Polymorphism of Phenylbutazone: Properties and Compressional Behavior of Crystals

H. G. IBRAHIM ˣ, F. PISANO, and A. BRUNO

Abstract □ Data from X-ray diffraction, thermal analysis, IR spectroscopy, and solubility studies were used for the identification and characterization of four crystalline modifications of phenylbutazone. The thermal behavior of the polymorphs under different treatment conditions also was investigated. Compression of the thermodynamically unstable forms, at a compression force of 1590–2040 kg, induced polymorphic changes in the crystals. Similar changes also were produced through grinding. The apparent equilibrium solubilities of polymorphs were determined, as was the dissolution of the polymorphs as compressed disks in an aqueous medium. The small effective surface area possessed by one polymorph resulted in slow dissolution.

Keyphrases □ Phenylbutazone—four polymorphic forms identified, thermal and compressional behavior and solubilities compared □ Polymorphism—phenylbutazone, four crystalline forms identified, thermal and compressional behavior and solubilities compared □ Thermal behavior—four polymorphic forms of phenylbutazone compared □ Compressional behavior—four polymorphic forms of phenylbutazone compared □ Solubility—four polymorphic forms of phenylbutazone compared □ Antirheumatic agents—phenylbutazone, four polymorphic forms identified, thermal and compressional behavior and solubilities compared

Different polymorphs are known to possess different physical properties. From a practical point of view, solubility, surface tension, density, crystal shape, and hardness are the most significant differences. The bioavailability of a drug as well as the chemical and physical stability of a solid compound in a particular dosage form can be modified by presenting the drug in the appropriate crystal form (1, 2). This approach, of course, requires a thorough knowledge of the properties and behavior of the different crystalline modifications.

While several reports discussed the bioavailability of drugs that can exist in more than one crystalline modification (3, 4), little information is available on the role of polymorphism and crystal habit in solid dosage form and powder technology. The orientation of crystals during a packing or compression process is influenced by the dominant faces in the crystal and, therefore, by crystal habit. Using data from X-ray powder diffraction, Shell (5) described crystal habit as it relates to a good or poor tableting performance.

Polymorphous transformations at high pressures occur in some inorganic and organic substances (6, 7). The possibility of phase transitions with pressure during tableting and their effects on dissolution rates and availability of drugs have not been adequately investigated, probably because of the general contention that tableting pressures will not induce phase transformations. Nevertheless, such phase changes during compression are conceivable and would occur at individual points of contact between particles where local pressures are extremely large (pressure being force per unit area). These pressures probably would promote transitions toward structures of higher coordination and higher density.

The present work reports on polymorphism in phenylbutazone and provides information regarding the feasibility of crystalline structural changes under tableting conditions.

EXPERIMENTAL

Crystal Forms—Cyclohexane (Form II), *n*-heptane (III), 2-propanol (IV), and isobutyl alcohol (I) were used as crystallization solvents for the polymorphs. All solvents were analytical grade. A single batch of commercial phenylbutazone[1] was used. The techniques of crystallization of the different polymorphs from the different solvents were essentially the same. An adequate amount of the drug was added to the warm solvent, and the resultant saturated solution was allowed to cool.

For the preparation of Form IV, water was added to the 2-propanol solution until the cloud point. Then the solution was warmed again and allowed to cool. The separated crystals were filtered off using a sintered-glass funnel and then dried under vacuum.

Polymorph Characterization—*Differential Scanning Calorimetry*—The thermograms of the different crystalline modifications were recorded on a thermal analyzer[2] equipped with a differential scanning calorimetry cell. Indium (99.99% purity) was used to check instrument calibration. The thermal behavior of the four polymorphs was studied at different heating rates and under different conditions of sample treatment; *i.e.*, crystals were heated in an open pan, covered pan, or as a crimped sample.

Heating rates of 2 and 5°/min and, to a much lesser extent, 10°/min promoted solid–solid transformation. To minimize such transformation, the samples routinely were heated throughout the investigation at 20°/min. Phase transition temperatures obtained from the thermograms were corrected for the nonlinear response of the chromel–alumel thermocouple.

IR Spectroscopy—A double-beam IR spectrophotometer[3] was used for recording the spectra of the polymorphs. Grinding, as will be shown later, induced polymorphic changes in the samples. Since the sample must be sufficiently ground to obtain a good mineral oil[4] mull, this technique and the potassium bromide disk technique were considered unsuitable for handling such grinding-sensitive material. For this reason, attenuated total reflectance, using a TR-9 ATR unit with a 45° KRS-5 (thallous bromide–iodide) crystal, was employed to record the IR spectra. An adhesive tape technique similar to that used by Kang *et al.* (8) was utilized in preparing the samples for IR analysis.

X-Ray Analysis—X-ray diffraction patterns were recorded using an X-ray diffractometer with K_α radiation[5]. The settings used with the instrument were: 1° beam slit, 0.2° detector slit, copper tube-K_α radiation, and nickel filter.

Dissolution and Solubility Studies—All dissolution studies were conducted in a 0.067 *M* aqueous phosphate buffer of pH 6.95. The apparatus used in the dissolution rate determinations was similar to that described by Wood *et al.* (9). Approximately 100 mg of the crystals was compressed[6] into a disk in an 8-mm stainless steel tablet die at approximately 1590 kg. The tablet die, with one face of the compressed disk exposed and in plane with the die surface, was placed in a plastic holder. The tablet assembly was rotated in 500 ml of dissolution medium at 50 rpm. The drug concentration in solution was continuously monitored by circulating the solution into a spectrophotometer[7] and continuously measuring the absorbance at 264 nm.

For the determination of the equilibrium solubility, an excess quantity of the crystals was shaken with 100 ml of the buffer solution in an erlen-

[1] Ciba-Geigy, Suffern, N.Y.
[2] Du Pont 990.
[3] Beckman model IR-33.
[4] Nujol.
[5] General Electric XRD-5.
[6] Carver press.
[7] Beckman DU.

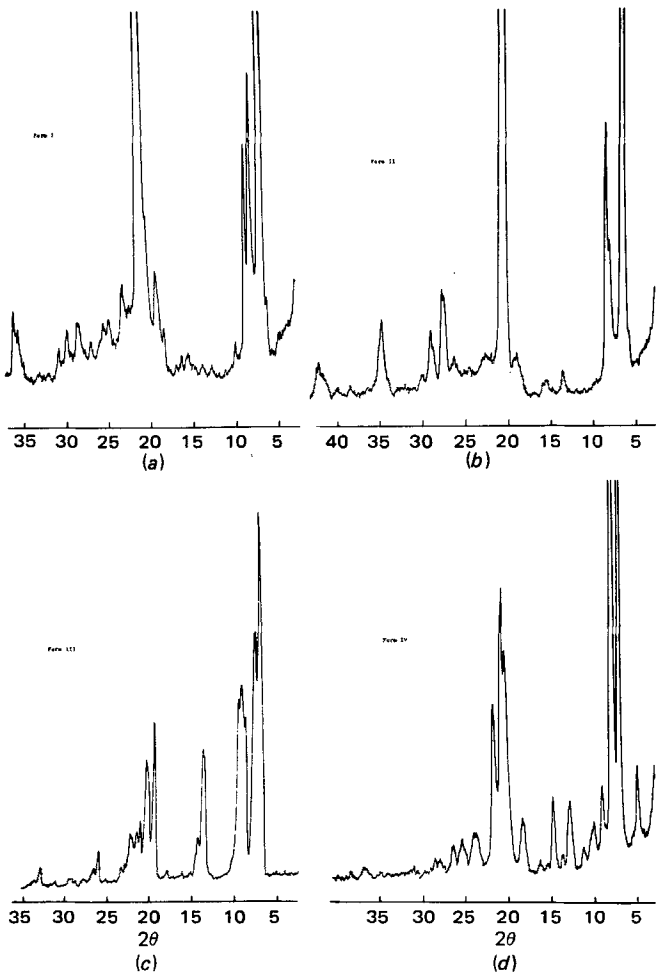

Figure 1—*X-ray diffraction patterns of phenylbutazone polymorphs. Forms I (a), II (b), and IV (d) were recorded at 1000-cps range, and Form III (c) was recorded at 2000-cps range.*

meyer flask immersed in a water bath thermostated to ±0.02°. No attempt was made to control the particle size of the crystals. At specific time intervals, 5 ml of the solution was withdrawn with a pipet fitted with a glass wool plug. Aliquots of 1 ml were withdrawn from the filtered solution and appropriately diluted, and the absorbance was measured spectrophotometrically at 264 nm.

Scanning Electron Microscopy—Compressed disks prepared in the same manner as those used for dissolution rate determinations were used for the scanning electron microscopy investigation[8]. The disks were flushed with air, and the photomicrographs were taken at magnifications ranging from 200 to 10,000×.

RESULTS AND DISCUSSION

Four crystalline modifications of phenylbutazone were obtained by the crystallization technique described and identified using data from X-ray diffraction, thermal analysis, and IR spectroscopy. Figure 1 shows the X-ray diffraction patterns of Forms I, II, III, and IV prepared from isobutyl alcohol, cyclohexane, *n*-heptane, and 2-propanol–water, respectively. Distinct differences are apparent and are attributed to differences in the arrangements of the molecules in the crystal lattices of the polymorphs.

The IR absorption spectra of the various forms showed recognizable differences in the detailed structure and intensities of some major absorption bands. Differences in the carbonyl stretching vibration region, specifically from 1760 to 1700 cm^{-1}, and in the 750–650-cm^{-1} region were peculiar for each form and could be used for the characterization and identification of the different crystalline phases. Differences in the ketone

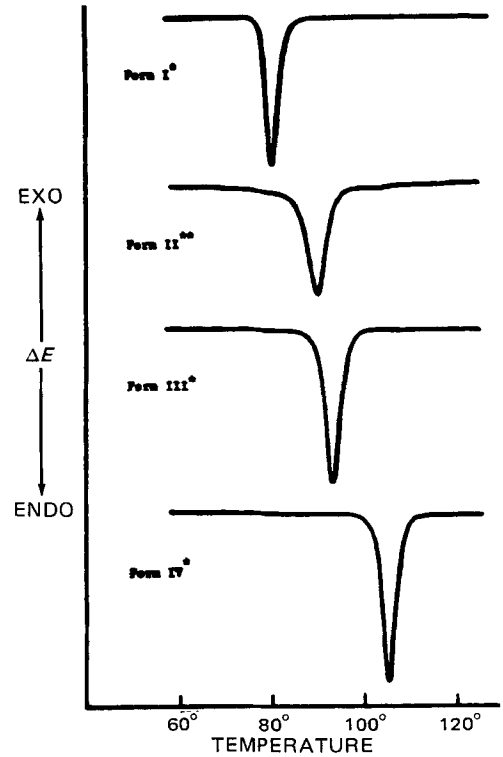

Figure 2—*Thermograms of the different crystal modifications at a heating rate of 20°/min. Key: *, crimped sample; and **, crystals heated in a covered pan with no pressure applied.*

skeletal vibration region (1350–1000 cm^{-1}) could also be attributed to differences in crystal structures. No attempt was made, however, to associate these differences with the modes of association of the molecules in the crystal lattice. The possibility of a solvate formation was excluded

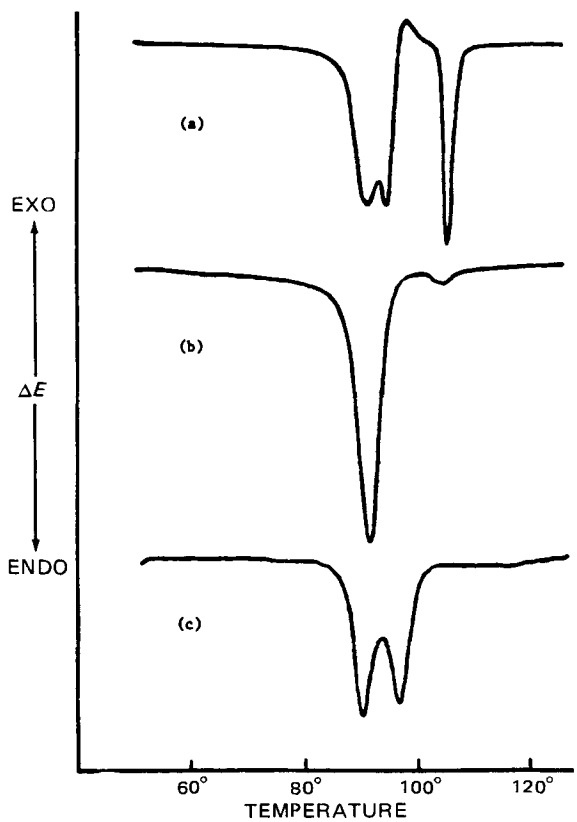

Figure 3—*Thermograms of polymorph II under different conditions of sample treatment. Key: (a), open pan; (b), covered pan; and (c), crimped sample.*

[8] Performed by Microne, Inc., Analytical & Consulting Services, Wilmington, DE 19807.

on the basis that both IR spectra and thermal analysis did not show any trace of the solvents used in the crystallization processes.

Differential scanning thermograms of I–IV are depicted in Fig. 2. In all instances, a lowering of 0.5–1° was noted in the recorded transition temperatures if the sample was crimped as compared to determinations in an open or covered pan. This decrease probably resulted from better thermal contact between the sample and the aluminum pan. Thermograms obtained for Forms III and IV were independent of the conditions of sample packing, whereas those of Forms I and II showed various phase changes depending on whether the heating was conducted in an open pan or a covered pan or whether the sample was crimped before heating.

The thermal behavior of Form II under different conditions of sample treatment is illustrated in Fig. 3. Samples heated in an open pan showed a noticeable solid–solid transformation and crystallization from melt. These effects are evident from the two endothermic peaks at 94 and 105° and the exotherm at 98° in the upper thermogram. The covered and crimped samples did not show any apparent crystallization from melt, probably because of the reduced thermal gradient within the sample.

The thermogram of the crimped sample in Fig. 3 is qualitatively in agreement with the middle thermogram in Fig. 4, where a small portion of a compressed disk of Form II was heated in a covered pan. Correlation between the two thermograms indicates that the appearance of an endotherm at 97–98° (which could possibly correspond to another form that has not been isolated as individual crystals yet) was caused by the compression pressure used in preparing the disk or even in crimping the sample.

Form IV, when heated up to 120°, cooled either naturally or with liquid nitrogen, and then subjected to thermal analysis, showed an endothermic peak at 97–98° instead of the original melting peak at 105°. On the other hand, slow controlled cooling of the melt resulted in the regeneration of the original crystals, *i.e.*, Form IV. Grinding of the rapidly cooled mass, as judged from the thermal behavior of the ground material, induced transformation to the most stable form, IV. Also, water caused such polymorphic changes when the rapidly cooled mass was kept in contact with aqueous buffer solutions. Despite the recorded differences in the X-ray diffraction patterns of the solidified mass and Forms III and IV, judgment on the authenticity of these differences should be made with great care because of the influence of the preferred orientations of the crystals in the solidified mass.

In a recent report concerning a nonclassical dissolution behavior of

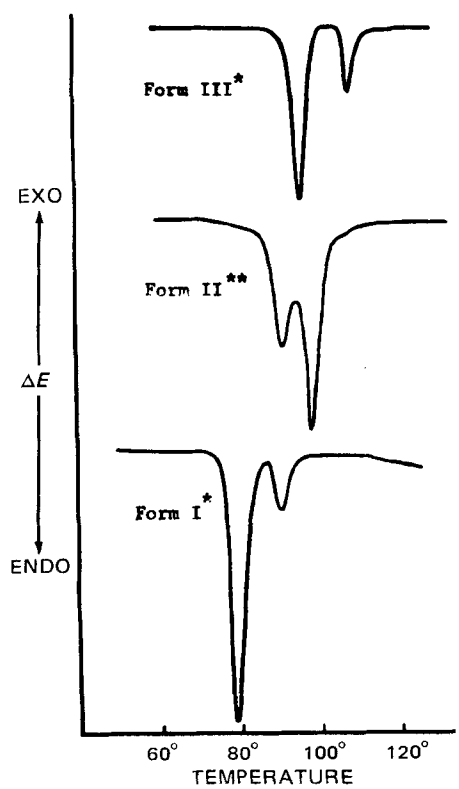

Figure 4—*Differential scanning thermograms of portions of compressed disks of Forms I–III. Key: *, crimped sample; and **, crystals heated in a covered pan with no pressure applied.*

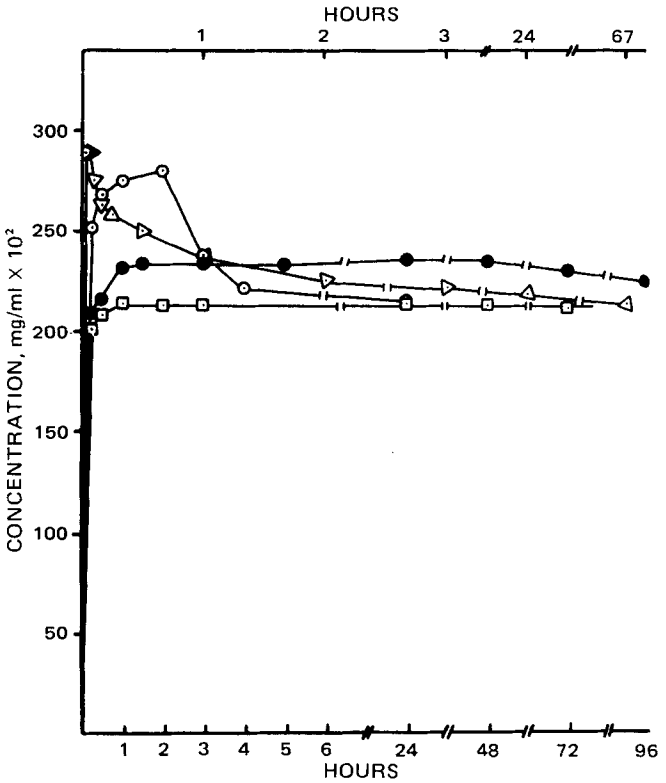

Figure 5—*Solubility profile of phenylbutazone polymorphs in phosphate buffer at 36°. Key: △, Form I (upper time scale); ⊙, Form II (lower time scale); ●, Form III (lower time scale); and □, Form IV (lower time scale).*

phenylbutazone, Stella (10) noted the existence of three crystalline phases of the compound. Melting points of 86, 96, and 106° were the only information provided about the polymorphs. The reported melting point of 96° is close to the melting point of 97–98° obtained for the rapidly cooled mass. So far, attempts to obtain phenylbutazone as individual

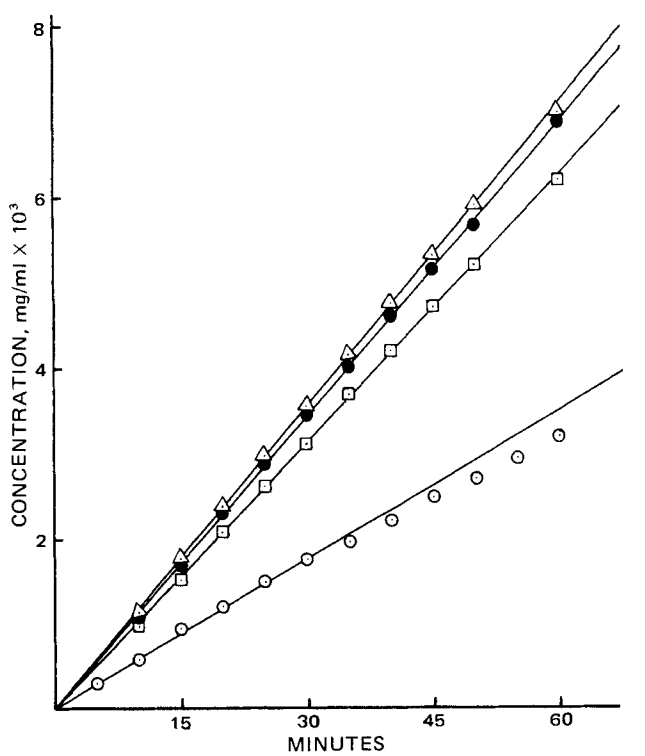

Figure 6—*Comparison of dissolution rates of phenylbutazone Forms I (△), II (⊙), III (●), and IV (□) in phosphate buffer at 36°.*

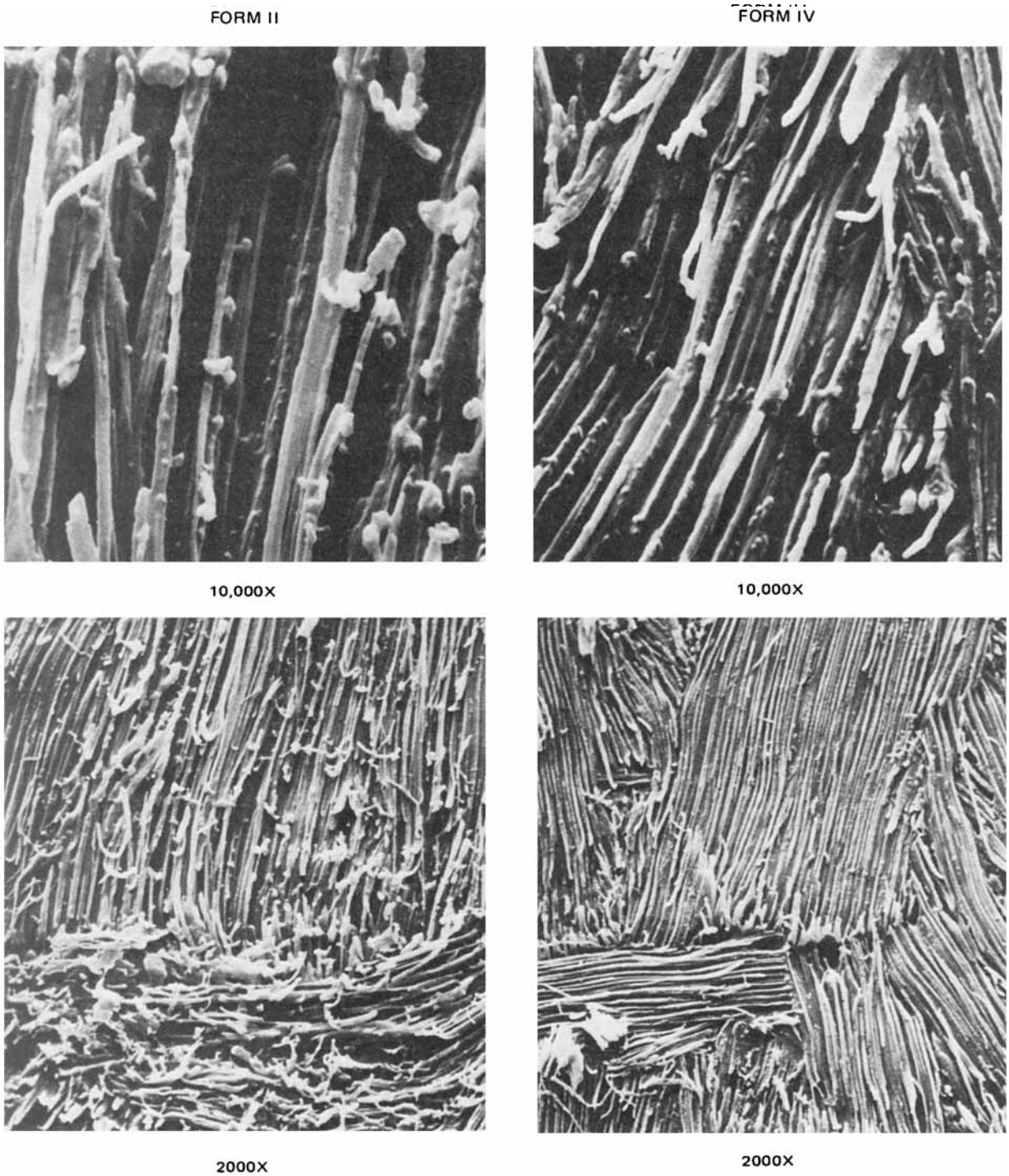

Figure 7—*Scanning electron photomicrographs of compressed disks of Forms II and IV.*

crystals with melting and spectral characteristics similar to those of the rapidly cooled mass, *e.g.*, by crystallization, have failed.

Similarly, Form I exhibited various transitions when heated under different conditions of sample treatment (Table I). Apparently, Form I is not as sensitive to crimping pressure as is Form II; however, heating of Form I in a covered pan induced solid–solid transformation to Form II.

Figure 4 shows thermograms obtained by heating a small portion of disks of Forms I–III, previously prepared by compacting approximately 100 mg of the crystals in an 8-mm die at 1590–2040 kg. Form III, during compression, was transformed to the most stable modification, Form IV. Forms I and II gave thermodynamically unstable phases, *i.e.*, Form II and a polymorphic species melting at 97–98°, respectively. Grinding of Forms I–III in a mortar induced polymorphic changes analogous to those observed when the respective crystal forms were compressed into disks. While compression of Form II into a disk consistently produced a polymorphic species melting at 97–98°, mortar grinding sometimes resulted in Form IV instead.

In view of the observed results, it is likely that similar effects on the crystals were produced by the shear stresses dominating in the mortar assembly and the shear stresses operative during compression and decompression of the disks. The notion of an active ingredient undergoing polymorphic changes during compression was discussed previously (11, 12). The variation and apparent increase in the dissolution rate of unlubricated sulfathiazole disks with pressure, as reported by Milosovich (13), were interpreted by Nogami *et al.* (14) to be caused by a change in the crystalline form. The effects of such polymorphic transformations on the dissolution rates as determined from compressed disks as well as from tablets containing transformation-labile ingredients are important to recognize. In fact, the determined dissolution rates vary depending

Table I—Phase Transitions in Form I when Heated under Different Conditions of Sample Treatment

Condition	Endothermic Transition	Exothermic Transition
Open pan	80°, 105°	92–94°
Covered pan	80°, 90°	—
Crimped sample	80°	—

on the type and proportions of the polymorphic species produced during compact preparation. This variation might affect drug bioavailability in an unpredictable and undesirable manner.

The dissolution profiles of the four crystal modifications (Fig. 5) show differences in solubilities and physical stabilities of the various forms in the aqueous medium. The apparent equilibrium solubilities (Table II) correspond in value to the peak solubilities as determined from the dissolution profiles. Form I gave the highest solubility in the aqueous buffer solution and was the fastest to achieve the degree of supersaturation necessary for the nucleation process. Apparent slower nucleation and crystal growth processes were associated with Form III compared to Forms I and II (Fig. 5). Since the degree of supersaturation achieved in a system containing Form III was much less than that in a system containing Form I or II, a much smaller driving force for the crystal growth process existed. Transformation of Forms I–III to the most stable modification, Form IV, at the end of the dissolution experiment was confirmed by IR and thermal analysis.

Solubility measurements at different temperatures were used to obtain information concerning enthalpy and entropy of transition from Form I to Form IV. The thermodynamic background of the relationship between polymorphism and solubility was extensively reviewed (15). A straight-line relationship between the logarithm of the solubility ratio of the two forms and the reciprocal of the absolute temperature was obtained, and the extrapolation of the line to a solubility ratio of unity corresponded to a transition temperature of 74.1°. The calculated enthalpy and entropy of transition were −1613 cal/mole and −4.6 eu, respectively. The observed entropy difference between phenylbutazone Forms I and IV suggests differences in the molecular association in the crystalline lattice of the two forms.

A comparison between the dissolution rates of the different crystal modifications is shown in Fig. 6. Because of the crystal changes that took place during the compression of Forms I–III into disks, the respective dissolution rates of the three forms are apparent rather than intrinsic dissolution rates. Unexpectedly, the dissolution rate of Form II was consistently lower than that of the most stable modification, IV. This low dissolution behavior persisted even for compressed disks prepared from 50% mixtures of II and IV and of II and I. The slopes of the concentration–time curves for the dissolution of such disks were of intermediate values between those of II and IV.

If a transport-controlled dissolution from the disk surface is assumed, the dissolution curves in Fig. 6 should adhere to the Noyes–Whitney equation and, in the initial stages of dissolution, the relationship between concentration in solution and time could be given by:

$$\frac{dC}{dt} = \frac{D}{Vh} AC_s \qquad \text{(Eq. 1)}$$

where D is the diffusion coefficient, h is the thickness of the diffusion layer, A is the surface area, and C_s is the saturated solubility of the crystalline solid in the medium. The volume of the dissolution medium, V, was kept constant by using 500 ml of the medium in each experiment. The four polymorphs should have the same values of D and h irrespective of the crystal form, and the increase in the slopes of the straight lines in Fig. 6 should follow the order reflected in their saturated solubilities. The latter holds true only when the area exposed to dissolution is the same for the four polymorphs. In view of the obtained results, it is likely that the physical characteristics of phenylbutazone Form II crystals are such that, upon compression, they produce disks with a smaller effective surface area compared to those of Form IV, even though the same conditions are maintained carefully during compression.

Table II—Differential Scanning Transition Temperatures and Peak Solubilities of the Different Polymorphs

Form	Solvent of Crystallization	Transition Temperature	Peak Solubility[a], mg/100 ml
I	Isobutyl alcohol	80°	288.7
II	Cyclohexane	90°	279.9
III	*n*-Heptane	93°	233.6
IV	2-Propanol–water	105°	213.0

[a] Solubility in phosphate buffer, pH 6.95, at 36°.

A qualitative assessment of the surfaces of compressed disks of Forms II and IV was sought through the use of the scanning electron microscope. Photomicrographs (Fig. 7) indicate differences in the surface characteristics of the disks. Also, it can be inferred from the pictures that the extent of corrugation per unit area of the surfaces differed. Although it is too difficult to describe differences in surface area in a quantitative manner, these differences reflect that crystals of different forms behave differently under compression. This fact could, at least in part, account for the observed anomaly in the dissolution rates of compressed disks of Form II compared to Form IV.

REFERENCES

(1) J. K. Haleblian, *J. Pharm. Sci.*, **64**, 1269 (1975).

(2) J. K. Haleblian and W. McCrone, *ibid.*, **58**, 911 (1969).

(3) D. L. Simmons, R. L. Ranz, and N. D. Gyanchandani, *Can. J. Pharm. Sci.*, **8**, 125 (1973).

(4) S. Khalil, M. Moustafa, A. Ebian, and M. Motawi, *J. Pharm. Sci.*, **61**, 1615 (1972).

(5) J. W. Shell, *ibid.*, **52**, 100 (1963).

(6) P. W. Bridgeman, *J. Appl. Phys.*, **27**, 659 (1956).

(7) H. G. Drickamer, *Science*, **156**, 1183 (1967).

(8) I. P. S. Kang, C. E. Kendall, and R. W. Lee, *J. Pharm. Pharmacol.*, **26**, 201 (1973).

(9) J. H. Wood, J. E. Syatto, and H. Letterman, *J. Pharm. Sci.*, **54**, 1068 (1965).

(10) V. J. Stella, *ibid.*, **64**, 706 (1975).

(11) J. E. Rees, *Bull. Chim. Farm.*, **112**, 216 (1973).

(12) J. K. Haleblian, R. T. Koda, and J. A. Biles, *J. Pharm. Sci.*, **60**, 1485 (1971).

(13) G. Milosovich, *ibid.*, **53**, 484 (1964).

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

(15) W. I. Higuchi, P. K. Lau, T. Higuchi, and J. W. Shell, *J. Pharm. Sci.*, **52**, 150 (1963).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 23, 1976, from *Pharmacy Research & Development, Pharmaceuticals Division, Ciba-Geigy Corporation, Suffern, NY 10901.*

Accepted for publication July 1, 1976.

The authors thank Dr. H. Stober of Analytical Research & Development for assistance in the X-ray diffraction work.

[x] To whom inquiries should be directed.