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Stability and Several Physical Properties of Amorphous and Crystalline Forms of Indomethacin[1,2]

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An X-ray diffraction method for determination of the degree of crystallinity of indomethacin was established, and the transition rate of indomethacin from amorphous to crystalline form was investigated. The transition of the amorphous form to crystalline form at 20°, 30° and 40° followed first-order kinetics and the Arrhenius plot showed good linearity. The amorphous form was shown to change to form I at 100% relative humidity (RH), to form I or II at 89% RH and to form I at 79% and 69% RH at 30°. The transition rate of the amorphous form to form II at 100% RH was larger than that at 89% RH. A good linear relation was observed between the maximum amount of water absorbed (log scale) and the degree of crystallinity at 100% or 89% RH at 30°. The dissolution rate of the amorphous form was higher than those of forms I and II. The amorphous form showed better tablet-forming properties than the crystalline form.

Keywords——indomethacin; polymorphism; degree of crystallinity; transition kinetics; dissolution rate; maximum amount of water absorbed; hardness of tablet

Amorphous forms of drugs have generally been reported to have a high solubility and also a high bioavailability compared with crystalline forms,[4,5] and these features have been utilized for the alleviation of gastric disorder.[6] The stability of the amorphous form is sometimes low, however, and conversion to stable crystalline forms occurs gradually.

The polymorphism of indomethacin (IMC) has been investigated by many workers.[7–10] Allen *et al.* reported that the relation between the dissolution rate and the degree of crystallinity of IMC in an IMC-polyethyleneglycol system showed a good linearity.[10]

Properties such as stability, solubility, hygroscopicity, and tablet-forming properties of amorphous forms are particularly important for pharmaceutical preparations. This study was intended to investigate these properties of amorphous IMC in comparison with the crystalline forms. The degree of crystallinity was determined by the X-ray diffraction method.

Experimental

Materials——Crystalline IMC form I (mp 160°—162°) and form II (mp 154°—155°) were prepared according to the methods reported by Yamamoto *et al.*[5] and Borka.[8] The amorphous form of IMC was prepared according to the method reported by Borka.[8] Other chemicals used were of reagent grade.

1) This paper forms Part XVIII of "Pharmaceutical Interaction in Dosage Forms and Processing." The preceding paper, Part XVII: Y. Machida, H. Masuda, N. Fujiyama, M. Iwata, and T. Nagai, *Chem. Pharm. Bull.*, **28**, 1125 (1980).
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4) A.T. Florence and E.G. Salole, *J. Pharm. Pharmacol.*, **28**, 637 (1976).
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X-Ray Diffraction Studies——Powder X-ray diffractometry was carried out using a Rigaku Denki Geigerflex model D-2 diffractometer with Ni-filtered Cu-Kα radiation.

Determination of Degree of Crystallinity——The degree of crystallinity was determined by X-ray diffraction, using modifications of the methods of Nakai *et al.*[11] and Black *et al.*[12] as follows: 20% lithium fluoride (LiF) was mixed with samples as a standard, regarding the degrees of crystallinity of forms I and II and of the amorphous form as 100% and 0%, respectively. As an example, in the X-ray diffraction pattern of IMC containing 60% crystalline form I and 20% LiF shown in Fig. 1, the ratio of X-ray diffraction intensity of form I at $2\theta=11.6°$ to that of LiF at $2\theta=37.8°$ was obtained, and the degree of crystallinity of the samples was determined from the calibration curve shown in Fig. 2. The reproducibility of this method was confirmed to be good in several experimental runs.

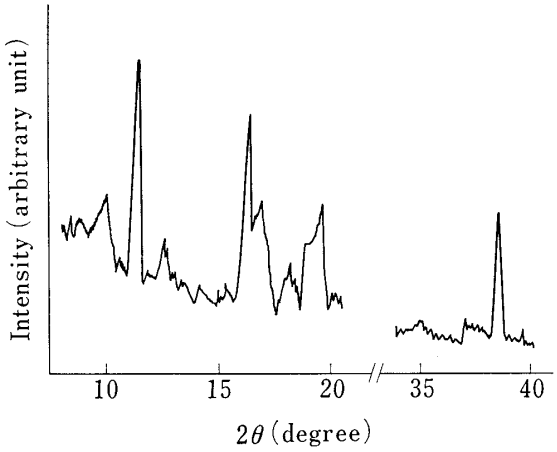

Fig. 1. X-Ray Diffraction Pattern of 60% Crystalline Indomethacin Containing 20% Lithium Fluoride

The peak at $2\theta=37.8°$ is due entirely to lithium fluoride.

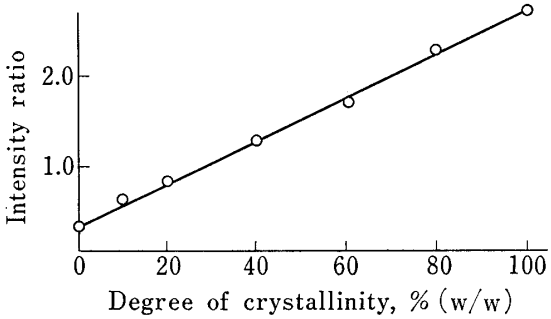

Fig. 2. Relation between the Degree of Crystallinity of Indomethacin and the Intensity Ratio of X-Ray Diffraction of Indomethacin ($2\theta=11.6°$) to That of Lithium Fluoride ($2\theta=37.8°$)

Stability of Amorphous Indomethacin against Heat and Moisture——The stability of amorphous IMC against heat in the absence of moisture was investigated by spreading samples of about 2 g on Petri dishes and placing them in a desiccator with silica gel at 20°, 30° and 40°. The transition rate constant K and the 50% transition time of the amorphous form to the crystalline form, T_{50} were obtained. The stability of amorphous IMC at relative humidities (RH) of 69, 79, 89 and 100% was also investigated in desiccators containing saturated solutions of various inorganic salts.

Measurement of Maximum Amount of Water Absorbed——Samples of about 3 g of amorphous form were spread on Petri dishes and placed in a desiccator kept at a constant RH of 69, 79, 89 or 100% at 30°. Samples were taken out at appropriate intervals and weighed, and the maximum amount of water absorbed was calculated from the weight increase.

Differential Scanning Calorimetry (DSC)——Differential scanning calorimetry was carried out using a Perkin-Elmer DSC 1B differential calorimeter, in the sample pan for solid samples at a scanning speed of 4°/min.

Measurement of the Hardness of Tablets——A Kiya hardness tester was used for measurements. Flat-faced tablets (300 mg, 13 mm diameter) were made by compressing IMC powder directly at 100 and 50 kg/cm^2 for 30 min using a Shimadzu hydraulic press for KBr tablets for infrared spectroscopy.

Measurement of Dissolution Rate and Solubility——Dissolution rate was determined by the dispersed amount method in the manner reported in a previous paper,[13] except that 5% methanol aqueous solution was used as the dissolution medium and measurement was done at 30°. The concentration of IMC was determined by the ultraviolet (UV) absorption method at 264 nm after dilution with 5% methanol aqueous solution. The solubility was determined by the method reported in a previous paper.[14]

11) Y. Nakai, E. Fukuoka, S. Nakajima, and J. Hasegawa, *Chem. Pharm. Bull.*, **25**, 96 (1977).
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Results and Discussion

Stability of Amorphous Indomethacin against Heat in the Absence of Moisture

The logarithm of the degree of crystallinity showed a good linearity with respect to time at every temperature, showing that the transition of the amorphous form to the crystalline form followed first-order kinetics. The transition rate constant K, and the 50% transition time of the amorphous form to the crystalline form, T_{50}, as calculated from the regression lines, are shown in Table I. The transition rate constant K at 40° was more than ten times larger than that at 20°. It was found that the temperature was an important factor influencing the stability of the amorphous form. Arrhenius plots of the transition rate constant K at various temperatures (Table I) are shown in Fig. 3. The activation energy of transition of the amorphous form to the crystalline form was 22 kcal/mol. This value is large for crystallization of the amorphous form, and this might indicate that the temperature is an important factor in the stability of amorphous IMC. As shown in Table I, the value of K at 10° obtained by extrapolation in Fig. 3 was 1.98×10^{-2} day^{-1} and T_{50} at 10° was 35.0 day, showing that the amorphous form was reasonably stable at low temperature.

Table I. Transition Rate Constant K and 50% Transition Time T_{50} at Various Temperatures

Temperature	K (day$^{-1}\times10^{2}$)	T_{50} (day)
10°	1.98[a]	35.0[a]
20°	8.54	8.12
30°	22.2	3.12
40°	99.8	0.70

a) Obtained by extrapolating the Arrhenius plot.

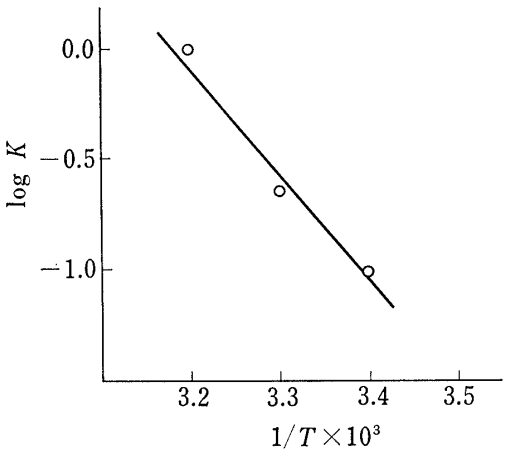

Fig. 3. Arrhenius Plot of the Transition Rate Constant K

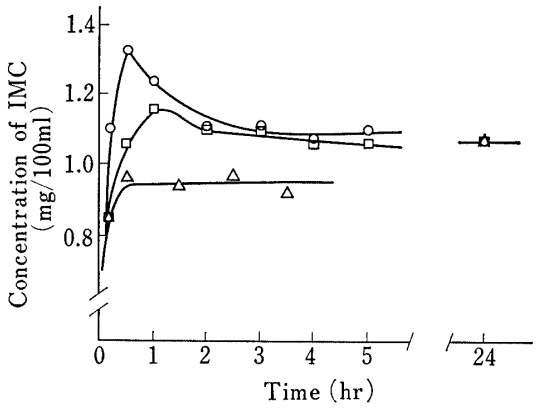

Fig. 4. Dissolution Curves of the Three Modifications of Indomethacin in 5% Methanol Aqueous Solution at 30°

○: amorphous form,
△: form I,
□: form II.

Table II. Transition of Amorphous Indomethacin to Crystalline Form under Various Relative Humidities at 30°

	100%RH	89%RH	79%RH	69%RH
Maximum amount of water absorbed (mg)[a]	16.7	13.1	9.6	8.3
Crystalline form	II	I, II	I	I
50% Transformation time T_{50} (hr)	12	48	48	48

a) Maximum amount of water absorbed per 1 g of amorphous indomethacin.

Stability of Amorphous Indomethacin at Various Relative Humidities

The maximum amount of water absorbed by the amorphous form at the initial stage was measured at various values of RH. The amount of water absorbed became nearly maximum after two or three hours at each RH, and then was almost constant for 6 hr. As shown in Table II, the maximum amount of water absorbed by the amorphous form increased with increase of RH. The amorphous form was shown to change to form II at 100% RH, to forms I and II at 89% RH, and to form I at 79% and 69% RH. It is considered that the amorphous form may dissolve well in water at high RH, accompanied by a super-saturation phenomenon of IMC to form nuclei for crystallization. In this case, the amorphous form changes to form II. On the other hand, at lower RH, water might be only absorbed by the amorphous form, and nuclei formation would be slow. In this case, the amorphous form changes to form I.

Dissolution Behavior of the Three Modifications of Indomethacin

Dissolution curves of the amorphous form and crystalline forms I and II in 5% methanol aqueous solution at 30° are shown in Fig. 4. The dissolution rate of the amorphous form was larger than those of forms I and II at the initial stage, indicating that the amorphous form should show better bioavailability than forms I and II. The solubility of the amorphous form became almost the same as that of form II after two hours. According to X-ray diffractometry, form II was formed from the amorphous form at the initial stage of dissolution, and the resulting form II changes gradually to form I.

Maximum Amount of Water Absorbed by the Amorphous Form

As shown in Fig. 5, the relation between the log of the maximum amount of water absorbed and the degree of crystallinity showed good linearity. The correlation coefficients of the regression lines at 100% RH and at 89% RH were 0.998 and 0.999, respectively. The maximum amount of water absorbed by the amorphous form was larger than that by the crystalline form, indicating a higher affinity of the amorphous form for water. This result may be explained by considering that the amorphous form has a disordered molecular arrangement with more scope for binding water.

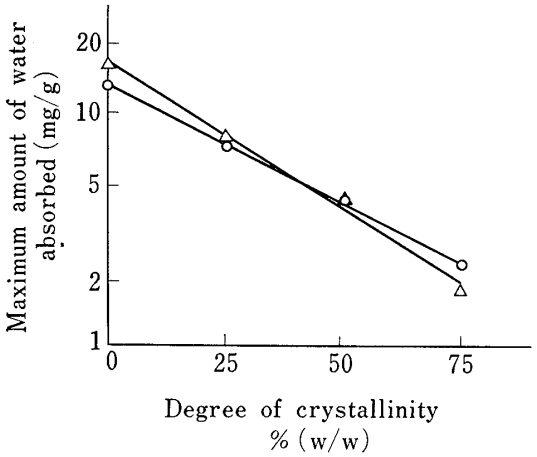

Fig. 5. Relation between Degree of Crystallinity and Maximum Amount of Water Absorbed per 1 g of Indomethacin at 30°

△: 100% RH
○: 89% RH

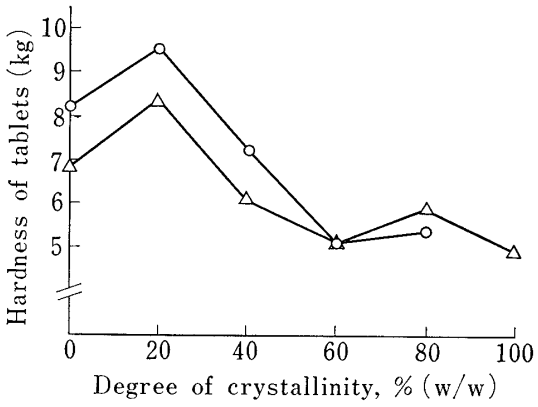

Fig. 6. Relation between Degree of Crystallinity and Hardness of Tablets

Compression pressure,
○: 100 kg/cm²,
△: 50 kg/cm².

Relation between Degree of Crystallinity and Hardness of Tablets

The relation between the degree of crystallinity and hardness of tablets is shown in Fig. 6. The hardness was highest when the degree of crystallinity was 20%, generally increasing with

the concentration of the amorphous form. Tablets of 100% crystalline form showed a capping phenomenon and the hardness fell below that of the material with 20% degree of crystallinity. The amorphous form sometimes shows stronger binding than the crystalline form in such a case as lactose.[15] The amorphous form might undergo plastic rather than elastic deformation compared with the crystalline form. As regards the hardness of tablets, therefore, the 100% crystalline state is not suitable for the preparation of hard tablets.

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