  form was 0.87 mg/100 ml at 7 h, and the solubility of the pure  $\gamma$  form was 0.69 mg/100 ml. The concentration of the  $\alpha$  form obtained by Yamamoto's method was about 0.80 mg/100 ml at 30 min but it decreased to 0.72 mg/100 ml at 6 h, which is consistent with the presence of about 10%  $\gamma$  form acting as seed in this preparation. This result suggests that the pure  $\alpha$  form is more soluble than the  $\alpha$  form obtained by Yamamoto's method, and its solubility is maintained for at least 6 h.

### Conclusion

Conflicting results in previously reported papers on the preparation of the  $\alpha$  form of IMC can be ascribed to the transformation of the  $\alpha$  form to the  $\gamma$  form during the process of recrystallization in ethanol. The transformation of the  $\alpha$  form to the  $\gamma$  form in ethanol followed the Avrami equation and its activation energy was calculated to be 14.2 kcal/mol. The pure  $\alpha$  form of IMC was obtained in the present study as a fine powder and its solubility was about 30% higher than that of the  $\gamma$  form up to 6 h. Thus, the pure  $\alpha$  form of IMC is likely to be more suitable as a bulk powder for use in the pharmaceutical industry.

**Acknowledgement** The authors are grateful to Takeshima Pharmaceutical Co., Ltd. for generous gifts of materials.

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