

Polymorphism of Phenylbutazone¹⁾

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The solid-solid transition of phenylbutazone polymorphs by heating was investigated by differential scanning calorimetry (DSC) and X-ray diffractometry, and also the difference in dissolution rate due to the polymorphism was confirmed.

There were observed three polymorphs of phenylbutazone. Form I melted at 103°, Form II twice at 93° and at 103°, and Form III at 93°. Furthermore, the mutual transition phenomenon by heating among these three polymorphs was observed by DSC.

Analyzing the dissolution curves of Forms I and II obtained by the stationary disk method and plotting the saturated concentration of the respective forms, the transition temperature estimated was 98° and the heat of transition 210 cal/mole.

Form III was transformed to Form II through compression above a certain compressional pressure and to the intermediate form of Form II and Form III (designated here as "pseudo-Form III") under the compressional pressure 1 ton/cm². Therefore, the intrinsic dissolution rate of Form III was not obtained. However, the dissolution rate of "pseudo-Form III" was faster than any of Form I and II. Accordingly, it was suggested that if the transition of Form III could be suppressed, more soluble preparations of phenylbutazone would be available.

The polymorphism has been discussed in regard to the stability, solubility and bio-availability of various drugs.^{3,4)} Concerning non-steroidal antiinflammatory drugs also, the polymorphs of indomethacine,⁵⁾ mefenamic acid,⁶⁾ and flufenamic acid⁷⁾ were reported. In a series of physico-chemical studies of non-steroidal antiinflammatory drugs,⁸⁾ the authors found that phenylbutazone gives three polymorphs.

In the present study, the solid-solid phase transition of phenylbutazone polymorphs by heating was investigated by differential scanning calorimetry (DSC) and X-ray diffractometry, and also the difference in dissolution rate due to the polymorphism was confirmed.

Experimental

Materials—Highly purified phenylbutazone Forms I and II used were supplied by Iwaki Pharmaceutical Co., Ltd. and Toshin Chemical Co., Ltd., respectively, which conformed to the standards and gave the DSC curves and X-ray diffraction patterns shown later. The other materials used were of the reagent grade.

Differential Scanning Calorimetry (DSC)—This was done using a Perkin-Elmer Model DSC 1B differential scanning calorimeter.

- 1) This paper forms Part XXX of "Physico-chemical Approach to Biopharmaceutical Phenomena"; Preceding paper, Part XXIX: N. Nambu, S. Sakurai, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **23**, 1404 (1975). A part of this work was presented at the 95 th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April 1975.
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- 8) a) J. Noda, H. Sakamoto, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **23**, 445 (1975); b) Y. Hamada, N. Nambu, and T. Nagai, *ibid.*, **23**, 1205 (1975).

Powder X-Ray Diffraction Studies—Powder X-ray diffractometry was done using a Rigaku Denki Geigerflex Model D-2 diffractometer by Ni-filtered Cu-K α radiation.

Formation of Polymorphs by Heating—To make a transformed one, a sample in a 50 ml of glass beaker was heated in the fixed temperature range at a speed of about 1°/min. When the temperature reached the final point of the range, the heating was stopped immediately and the sample was kept standing on cooling. Mutual transformation of polymorphs did not take place at room temperature. The polymorphism was confirmed by DSC and X-ray diffractometry.

Grinding and Compression of Powder Samples—The grinding was done in a mortar for compounding by usual way. The compression was done in the same way as making a disk for the determination of dissolution rate, as described below.

Procedure for the Determination of the Dissolution Rate—The dissolution rate was determined by a stationary disk method, using the apparatus described in a previous paper.^{8b)} Two tenths gram of powder sample was compressed in a cylindrical die by a Shimadzu hydraulic press for KBr tablets for infra-red spectroscopy. The compressed disk was not ejected out of the die, and the die cavity was stoppered. The die wearing the compressed disk was set on the dissolution apparatus so as to make the disk face to the stirrer.^{8b)} Every experiment was done under the following conditions: 150 ml of 1/30 M phosphate buffer solution of pH 7.5 as the dissolution medium; at 40°, 30°, 25°, and 20°; 300 rpm of rotating velocity of the stirrer; 1.0 cm diameter of the disk of the drug compressed under 1 ton/cm². One ml of the solution was sampled out at appropriate time intervals, the resultant want of volume was compensated by adding the dissolution medium of the same temperature. The concentration of drugs was determined according to ultra-violet (UV) absorption method at 264 m μ .

Results and Discussion

Transition Temperature of Three Polymorphs of Phenylbutazone

There were observed by DSC three polymorphs of phenylbutazone, as shown in Fig. 1. Form I melted at 103°, Form II twice at 93° and 103°, and Form III at 93°. According to the usual test in a capillary tube, Form II melted to an opaque paste at 93°, solidifying immediately, and melted again at 103°. Phenylbutazone on the market is considered to belong to Form I or II. The difference in crystalline form among these three polymorphs was also confirmed by the powder X-ray diffraction patterns as shown in Fig. 2.

Furthermore, the mutual transition phenomenon among these three polymorphs by heating was observed when the respective sample was heated in the way of DSC and kept standing on cooling, as shown in Fig. 3. Form I was transformed to Form II above 100° and just below the melting point of Form I (way 1), and to Form III by heating above 103°

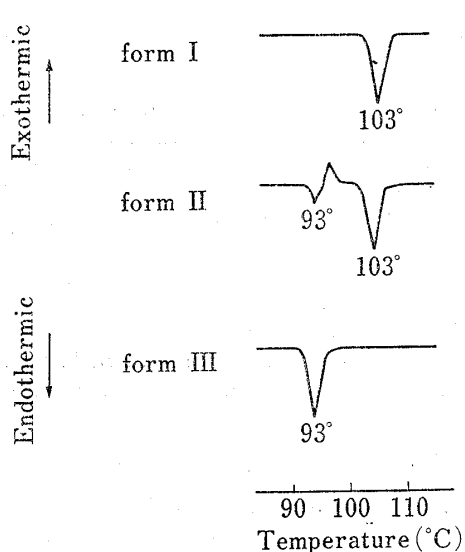


Fig. 1. DSC Curves of Phenylbutazone Polymorphs

scanning speed: 8°/min

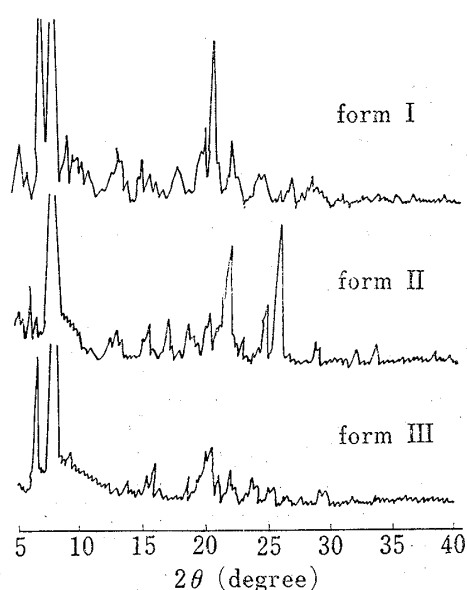


Fig. 2. Powder X-Ray Diffraction Patterns of Phenylbutazone Polymorphs

(way 5). Form II was transformed to Form I above the first melting point 93° and just below the second melting point 103° (way 2), and to Form III by heating above 103° (way 3). Therefore, the way 5 corresponded to skipping the ways 1 and 3. Form III, which was formed from Forms I and II by heating, was transformed to Form II above 93° and just below 103° (way 4), but the transformed one was not obtained by heating over 103° . The ways 2 and 4 were observed in the same temperature range, but the respective thermograms were different. Thus, the mutual transition among the three polymorphs is made take place by the controlled heating.

The Dissolution Rate and Thermodynamics of Transition

Phenylbutazone Forms I and II were stable and any change of crystalline form was not observed through grinding and compression. However, Form III was transformed to Form II or the similar form to Form II through grinding and compression, as will be discussed later. Therefore, the dissolution rate of Form III was not determined because the disk for the experiment of this crystalline form was hardly obtained.

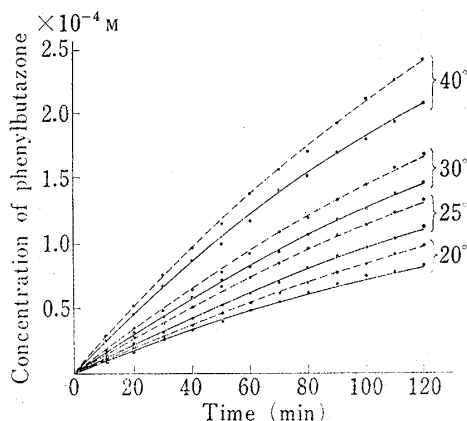


Fig. 4. Dissolution Curves of Phenylbutazone Polymorphs in 1/30M Phosphate Buffer Solution at pH 7.5 at Various Temperatures by the Stationary Disk Method

—: form I - - - -: form II

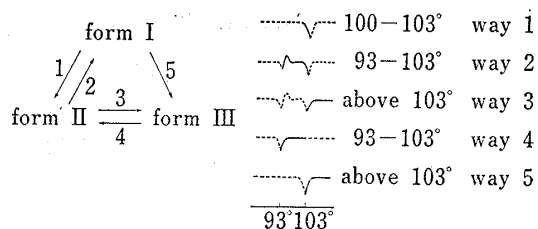


Fig. 3. Mutual Transition of Phenylbutazone Polymorphs

The solid line in the thermograms shows the temperature range where the sample was heated to make transformed.

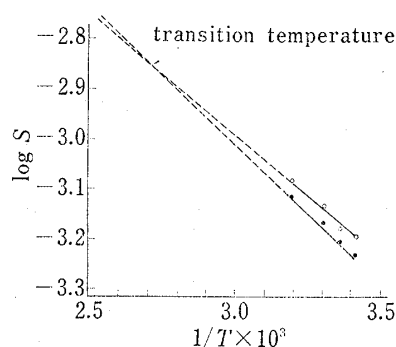


Fig. 5. van't Hoff's Plot for Phenylbutazone Forms I and II in 1/30 M Phosphate Buffer Solution at pH 7.5

S: solubility
●: form I ○: form II

The dissolution curves of Forms I and II were shown in Fig. 4. Form II dissolved faster than Form I. Analyzing these curves, the saturated concentration of each form in pH 7.5 phosphate buffer solution was determined according to the procedure of Nogami, *et al.*⁹⁾ Plotting the saturated concentration of the respective forms according to van't Hoff's equation as shown in Fig. 5, the transition temperature was estimated from the intersection point of the two straight lines and the heat of transition was estimated from the difference in the slope between these two straight lines. The results are shown in Table I. The transition temperature estimated was 98° and the heat of transition 210 cal/mole. This transition temperature 98° approximately corresponded to that obtained by DSC, *i.e.*, $100\text{--}103^\circ$ from

9) H. Nogami, T. Nagai, and A. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **14**, 329 (1966).

TABLE I. Thermodynamic Values Calculated for Phenylbutazone Forms I and II

	Transition temperature (°C)	Heat of solution (kcal/mole)	Heat of transition (kcal/mole)
Form I	—	2.50	—
Form II	98	2.29	0.21

Form I to II and 93—103° from Form II to I. If the dissolution rate of complete Form III was determined, more detailed discussions could be made about the mutual transition among phenylbutazone polymorphs.

Changes of Crystalline Form of Form III through Grinding and Compression, and the Dissolution Rate of the Partly Transformed Form III

Grinding in a mortar, Form III was easily transformed to the similar form to Form II, melting at 93° and again at 103°, as shown in Fig. 6. Form III was completely transformed to Form II through compression above a certain compressional pressure. However, under the compressional pressure 1 ton/cm², Form III was transformed to the intermediate form of Forms II and III (designated here as "pseudo-Form III"), which might be a mixture of Form II and III, as shown in Fig. 6.

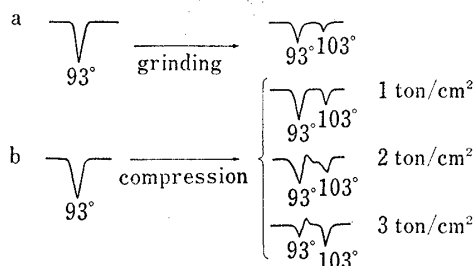


Fig. 6. Transition of Phenylbutazone Form III through Grinding (a) and Compression (b)

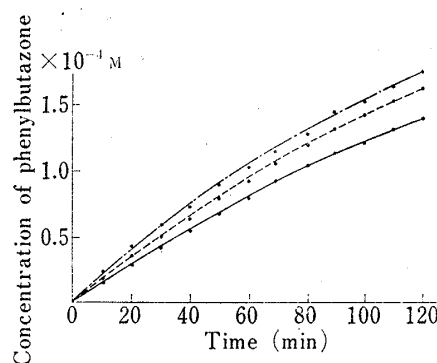


Fig. 7. Dissolution Curves of Phenylbutazone Polymorphs in 1/30 M Phosphate Buffer Solution at pH 7.5 at 30° by the Stationary Disk Method

—: form I
 - - -: form II
 ···: "pseudo-form III"

Investigating the dissolution rate of "pseudo-Form III" in comparison with those of Forms I and II under the same conditions, the former was the fastest among the three forms, as shown in Fig. 7.¹⁰⁾ This fact suggested that the complete Form III, if obtained, might dissolve faster than any of Forms I and II. If the transition of Form III to II through grinding and compression could be suppressed, more soluble preparations of phenylbutazone would be available. In this connection, further investigations should be made.

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10) A disintegration of the disk of the "pseudo-Form III" due to the low compressional pressure did not take place in the present experimental condition and the determination of dissolution rate had no trouble.⁹⁾