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Some Physicochemical Properties of Glassy Indomethacin[1)]

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Glassy indomethacin was prepared by cooling the melt, and the glassy state was confirmed by the jump of heat capacity and the anomalous endothermic peak (heat capacity maximum) in the differential scanning calorimetry (DSC) curve. The influences of the cooling rate of the melt and the heating rate of the glass formed on the glass transition temperature (T_g) were examined, and the apparent activation energy of glass transition was calculated to be 212.5 kJ/mol. The relaxation process below T_g was traced in terms of the area under the anomalous endothermic peak of the DSC curve and the rate of relaxation during annealing was found to reach the maximum at about 303 K. The rate of dissolution of glassy indomethacin was far greater than that of crystalline indomethacin. Although indomethacin remained as a glass for 2 years at room temperature, pulverized glassy indomethacin was found to crystallize, and the rate of crystallization was determined by the X-ray diffraction method. The degree of crystallization was determined by Hermans' method, and was found to reach a maximum of 60% after 2 months. The process of crystallization followed first-order kinetics.

Keywords——indomethacin; glassy state; relaxation process; glass transition temperature; differential scanning calorimetry; X-ray analysis; dissolution rate

There have been numerous reports on the glassy state of high-molecular compounds, but the nature of the glassy state of low-molecular compounds has been less well investigated.[2)] The glass behavior and glass properties of some pure low molecular compounds have been investigated in detail for the most part by Seki *et al.*[3)] from the thermodynamic point of view.

The glassy state may be a favorable state of drugs from the standpoint of bioavailability if it increases the rates of dissolution and absorption of drugs. Several drugs have been reported to form glasses with citric acid, and various barbiturates have also been reported to be capable of glass formation.[4)] However, the nature of the glassy state of pure drugs has not been studied in detail and the descriptions of the glass transition process and the glassy state are more or less empirical in nature. The properties of solids formed by cooling the melts have been reported by several workers.[5)] Borka reported that indomethacin solidified after melting as a brittle, glassy amorphous mass which remained uncrystallized for at least 2 months at room temperature, and that the melting point was 55—57 °C.[5)] However, he did not confirm that the solidified indomethacin existed in the glassy state.

In the present work, glassy indomethacin was prepared by cooling the melt, and its glass transition temperature (T_g), jump of heat capacity and anomalous endothermic peak were determined by differential scanning calorimetry (DSC). Moreover, the isothermal enthalpy relaxation process of the glass below T_g was studied by thermal analysis. The rate of dissolution and the effect of pulverization on the stability of glassy indomethacin were also studied in the present investigation.

Experimental

Materials——Indomethacin (γ-type)[6)] was obtained from Merck-Banyu Co., Ltd.

Preparation of Glass——γ-type crystals of indomethacin were melted in an aluminium sample pan equipped with an Intracooler I system and the melts were solidified by cooling them to 270 K at various rates. For dissolution studies, the crystals were melted by heating with a mantle heater and the melts were solidified by allowing them to cool to room temperature on standing.

X-Ray Diffraction Studies (Powder Method)——A Rigaku Denki Geigerflex instrument equipped with a scintillation counter as a detector was used for these studies. Every experiment was carried out under the following conditions: target, Cu; filter, Ni; voltage, 35 kV; current, 15 mA; receiving slit, 0.3 mm; time constant, 1—5 s; scanning speed, 0.5—2 °/min.

Thermal Analysis——A Perkin Elmer DSC-2 differential scanning calorimeter was used. The Intracooler I was used to cool the sample to 270 K. The glass transition was observed as a discontinuity due to an increase of heat capacity of the material in the ordinate of the DSC curve, as shown in Fig. 1. There has been no general agreement as to the method for determination of the T_g value. However, T_g has been widely determined as the B point (the crossing point of the extrapolated lines), so the B point method was employed in the present investigation. The area under the anomalous endothermic peak was determined by extrapolating the baseline after the transition point and is shown with oblique lines in Fig. 1. The absorbed or evolved energy of the sample was calculated by measuring the peak area of the sample and by comparing it to the area under the fusion peak of a known weight of indium as a standard material. The areas were determined by weighing the peak areas after cutting them from chart paper equilibrated for 24 h at room temperature.

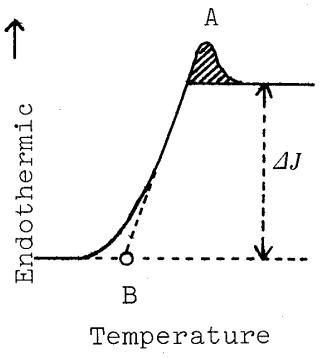

Fig. 1. Determination of Glass Transition Temperature

A, anomalous endothermic peak (heat capacity maximum); B, the glass transition temperature extrapolated from the linear portion of the curve; ΔJ, jump of heat capacity.

Thin-Layer Chromatography (TLC)——The chemical stability of indomethacin during the treatment employed was studied by using TLC. The indomethacin samples dissolved in acetone were spotted on silica gel plates, which were developed with a solvent system of ethyl acetate–ethanol–acetic acid (100 : 20 : 1). Indomethacin was detected under ultraviolet (UV) light.

Dissolution Studies——The beaker method was employed. The dissolution was performed in 100 ml of distilled water or distilled water–ehtanol (1 : 1, v/v). The bath was maintained at 20±0.1 °C and the solution was agitated at 103 rpm.

Samples: A disk of γ-type crystals of indomethacin was prepared by compressing the powder at 1100 kg/cm^2 in a die of 1.3 cm diameter at low pressure in a hydraulic press. Matrix of glassy indomethacin was prepared by allowing the melt to cool down to room temperature in a mold made of aluminium foil with an internal diameter of 1.3 cm. The concentration of indomethacin dissolved in the solvent was determined by UV absorption measurement at 318 nm in a Hitachi 340 spectrophotometer.

Results and Discussion

1) Confirmation of Amorphous State of the Solidified Melt by X-Ray Diffraction Method

Figure 2 shows X-ray diffraction patterns of γ-type crystals and the solidified melt of indomethacin. The solidified melt was a transparent and brittle glassy mass. A halo was observed in the X-ray diffraction pattern, and the solidified melt was in an amorphous state.

2) Thermal Analysis

(1) Influence of Heating Rate on Glass Transition——The melts were rapidly cooled to 270 K and reheated at various heating rates. The DSC results are shown in Fig. 3; a jump of heat capacity and an anomalous endothermic peak (heat capacity maximum) can be seen. These results indicated that the solidified melt existed in a glassy state. The glass showed different DSC curves due to the structural relaxation mentioned later during continuous

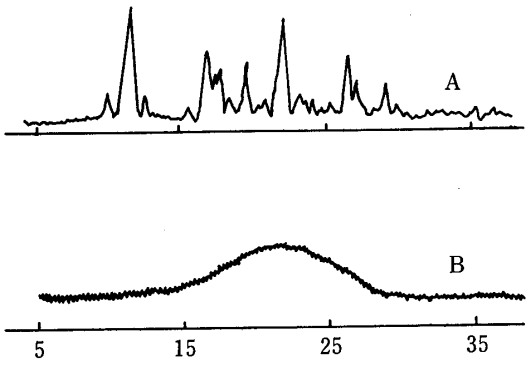

Fig. 2. X-Ray Diffraction Patterns of γ-Type Crystals and Glass of Indomethacin

A, γ-type crystals; B, glass.

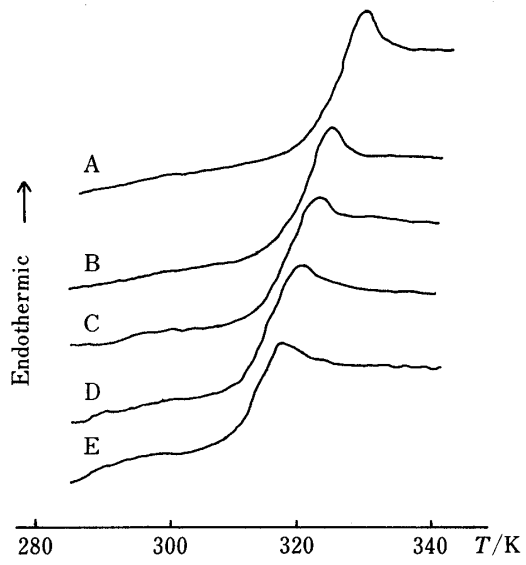

Fig. 3. Variation of T_g with Heating Rate of the Glass

Heating rate: A, 40; B, 20; C, 10; D, 5; E, 2.5 K/min.

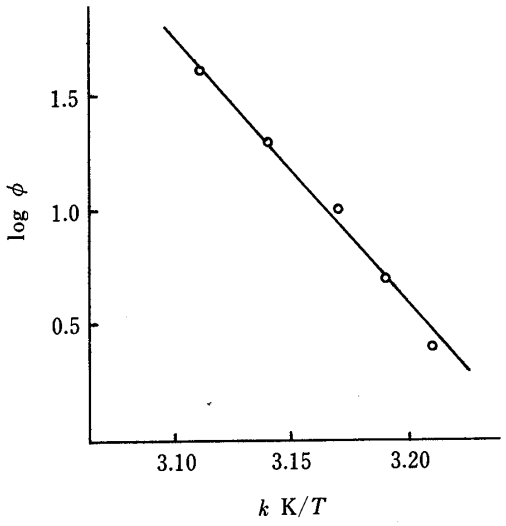

Fig. 4. log Heating Rate *vs.* $1/T_g$

ϕ: heating rate.

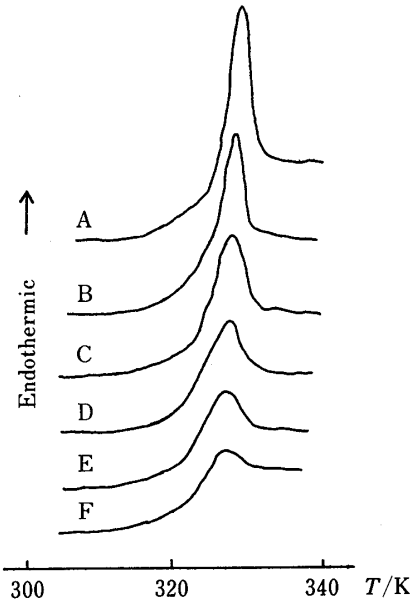

Fig. 5. DSC Curve of Glassy Indomethacin Prepared at Various Cooling Rates

Cooling rate: A, −0.62; B, −1.25; C, −2.5; D, −5; E, −10 K/min; F, quenching.

heating at different heating rates. Thus, to prevent the glass from recovering enthalpy of relaxation during heating, a fast heating rate was desirable. The most suitable heating rate to detect the glass transition and anomalous endothermic peak was found to be 20 or 40 K/min. Therefore, the heating rate of 20 or 40 K/min was adopted to observe T_g and the anomalous endothermic peak. Studies on the effect of heating rate on T_g revealed that the T_g increased as the heating rate was increased. A linear relationship was observed when the logarithm of the heating rate was plotted against $1/T_g$ (Fig. 4). The apparent activation energy of glass transition was calculated to be 212.5 kJ/mol according to an equation derived by Barton.[7]

(2) Influence of Cooling Rate during Glass Preparation on the Glass Transition——It is generally accepted that glass formation depends on the cooling rate of the melt. To examine the effect of the cooling rate on the glass formation, glassy indomethacin was prepared at various cooling rates and the glasses thus obtained were reheated under the conditions described above (Fig. 5). As a jump of heat capacity was observed under all the conditions employed, it was suggested that a glass was formed irrespective of the cooling rate. The magnitude of the jump was almost the same in all cases, as shown in Fig. 5. However, the T_g varied from 320 K in the case of quenching to 324 K in the case of a cooling rate of -0.62 K/min. Thus, T_g increased with decrease in the cooling rate of the melt. The anomalous endothermic peak became larger. These results indicate that a relaxation process takes place during cooling. The endothermic peak that accompanied the jump is concerned with the dynamics of freezing of molecular movement. Several authors[8] have explained the mechanism of formation of the anomalous endothermic peak by using the Hirai–Eyring hole theory. The energy of the anomalous endothermic phenomenon was reported to reflect the quantity of relaxation of the glass; the process of relaxation will be discussed later.

(3) Effect of Isothermal Aging Process below T_g on the Glassy State——After the melt was

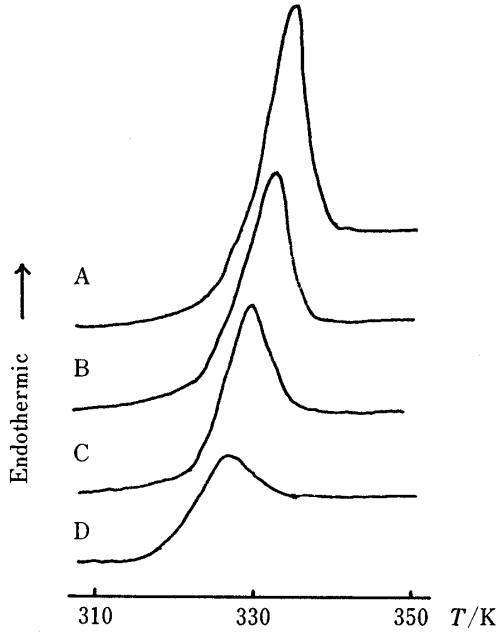

Fig. 6. Effect of Isothermal Aging at 303 K on the Area under the Anomalous Endothermic Peak of the DSC Curve

Aging time: A, 60; B, 35; C, 16; D, 0 min.

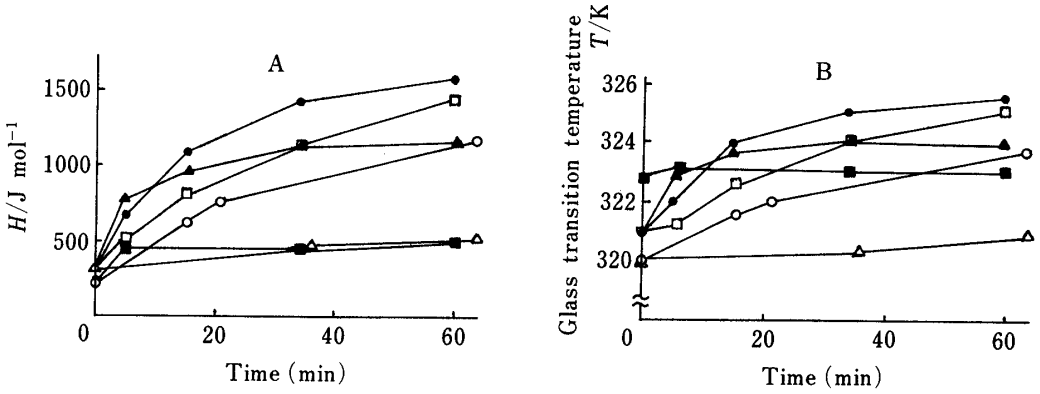

Fig. 7. Influence of Temperature on the Rate of Enthalpy Relaxation during Isothermal Aging below T_g

A, the area under the anomalous endothermic peak of the DSC curve; B, T_g.
Temperature for isothermal aging: △, 283; ○, 293; □, 298; ●, 303; ▲, 308; ■, 313 K.

rapidly cooled to a specified temperature (T_b) below T_g in the region of 283—313 K, the sample was kept at constant temperature to trace the isothermal relaxation process. Then it was reheated to above T_g at a heating rate of 40 K/min to determine the extent of relaxation during isothermal aging. The area under the anomalous endothermic peak of the DSC curve was determined as described before. The increase in the area under the anomalous endothermic peak (heat capacity maximum) with aging corresponds to the regained enthalpy of the sample lost during standing at T_b. Figure 6 shows the effect of the isothermal aging process on the area under the anomalous endothermic peak of the DSC curve at 303 K. The anomalous endothermic peak thus obtained increased with aging time, showing that the enthalpy relaxation proceeded gradually during standing at temperatures below T_g. T_g also increased in the same manner as the anomalous endothermic peak as shown in Fig. 6.

The influence of temperature on the rate of enthalpy relaxation during isothermal aging was examined. Figure 7(A) shows the increase in the area of the anomalous endothermic peak of the glass during standing at various temperatures. The rate of relaxation increased as the temperature increased up to 303 K and decreased at higher temperatures. At 283 and 313 K, the increase in the area under the anomalous endothermic peak of the DSC curve was barely observed. Figure 7(B) shows the effect of the isothermal aging process on T_g of the glass during standing at various temperatures. T_g reached a maximum at 303 K as shown in Fig. 7(B). Figure 8 shows the area under the anomalous endothermic peak (A) and the T_g (B) from the DSC curve plotted against temperature at aging times of 20, 40 and 60 min. Both the area

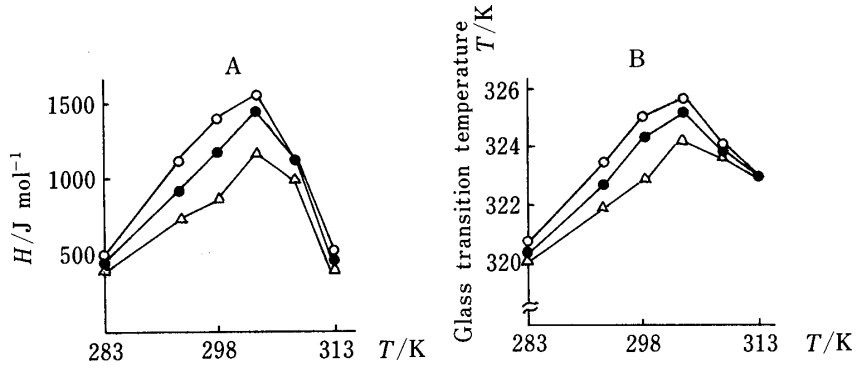

Fig. 8. The Area under the Anomalous Endothermic Peak and T_g in the DSC Curve for the Isothermally Aged Samples

A, the area under the anomalous endothermic peak in the DSC curve; B, T_g.
Aging time: △, 20; ●, 40; ○, 60 min.

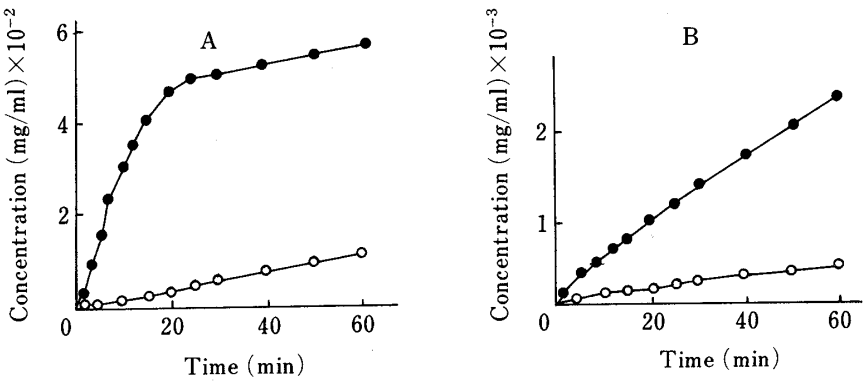

Fig. 9. Dissolution of γ-Type Crystals and Glass by a Beaker Method

A, in water–ethanol; B, in water.
●, glass; ○, γ-type crystal.

under the anomalous endothermic peak and T_g varied similarly and reached the maximum at 303 K. This phenomenon can be explained by the relaxation theory and it may be concluded that the main factors influencing the relaxation process are aging time and temperature. Two possibilities for the effect of temperature on the relaxation process should also be taken into consideration. First, the quantity of frozen holes at the equilibrium state, as explained by the hole theory, may decrease with decrease of the temperature.[9] Second, the molecular mobility may decrease with decrease of temperature. These mechanisms could explain the presence of an optimum temperature at which the area under the anomalous endothermic peak and T_g are maximum.

3) Chemical Stability Studies

To examine whether or not indomethacin was decomposed during the fusion process, the properties of crystalline and glassy samples were studied by TLC. Both samples gave just one spot with the same *Rf* value. These results indicate that decomposition did not occur during the process of glass formation.

4) Dissolution Studies

Figure 9 shows the dissolution profiles of matrices of γ-type crystalline and glassy indomethacin in water–ethanol (1 : 1, v/v) and water systems. In a water–ethanol system,

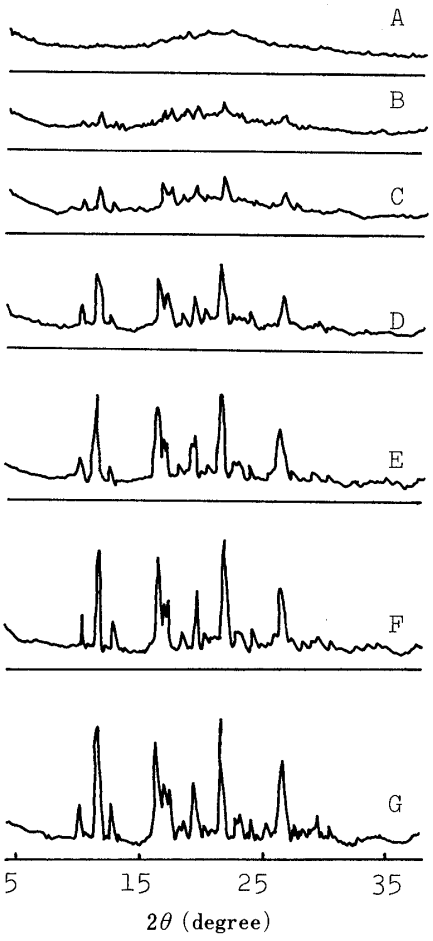

Fig. 10. The Variation of X-Ray Diffraction Patterns of Pulverized Glassy Indomethacin with Time

A, immediately after pulverization; B, 24 h; C, 48 h; D, 7 d; E, 14 d; F, 30 d; G, 67 d.

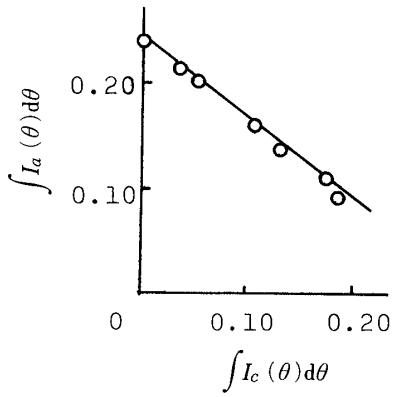

Fig. 11. The Regression Line for the Scattering Intensities from Crystalline and Amorphous Regions of Indomethacin Samples with Different Crystallinities, Obtained by Hermans' Method

glassy indomethacin had a rate of dissolution which was 15 times larger than that of γ-type crystals at the initial stage, but the slope of the dissolution curve of the glass decreased gradually and after 20 min it became equal to that of the γ-type crystals. It was also observed that at about 15 min from the onset of dissolution, the surface of the matrix of transparent glassy indomethacin started to become opaque and gradually turned white. This change of the surface coincided with that of the dissolution curve. In water, glassy indomethacin had a dissolution rate which was 5 times larger than that of γ-type crystals. In this system, the surface of the matrix started to become opaque at 7 h. A marked increase in the rate of dissolution of drugs may influence their absorption characteristics when they are administered orally. This could give the glass an important advantage over the crystalline solid in terms of bioavailability.

5) Crystallization of Glassy Indomethacin during Standing at Room Temperature after Pulverization

Glassy indomethacin was stable, and devitrification did not occur for more than 2 years in the laboratory at room temperature. An attempt was made to elucidate the influence of grinding of the glass on the transition to crystals by the X-ray method. A mass of glassy indomethacin was pulverized in a mortar and the 50—100 mesh fraction was collected by using standard sieves and stored at room temperature. Figure 10 shows the X-ray diffraction patterns of pulverized glassy indomethacin at various storage times. Scattering intensity of crystalline indomethacin increased with the lapse of time. The increase leveled off after 2 months, and the crystals formed were of γ-type. The degree of crystallization of indomethacin was evaluated by Hermans' method.[10] In the present work, the diffraction angles were confined to the region between 4 and 38 °. The ratios of the intensities of individual peaks to the whole intensity of crystalline peaks were constant, so the corrections for the Lorentz factor and polarization effect were not required. Integrated intensities for scattering from crystalline and amorphous regions were separated into two parts, *i.e.* $\int I_c(\theta)\mathrm{d}\theta$ and $\int I_a(\theta)\mathrm{d}\theta$. $\int I_c(\theta)\mathrm{d}\theta$ was plotted against $\int I_a(\theta)\mathrm{d}\theta$ as shown in Fig. 11, and the result indicated a linear relationship between $\int I_a(\theta)\mathrm{d}\theta$ and $\int I_c(\theta)\mathrm{d}\theta$. The slope k was calculated to be -0.765 by the least-squares method, and the crystallinity (X_{cr}) of indomethacin was calculated by means of the following equation;

$$X_{cr}=\frac{\int I_c(\theta)\mathrm{d}\theta}{\int I_c(\theta)\mathrm{d}\theta-(1/k)\int I_a(\theta)\mathrm{d}\theta} \quad (1)$$

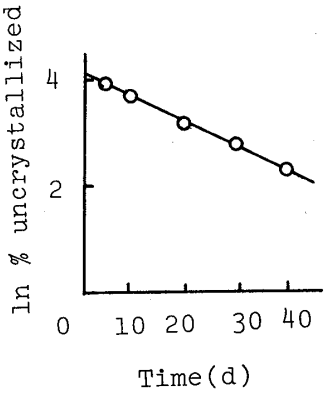

Fig. 12. Crystallinity *vs.* Time Curve for Pulverized Glassy Indomethacin

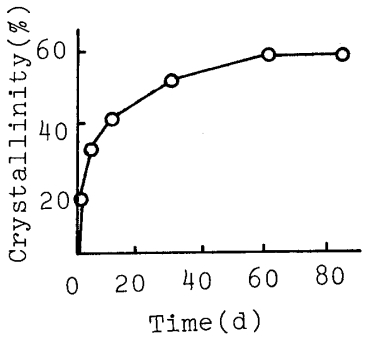

Fig. 13. The Rate of Crystallization of Pulverized Indomethacin (Plotted according to First-Order Kinetics)

The results are shown in Fig. 12 as a function of time. It took 2 months to reach maximum crystallization, and at this stage indomethacin had 60% crystallinity. In Fig. 13, the logarithm of percentage of uncrystallized indomethacin is plotted against time. This result clearly indicates that the transition of glassy indomethacin to the crystalline form follows first-order kinetics with a rate constant of $0.044\,d^{-1}$.

References and Notes

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