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# POLYMORPHIC TRANSFORMATION OF INDOMETHACIN IN PRECIROL SOLID DISPERSION SYSTEM

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## Abstract

The polymorphic transformation of indomethacin (IMC) in the presence of Precirol during heating was investigated by differential scanning calorimetry (DSC), infrared (IR) spectroscopy, microscopic Fourier transform infrared (FT-IR)/DSC system, and powder X-ray diffractometry with heating. The results indicate that in the presence of Precirol the original γ form of IMC was first transformed to a transition state, and then to a new polymorph by heating or exposure to IR radiation. The transition state of the melted sample gave three endothermic peaks, at 34, 48 and 127°C, and one exothermic peak, at 54°C. The stable melted sample exhibited two endothermic peaks, at 58 and 127°C, which were due to the fusion of Precirol and the new polymorph of IMC, respectively. This new polymorph of IMC also exhibited two specific IR absorption peaks, at 1693 and 1675 $cm^{-1}$. Microscopic FT-IR/DSC was used to examine the correlation between the structural transformation and its thermal response, and demonstrated the existence of the transition state of the melted sample. X-ray diffractometry with heating confirmed the appearance of the new polymorph of IMC in the presence of Precirol after heating.

**Keywords:** FT-IR/DSC system, indomethacin, new polymorph, Precirol, transformation

## Introduction

The solid dispersion technique has been used not only to enhance the solubility, dissolution rate and bioavailability of poorly water-soluble and water-insoluble drugs by using water-soluble inert carriers or water-soluble polymers [1–3], but also to delay or control the rate of release of water-soluble (or water-insoluble) drugs and short-acting drugs by using enteric-coating polymers, water-soluble polymers with high molecular weights, or hydrophobic materials [4–6]. Many

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methods have been employed to prepare these solid dispersion systems, such as melting, solvent-evaporation, melting-solvent and spray-drying [1–3, 7].

Indomethacin (IMC) is a useful poorly water-soluble non-steroidal anti-inflammatory agent. In order to improve its dissolution rate, the solid dispersion technique has been extensively investigated by using polyethylene glycol, polyvinyl pyrrolidone, polyvinyl polypyrrolidone, phosphatidylcholine and other water-soluble polymers as carriers [7–13]. The rate of dissolution of IMC is enhanced by these solid dispersion systems, mainly through the improvement in wettability caused by the water-soluble carrier, and the decrease in crystal size and crystallinity. Disappearance of the IMC crystalline structure in the solid dispersion system as an amorphous state was the most general case when the water-soluble carrier used was optimal. However, the amorphous form of IMC was unstable and might be converted to the α and γ forms of IMC after aging [14–16]. Monkhouse and Lach found that the partial γ form of IMC was transformed to the α form in a minuscular sample of IMC and fumed silica after evaporation of the organic solvent [17]. Lin reported a new crystal from of IMC precipitated form aqueous solutions of IMC- β-cyclodextrin [18]. Recently, Lin and Perng also indicated that a drug-polymer interaction occurred in IMC-Eudragit *E* film, but the γ form of IMC was converted to the α form after the evaporation of acetone from an IMC-Eudragit RL mixture. However, the α and γ forms of IMC might coexist in the solid state of IMC-Eudragit *S* film [19].

Precirol is a glycerol palmitostearate with low melting point, which has been used as a lubricant for tablet formulation, but it is now used for the preparation of sustained-release dosage forms [20, 21]. In the development of sustained-release IMC granules with Precirol as a retarding material, a polymorphic transformation of IMC from the γ form to a new polymorph was unexpectedly found when the melted IMC-Precirol mixture was prepared by the hot fusion method. In the present study, the mechanism of the polymorphic transformation from the γ form of IMC to a new polymorph in the presence of Precirol during heating was investigated. The characteristics of this new polymorph of IMC were examined.

## Materials and methods

### *Materials*

Indomethacin (IMC, γ form) was purchased form Sumitomo Chemical Company Ltd., Osaka, Japan. Precirol (Precirol 5, *m.p.* 52 –55°C) was kindly supplied by Gattefosse, St. Priest, France.

### *Preparation of α, β and γ polymorphic forms of indomethacin*

The α, β and γ forms of IMC were prepared as follows: the α form was prepared from aqueous ethanolic solution; the β form was recrystallized from ben-

zene; and the γ form was recrystallized from diethyl ether [18, 22, 23]. All the polymorphs were dried in a silica gel desiccator at room temperature.

*Preparation of the melted IMC-Precirol mixture by hot fusion*

The γ form of IMC and Precirol (weight ratio = 1:1) was mixed in a mortar, then added a DSC pan, heated to the prescribed temperature, maintained there for 10 min, and then slowly cooled to room temperature. The melted samples were used for further examination.

*DSC study*

The DSC curves of the Precirol, the IMC polymorphs and the melted samples were measured with a differential scanning calorimeter (DuPont DSC-910, USA) at a scanning rate of 10°C, under a stream of $N_2$ gas, from 25°C to the prescribed temperature.

*IR spectroscopy and microscopic Fourier transform IR/DSC system*

IR spectra of the samples were recorded with an IR spectrophotometer (IR-700, Jasco, Japan), using the KBr disk method. In order to analyze the microscopic structural changes associated with the thermal response of the samples, a system which combines the Fourier transform infrared (FT-IR) microscope spectrometer (Micro FT-IR 100, Jasco, Japan) with DSC (FP-84, Mettler, Switzerland) was used to measure simultaneously the thermal response and IR spectra of microsamples [18, 24].

*Powder X-ray diffractometry with heating*

X-ray powder diffraction patterns of Precirol, β-IMC and the melted IMC-Precirol mixture at 25, 60, 120 and 150°C were determined with an X-ray diffractometer (XD-D1, Shimadzu, Japan) with a heating system. The measuring conditions for the X-ray diffractometer were as follows: target Cu, filter Ni, voltage 40 kV, and current 30 mA. The heating rate in the heating system (HX-3, Shimadzu, Japan) was controlled at 20 deg·min$^{-1}$. When the prescribed temperature was reached, the sample was maintained under isothermal conditions for 5 min and its diffraction patterns were determined.

## Results and discussion

The DSC curves and IR spectra of Precirol, the β and γ forms of IMC, their physical mixture and melted samples of IMC and Precirol are shown in Fig. 1. Each individual endothermic peak at 62°C for Precirol and at 161°C for the γ

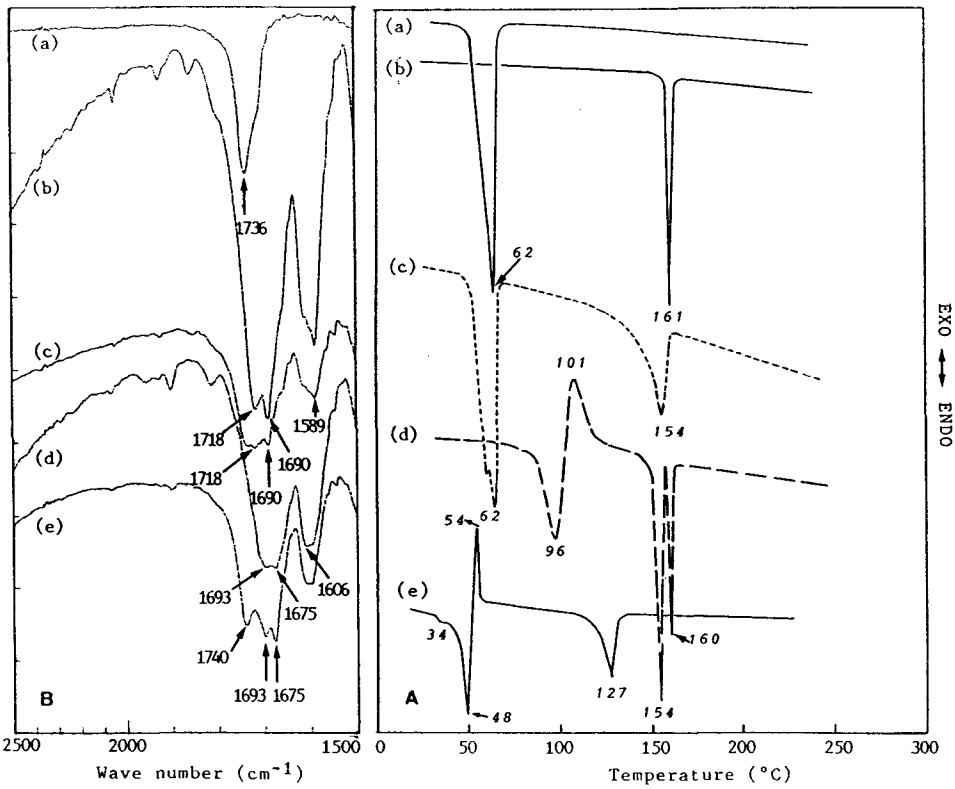


**Fig. 1** DSC curves (A) and IR spectra (B) of Precirol, indomethacin and it's physical mixture. a) Precirol; b) γ-Indomethacin; c) Physical mixture of (a) and (b); d) β-Indomethacin; e) Sample (c) preheated to 160°C and then stored for 24 h

form of IMC appeared in the DSC curves due to the fusion of the materials, per se. Two endothermic peaks, at 62 and 154°C, were observed for the physical mixture of the γ form of IMC and Precirol: the former might be related to the fusion of Precirol and the latter to fusion of the γ form of IMC, influenced by melted Precirol (Fig. 1A–c). The endothermic and exothermic peaks for the β form of IMC at around 90–110°C were attributed to the desolvation of benzene (96°C) and recrystallization of IMC (101°C), while two other endothermic peaks, at 154 and 160°C, were caused by the transformation from the β form of IMC to the α and γ forms [16, 18, 22, 23]. The transformation of IMC from the β to the γ form has been found to depend on the time for the cooling process during recrystallization in benzene solution [16]. Three endothermic peaks, at 34, 48 and 127°C, and one exothermic peak, at 54°C, were observed in the DSC curve on immediate determination of the 160°C-preheated sample (Fig. 1A–e). These endo- and exothermic peaks were confirmed in the following study.

The IR spectra of the samples are shown in Fig. 1–B. IR absorption peaks for the γ form of IMC were found near 1718, 1690 and 1589 $cm^{-1}$, with those for the β form of IMC near 1693, 1675 and 1606 $cm^{-1}$ (Fig. 1B–b,d). The peaks at 1718 and 1675 $cm^{-1}$ were assigned to the carboxy carbonyl stretching bands for the γ and β forms of IMC, respectively; the peak at 1690 or 1693 $cm^{-1}$ was due to the benzoyl carbonyl stretching bands for the β or γ form of IMC [25]. The positions of these IR spectra were almost consistent with those found in other studies [16, 22, 23]. The IR absorption peak for Precirol was located near 1736 $cm^{-1}$, while the IR peaks for the physical mixture of the γ form of IMC and Precirol were located at the individual peak positions of the γ form of IMC and Precirol (Fig. 1B–c). However, the IR absorption spectrum of the melted sample (physical mixture preheated to 160°C) was different: it exhibited three IR peaks, near 1740, 1693 and 1675 $cm^{-1}$ (Fig. 1B–e). The peak at 1740 $cm^{-1}$ might be the IR absorption peak of Precirol, but the peaks at 1693 and 1675 $cm^{-1}$ were similar to those in the IR spectrum of the β form of IMC (Fig. 1B–d). However, it must be noted that the β form of IMC was obtained by recrystallizing IMC from benzene. In the present study, no benzene was added to the mixture. The appearance of the 1693 and 1675 $cm^{-1}$ bands suggests that IMC might transform from the original γ form to a new polymorph in the presence of Precirol during fusion. It also implies that the heating process may be a predominant factor to induce the polymorphic transformation of IMC.

In order to investigate the possible formation of a new polymorph of IMC, the effects of different preheating temperatures on the polymorphic transformation of IMC in the presence of Precirol were examined. These physical mixtures of the γ form of IMC and Precirol were preheated to the prescribed temperature; their IR spectra are depicted in Fig. 2. Obviously, the IR absorption peaks at 1693 and 1675 $cm^{-1}$ appeared after the physical mixture was preheated to 150°C, but the peak at 1718 $cm^{-1}$ still existed (Fig. 2–e). The IR peaks at 1693 and 1675 $cm^{-1}$ were assigned to the new polymorph of IMC, and the IR peak at 1718 $cm^{-1}$ was related to the γ form of IMC, indicating that the two polymorphs coexisted in the mixture. A transition state with an IR absorption peak at 1685 $cm^{-1}$ was found for the 145°C-preheated sample (Fig. 2–d). However, the IR absorption peak at 1718 $cm^{-1}$ for the γ form of IMC completely disappeared when all the samples were melted beyond 152°C (Fig. 2–g→i). This suggests that preheating can induce the polymorphic transformation of IMC from the γ form to a new polymorph in the presence of Precirol.

The progress of the polymorphic transformation of IMC is also indicated in Fig. 3. Three endothermic peaks, at 34, 48 and 127°C, and one exothermic peak, at 54°C, were observed in the DSC curves on immediate examination of the 154°C-preheated sample (Fig. 3A–b). Moreover, a new IR absorption peak appeared at 1685 $cm^{-1}$ for this instantly examined sample (Fig. 3B–b). The re-

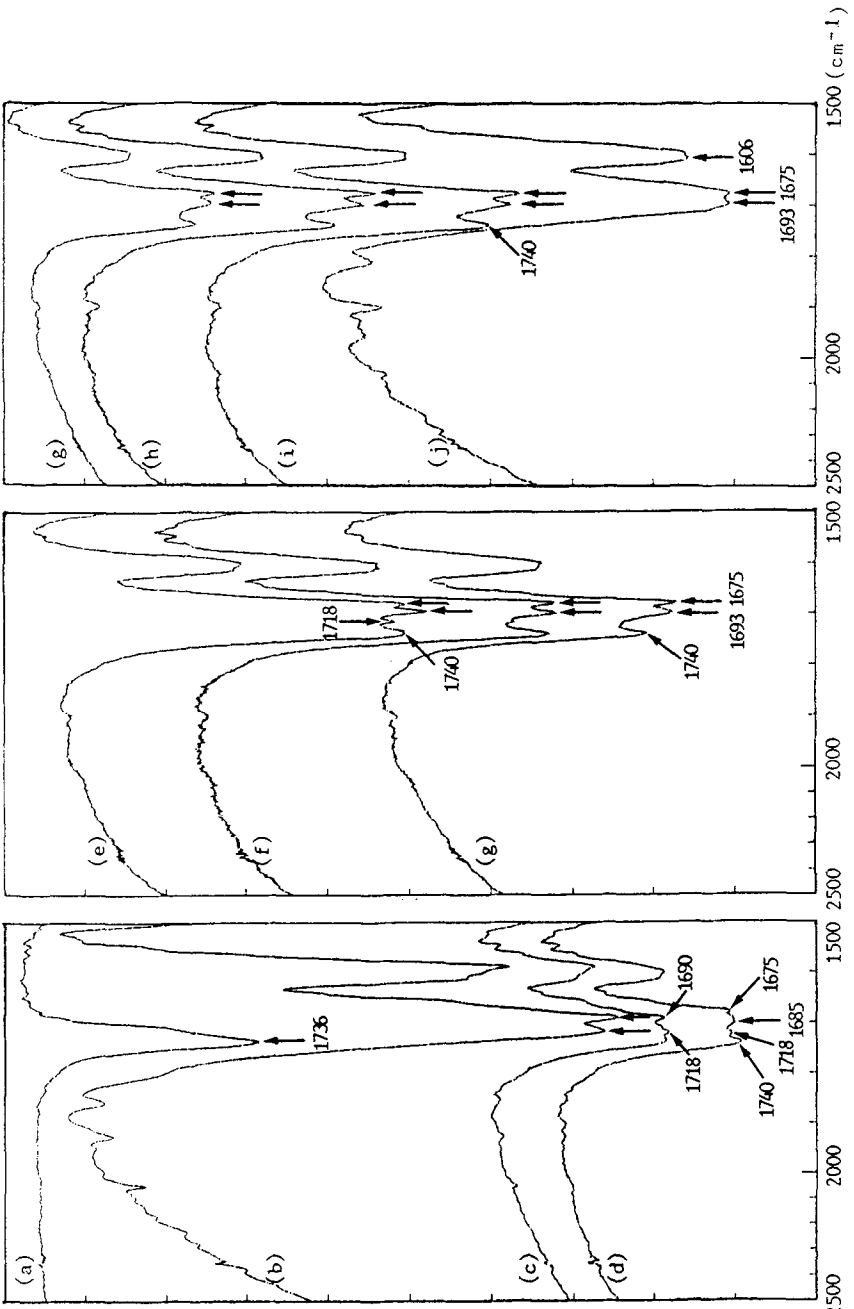


**Fig. 2** IR spectra for physical mixture of Precirol and γ-Indomethacin, and the samples preheated to different temperatures and then storage for 24 h. a) Precirol; b) γ-Indomethacin; c) Physical mixture of (a) and (b); d–i) Sample (c) preheated to 145°C (d), 150°C (e), 151°C (f), 152°C (g), 153°C (h), 154°C (i), and then stored for 24 h; j) β-Indomethacin

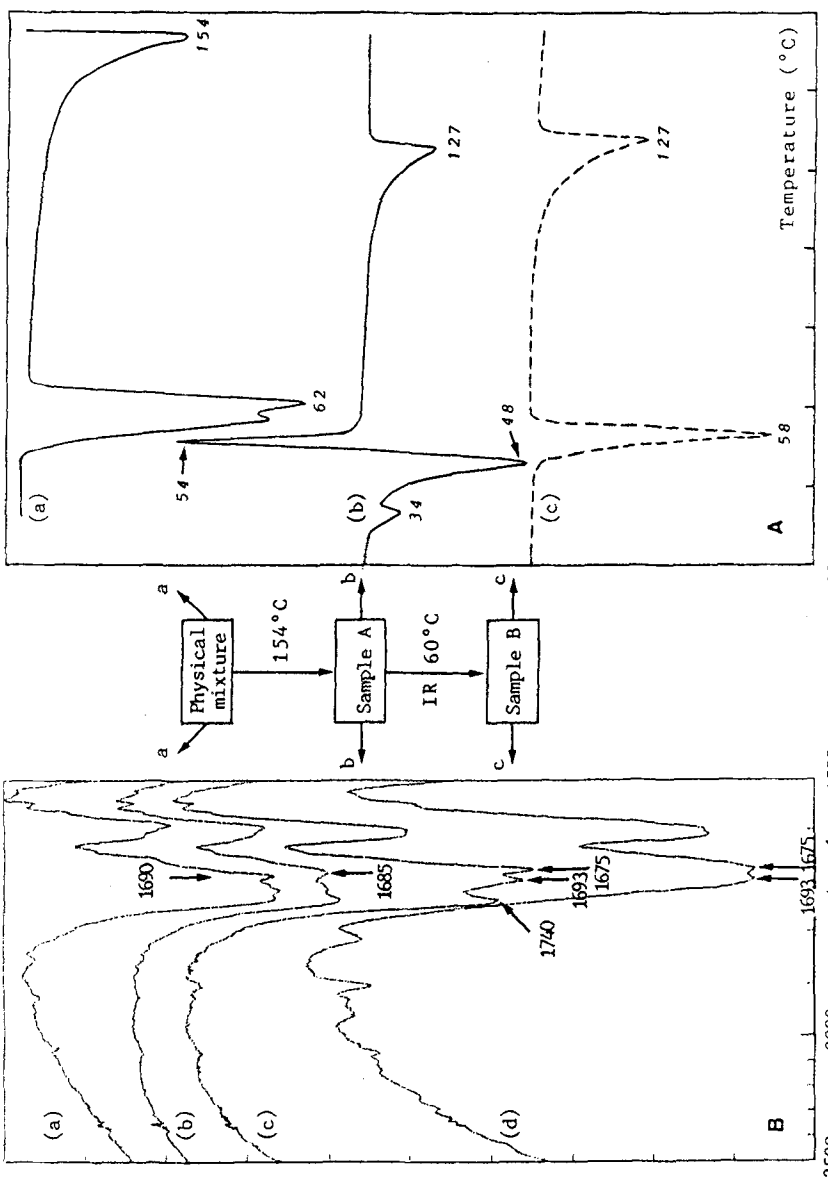


**Fig. 3** Effect of heat and IR ray on the DSC curves (A) and IR spectra (B) of physical mixture and melted samples of Precirol and γ-Indomethacin. a) Physical mixture of Precirol and γ form of indomethacin; b) Sample (a) preheated to 154°C and then determined immediately; c) Sample (b) heated to 60°C or exposed under IR ray for 5 min; d) β-Indomethacin

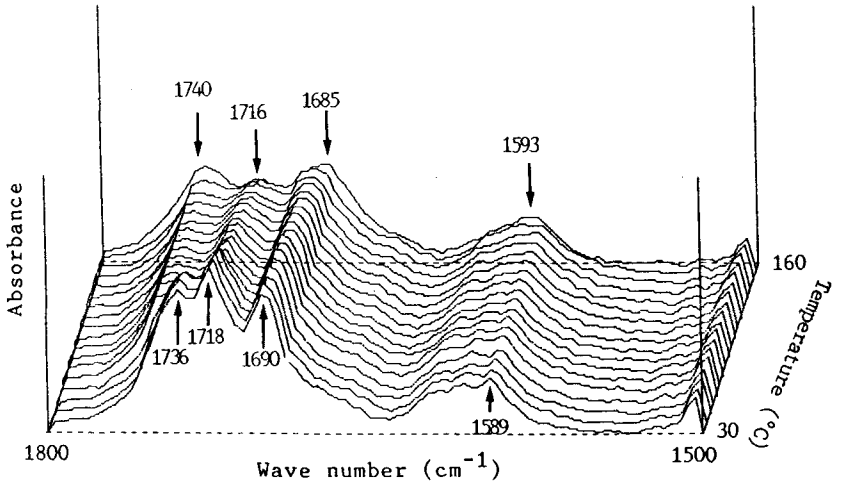


**Fig. 4** Three dimensional plot of IR spectra of physical mixture of Precirol and indomethacin with respect to temperature

sults in Fig. 2 led us to suppose that this sample involved a transition state. When the KBr disk containing this transitional sample was exposed to IR radiation for 5 min, or incubated in a 60°C dryer for 2 min, only two endothermic peaks, at 58 and 127°C, appeared in the DSC curve with bands at 1693 and 1675 $cm^{-1}$ in the IR spectrum, which were the same as in the DSC curve and IR spectrum of the new polymorph. This strongly indicates that preheating of the physical mixture of the γ form of IMC and Precirol induced IMC to form an unstable transition state (sample A), and then to transform to a stable new polymorph after a further supply of heat (sample B). The transformation from the unstable to the stable state resulted in the melting (34 and 48°C) and recrystallizing (54°C) of Precirol and IMC. The existence of this unstable IMC as a transition state in the presence of Precirol during heating is confirmed by microscopic FT-IR/DSC system, as shown in Fig. 4. Figure 4 depicts a three-dimensional plot of the IR spectrum of the physical mixture of Precirol and the γ form of IMC with respect to temperature. The correlation between the thermal response and the structural changes in the sample was obtained. Apparently, the γ form of IMC in the presence of Precirol was gradually transformed to an unstable state with increasing temperature. Near the melting point of IMC, the IR peak at 1685 $cm^{-1}$ clearly appeared. Moreover, the peak at 1736 $cm^{-1}$ was also observed to shift to 1740 $cm^{-1}$.

The temperature-dependent X-ray diffraction profiles of Precirol, β-IMC and the melted sample of IMC and Precirol are shown in Fig. 5. The characteristic X-ray diffraction peaks of Precirol occurred at $2\theta = 19.4$, 21.1 and 22.8° at 25°C, but the number of peaks decreased with increase of temperature. When the sample was heated to 60°C, only one peak was found, at 21.1°; and on heat-

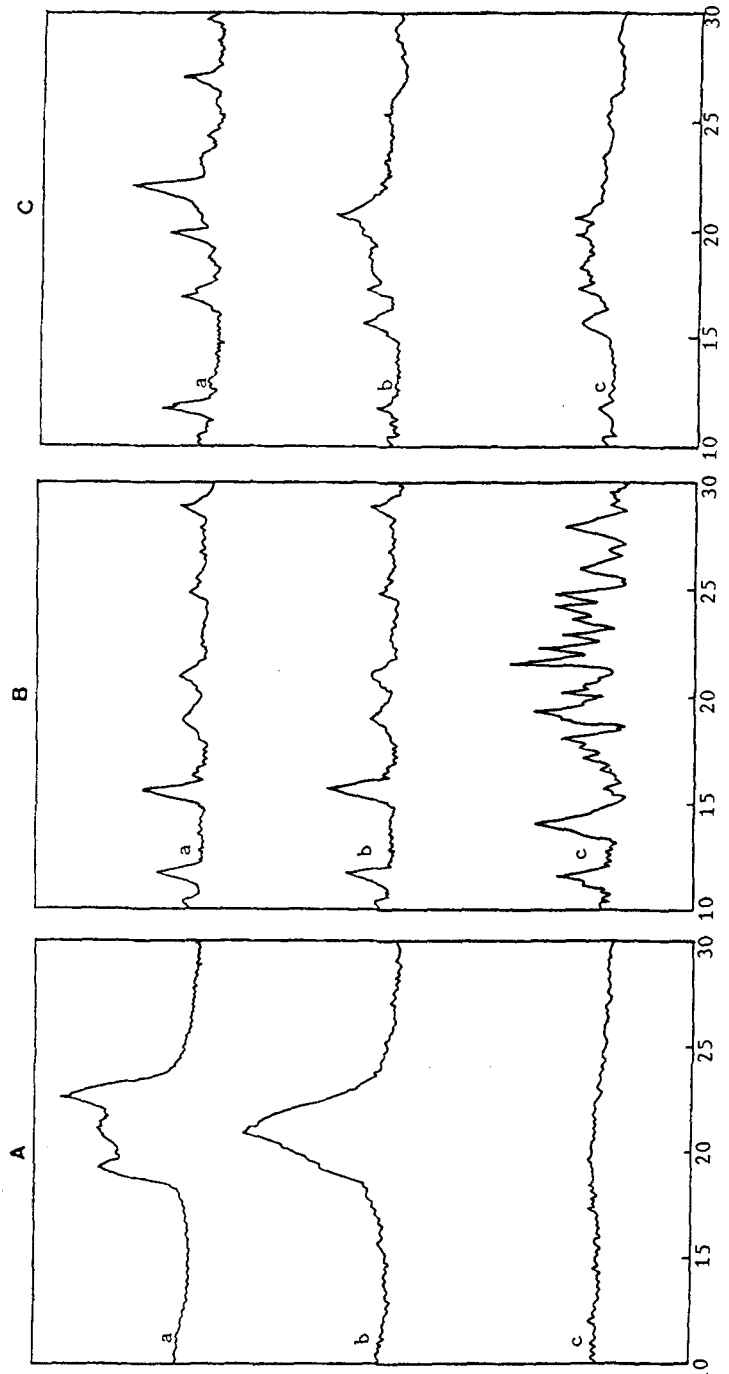


**Fig. 5** Temperature-dependent X-ray diffraction patterns of Precirol (A), β form of IMC (B) and 154°C-preheated sample of γ form of IMC and Precirol (C). a) 25°C; b) 60°C; c) 120°C

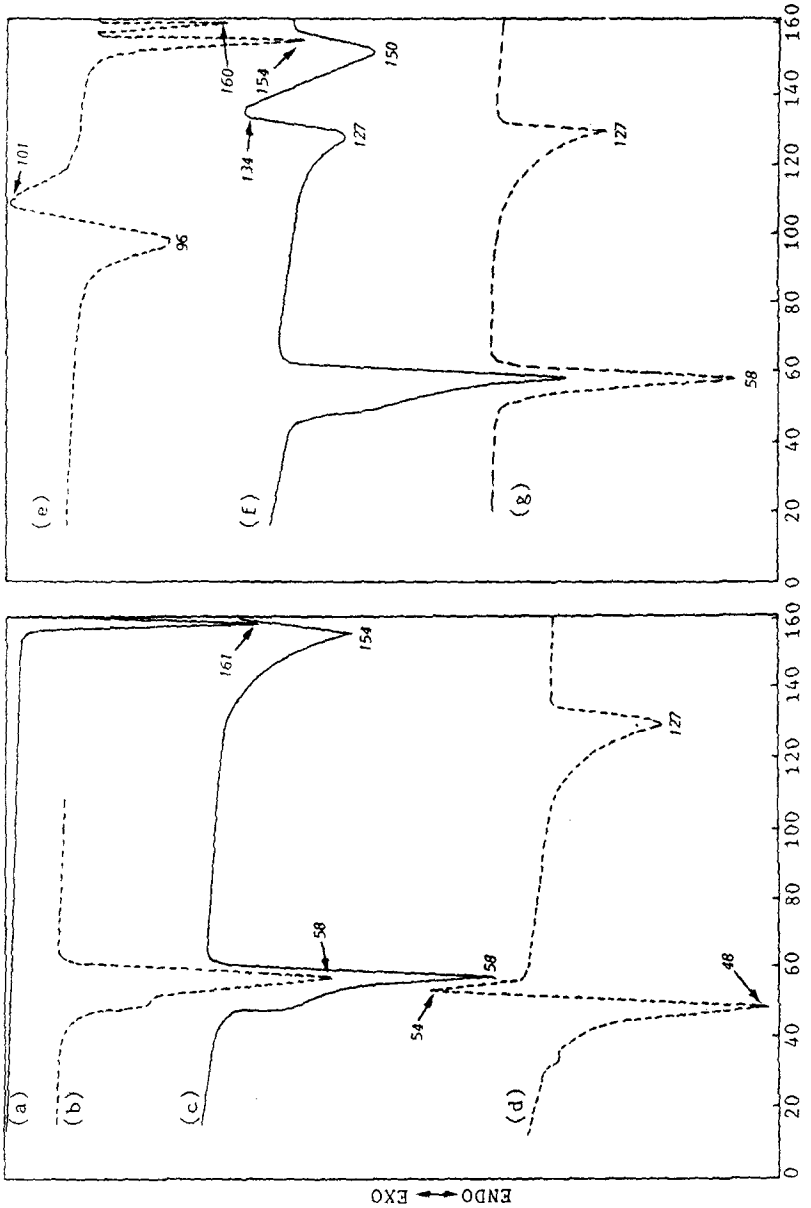


**Fig. 6** DSC curves of indomethacin, Precirol preheated to 154°C, and its mixture. a) γ-Indomethacin; b) 154°C-preheated Precirol; c) Physical mixture of (a) and (b); d) Sample (c) preheated to 160°C and then determined immediately; e) β-Indomethacin; f) Physical mixture of (b) and (e); g) Sample of (f) preheated to 160°C

ing to 120°C, no peak due to the fusion of Precirol could be observed (Fig. 5A–c). The diffraction peaks of the β form of IMC occurred at $2\theta = 10.5$, 11.8 and 15.9° at 25°C (Fig. 5B–a), which was consistent with other reports [18, 22, 23]. When the sample was heated to 60°C, the characteristic diffraction peaks for the β form of IMC were almost the same as the original peaks (Fig. 5B–b), since the desolvation process occurred between 96 and 101°C. Beyond this temperature range, however, the diffraction patterns of the β form of IMC became complex, e.g. on heating of the sample to 120°C (Fig. 5B–c). These complicated diffraction patterns were mainly contributed to by the α and γ forms of IMC; $2\theta = 11.5$, 14.0, 17.1 and 18.1° for the α form, and $2\theta = 11.6$, 19.5, 20.3, 21.7, 24.2, 26.2 and 28.0° for the γ form. The thermally-dependent polymorphic transformation of the β form of IMC was confirmed by the DSC curve, as shown in Fig. 1A–d, in which the endothermic peaks at 154 and 160°C were due to fusion of the α and γ forms of IMC, respectively. The X-ray peaks for the 154°C-preheated sample of the γ form of IMC and Precirol appeared at $2\theta = 11.8$, 17.0, 20.0, 22.1, 27.0° at 25°C (Fig. 5C–a). It clearly exhibited a different X-ray diffraction pattern from those of Precirol and the β form of IMC, suggesting that the new polymorph of IMC was formed in the 154°C-preheated sample of Precirol and the γ form of IMC. These peaks also changed with temperature, but their changes were not so complicated as for the β form of IMC.

To determine which material contributed to the endothermic DSC peaks at 58 and 127°C for the melted sample, further study was undertaken. Figure 6 shows the DSC curves of IMC, 154°C-preheated Precirol and their mixture. When Precirol was preheated to 154°C, the endothermic peak at 62°C in the DSC curve of unheated Precirol shifted to 58°C. The DSC curve for the physical mixture of the γ form of IMC and 154°C-preheated Precirol was almost the same as that for the physical mixture of Precirol and the γ form of IMC (Fig. 3–a). When the β form of IMC was previously mixed with the 154°C-preheated Precirol for thermal analysis, its DSC curve was different (Fig. 6–f). Three endothermic peaks were observed at 58, 127 and 150°C, and one exothermic peak at 134°C. The peak at 58°C was due to fusion of the 154°C-preheated Precirol, while the peak at 127°C might be attributed to fusion of the new polymorph of IMC. The residual β form of IMC was converted to the γ form through recrystallization, as shown by the exotherm at 134°C, and this γ form of IMC then fused at 150°C in the presence of Precirol, which was near the 154°C shown in Fig. 1A–c. The disappearance of the thermal peaks at 96 and 101°C for the β form of IMC (Fig. 6–f) might possibly be due to the β form of IMC being embedded in the melted Precirol matrix, which could delay the thermal effect, leading to the formation of a complicated system with different thermal behavior. When the melted sample was determined again by thermal analysis (Fig. 6–g), the DSC curves displayed only two endothermic peaks, at 58 and 127°C, consistent with the previous results (Fig. 3). This suggests that the en-

dothermic peak at 58°C was contributed by Precirol, and the endothermic peak at 127°C was due to fusion of the new polymorph.

In conclusion, heating may induce polymorphic transformation of the γ form of IMC into a new polymorph in the presence of Precirol. A temporarily unstable state of IMC may occur during the process of polymorphic transformation.

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**Zusammenfassung** — Mittels Differential-Scanningkalorimetrie (DSC), Infrarot-(IR) Spektroskopie, mikroskopischer Fourier-Transformations-Infrarot-(FT-IR)/DSC und Röntgen-Pulverdiffraktometrie mit Erhitzen wurde die polymorphe Umwandlung von Indomethacin (IMC) in Gegenwart von Precirol beim Erhitzen untersucht. Die Ergebnisse zeigen, daß in Gegenwart von Precirol die Original-γ-Form von IMC zuerst in einen Übergangszustand und dann durch Erhitzen oder durch Bestrahlung mit IR-Strahlung in eine neue polymorphe Gestalt umgewandelt wird. Der Übergangszustand der geschmolzenen Probe liefert drei endotherme Peaks bei 34, 48 und 127°C und einen exothermen Peak bei 54°C. Die stabile geschmolzene Probe zeigt zwei endotherme Peaks bei 58 und 127°C (entsprechend dem Schmelzen von Precirol und der neuen polymorphen Gestalt von IMC). Diese neue polymorphe Form von IMC zeigt

auch zwei spezifische IR-Absorptionspeaks bei 1693 und 1675 $cm^{-1}$. Mikroskopische FT-IR/DSC wurde eingesetzt, um die Korrelation zwischen der strukturellen Umwandlung und der Thermoantwort zu untersuchen und bewies die Existenz des Übergangszustandes der geschmolzenen Probe. Röntgendiffraktometrie mit Erhitzen bestätigte das Auftreten der neuen polymorphen Form von IMC in Gegenwart von Precirol nach dem Erhitzen.