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Thermal behaviour and dissolution properties of phenylbutazone polymorphs

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Five different polymorphic forms of phenylbutazone were prepared and characterized by differential scanning calorimetry (D.S.C.). Rapid heating rates produced single endothermic peaks due to melting but slower heating rates resulted in interconversion of three of the polymorphs to the more stable form. Interconversion on grinding the polymorphs was also observed. From equilibrium solubility and intrinsic dissolution rates it was concluded that the dissolution process could be described by the Berthoud model. The effect of some tablet excipients on the dissolution process is briefly reported.

Phenylbutazone has been reported to exist in several polymorphic forms. Matsunaga et al (1976) reported the existence of three polymorphs; Form I melting at 103 °C, Form II partly melting at 93 °C and then at 103 °C and Form III melting at 93 °C. Ibrahim et al (1977) reported four polymorphic forms; Form I melting at 80 °C, Form II at 90 °C, Form III at 93 °C and Form IV at 105 °C. They prepared Form I from a saturated solution of isobutyl alcohol, Form II from cyclohexane, Form III from n-heptane and Form IV from 2-propanol. Müller (1978) tried to reproduce the findings of those workers and in his investigation he showed that Forms I and II reported by Ibrahim et al (1977) were solvates. By using simultaneous DTA/TG/DTG he showed that Form I crystals contained 8·0% isobutanol and Form II crystals contained 7·0% cyclohexane. Müller (1978) also reported the existence of two new polymorphs of phenylbutazone. He obtained one of the new polymorphs, Form β (m.p. 95·1 °C) by melting and recrystallizing the commercial phenylbutazone and also by the addition of water to an ethanolic solution. He could not isolate the other polymorph, Form γ.

All the above workers used a different nomenclature for their polymorphs. Their nomenclature and the melting points of the polymorphs are shown in Table 1. The nomenclature adopted by us is to name the polymorphs A to E in descending order of their melting points.

In the present paper we report on the preparation and characterization of the polymorphs by differential scanning calorimetry and study their dissolution properties in aqueous buffer at pH 7·5.

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Table 1. Reported melting points (°C) of phenylbutazone polymorphic forms.

Matsunaga et al (1976)		Ibrahim et al (1977)		Müller (1978)	
Form	D.S.C. max. peak temp. 8 °C min^{-1}	Form	D.S.C. max peak temp. 20 °C min^{-1}	Form	D.S.C. max. peak temp 10 °C min^{-1}
I	103°	I	80°	α	93·4°
II	93°, 103°	II	90°	β	95·1°
III	93°	III	93°	γ*	106·0°
		IV	105°	δ	107·5°

* Detected but not isolated.

MATERIALS AND METHODS

Preparation of the crystal forms

Commercial phenylbutazone (Berk Pharmaceuticals) m.p 105 °C (Form A) was used to prepare the different crystal forms of phenylbutazone by crystallization from n-heptane (BDH lab reagent) under different conditions of concentration and crystallizing temperatures.

Form A: Commercial phenylbutazone was used as such. Recrystallized material was also prepared by adding water to a 2-propanol solution until the cloud point. The solution was warmed to redissolve the drug and allowed to cool at 20–25 °C when the crystals were filtered off (0·45 μm membrane filter) under vacuum.

Form B: 5 g of commercial phenylbutazone were dissolved in 100 cm^3 of n-heptane by heating on a water bath maintained at about 90 °C. The clear solution was then poured into a hot vacuum conical flask to avoid immediate crystallization. After slow crystallization on cooling, the solution was then evaporated under vacuum until the crystals were dry.

Form C: 5 g of commercial phenylbutazone were dissolved in 550 cm^3 of n-heptane by heating on a

water bath maintained at 70 °C. The solution was then filtered through a 0·45 μm membrane filter. A hot filtration unit was used to avoid immediate crystallization. The filtered solution was then allowed to cool at room temperature (20–25 °C).

After 2–3 h the crystals formed were separated by filtering through a sintered glass funnel and dried under vacuum at room temperature.

Form D: The filtered solution obtained in the preparation of Form C was filtered through a 0·45 μm membrane filter and allowed to crystallize by leaving at room temperature for about 24 h. The crystals thus obtained were separated by filtering through a sintered glass funnel and dried under vacuum at room temperature.

Form E: The filtered solution obtained in the preparation of Form D was filtered through a 0·45 μm membrane filter and was allowed to crystallize by cooling in an ice bath for 2–3 h. The crystals formed were then separated by filtering through a sintered glass funnel and dried under vacuum at room temperature. The moisture content of the different crystal forms was determined by drying to constant weight at 40 °C in a vacuum oven. The percentage moisture content of Forms A, B, C, D and E was 0·02, 0·09, 0·08, 0·1, 0·1 respectively.

Gas liquid chromatography. A Perkin-Elmer F-33 gas chromatograph was used to check whether the crystals contained solvent of crystallization. A 1 metre glass column packed with 15% PEG 20M in chromosorb WAW was used. The conditions used were injection/detection temperature 150 °C; oven temperature 115 °C; the internal marker was ethanol; the nitrogen flow rate was 40 cm^3 min^{-1}. Retention times (min): cyclohexane 1·6, ethanol 2·3, propanol 3·0, isobutanol 5·8 butane-2-ol 4·0. Head space sampling was not used. Limits of solvent in the drug were: cyclohexane 0·01, butanol 0·03 and heptane 0·005%.

Differential scanning calorimetry (D.S.C.). The thermograms of the different crystal forms were recorded on a Perkin-Elmer D.C.S. 1B calibrated with pure indium, M.p. 155 °C. The thermal behaviour of the five polymorphs was studied at different heating rates (2 °, 4 °, 8 °, 16 °, 32 ° and 65 °C min^{-1}). The samples were heated in covered pans. Melting points were defined as being the point of intersection between the base line and the linear section of the ascending endothermic curve (Wendlant 1974).

Infrared spectroscopy. Nujol mulls of the powdered crystals were prepared and the spectra determined using a Perkin-Elmer grating infrared spectrophotometer 157G.

Vibratory ball milling. The apparatus (Alfred Fritsch, W. Germany) was an electro-magnetic powered mortar which generates vertical oscillations to an agate grinding ball. The mill can be operated at different oscillation rates.

X-ray diffraction. A Guinier Powder Camera (Imperial College, University of London) was used to obtain X-ray diffraction photographs. Powder samples of the polymorphs were spread lightly over Sellotape for use in the camera. By using four samples simultaneously, comparisons of band intensity could be made. Quartz monochromated CuK_α radiation was used.

Diffusion coefficient measurement. A diaphragm diffusion cell as described by Cadman et al (1981) was used to determine the diffusion coefficient of phenylbutazone.

Solubility and dissolution rate. For the determination of the equilibrium solubility, an excess quantity (1 g) of phenylbutazone crystals was shaken with 100 cm^3 of 0·2 M aqueous phosphate buffer pH 7·5 in a 250 cm^3 stoppered conical flask immersed in a water bath maintained at 37 °C. The flask was shaken at a fixed rate and samples were withdrawn at specific intervals by filtering 2 cm^3 of solution through a 0·45 μm membrane filter. The absorbance of the solution was measured at 264 nm after suitable dilution with buffer solution.

The apparatus used for the dissolution rate determinations was similar to that described by Wood et al (1965). About 300 mg of crystals were compressed to a disc in a 12 mm stainless steel tablet die at 130·1 MNm^{-2}. At this compression pressure, no phase change occurred in Forms A, B, D, and E and only a very small change occurred in Form C as detected by D.S.C. The tablet was attached to the holder by brushing melted wax around the side of the tablet so that only one face of the tablet was exposed. The holder of the tablet was then rotated in 500 cm^3 0·2 M phosphate buffer (pH 7·5) dissolution medium at 100 rpm. The drug concentration in the solution was then measured by taking a sample of 5 cm^3 every 30 min and measuring the absorbance at 264 nm.

RESULTS AND DISCUSSION

Five crystal forms of phenylbutazone were obtained by the crystallization technique described above and identified using data from X-ray diffraction, thermal analysis and dissolution studies.

X-Ray diffraction patterns of the crystal forms showed only small differences in the characteristic 'd' values and intensity of the diffraction bands (Table 2). Although Ibrahim et al (1977) and Müller (1978)

Table 2. Characteristic 'd' value and intensity in the diffraction pattern of the phenylbutazone crystal forms.

Crystal form	Characteristic 'd' value (Å)	Intensity visibly established
A	10·7	Strong
B	10·8	Medium
C	10·4	Weak
D	10·1	Strong
E	10·15	Medium

claimed distinct differences in X-ray diffraction patterns of the different crystal forms, the differences in characteristic 'd' value in their study were similar to the differences obtained in this study (Dr R. Osborne, personal communication).

The infrared absorption spectra (Nujol mull) of the various forms showed only slight differences in the region of 1500–1450 cm^{-1}, 1425–1300 cm^{-1} and 750–640 cm^{-1} and would not be very useful for differentiating between the crystal forms (Tuladhar 1982).

The possibility of solvate formation was investigated by gas liquid chromatography. The chromatograms of Forms A, B, C, D and E showed the prepared crystal forms were solvent free, but the crystal Forms I and II prepared by the method reported by Ibrahim et al (1977) showed the presence of the solvents isobutanol (Form I) cyclohexane (Form II) and the molar ratio of drug to solvent present was 3:1 and 4:1 respectively. This result is similar to that observed by Müller (1978).

D.S.C. thermograms (heating rate 32 °C min^{-1}) of Forms A–E (Fig. 1) showed sharp single peaks with characteristic melting points. Melting points of the crystal forms were also determined by using a hot stage microscope (Mettler FP5 + FP52) and found to be similar to those obtained from the D.S.C. traces (Table 3). The heat of fusion of the crystal forms (calculated from the thermogram peak areas) also differed from each other (Table 3).

The effect of heating rate on the thermograms of phenylbutazone crystal Forms A–E is also shown in Fig. 1. Thermograms obtained for Forms A and B were single endothermic peaks at all different heating rates, while single peaks were only obtained for Forms C, D and E at high rates of heating, e.g. >16 °C min^{-1} for Form C and >32 °C min^{-1} for Forms D and E. These results indicate that Form A and Form B did not undergo any change, except melting, at any heating rate. However, Forms C–E first melted and then recrystallized to the more stable Form A, when they were heated at slower rates. This effect was evident from their thermograms at slow heating rates, which showed two endothermic peaks and one intermediate exothermic peak. The amount of Form A (based on area of exothermic peak)

Table 3. Melting points and heat of fusion of phenylbutazone crystal forms (°C).

Form	D.S.C. (32°C min^{-1}) max. peak temp.	M.p.†	Hot stage M.p.	Heat of fusion* (32 °C min^{-1}) J g^{-1}
A	108·5	105	105·5	85·4
B	107	103	103·9	89·2
C	100	96	95·8	81·2
D	98·5	94	94·2	47·7
E	97	92·5	92·9	96·7

* Mean of 5 determinations.
† Determined from onset of melting.

recrystallized from Forms C–E was found to be dependent upon the rate of heating. As the heating rate was decreased, more Form A was found to recrystallize which was evident from the increased areas of the exothermic and endothermic (second) peaks. Of particular interest is the occurrence of the exothermic peak for forms C–E at heating rates from 2 ° to 8 °C min^{-1}. The magnitude of this peak decreases as the heating rate increases and would appear to be a result of the more stable form (A), crystallizing from the melt. Under rapid heating conditions, it does not have time to crystallize and only the endothermic single peak due to melting of the original polymorph is shown. This illustrates the importance of studying the thermal behaviour of polymorphs over a range of heating rates. In addition it is important to distinguish between endothermic reactions due to melting and those due to desolvation of the crystals. In this work it was established by g.l.c. that all the polymorphs were solvent-free.

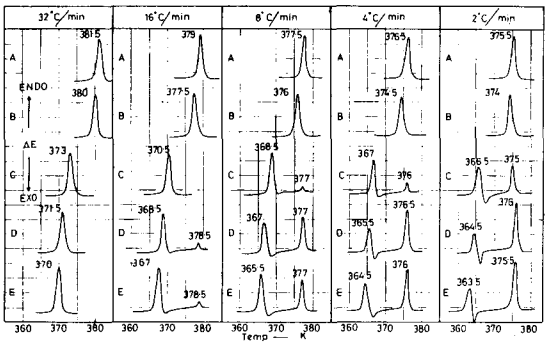

FIG. 1. The effect of heating rate on the thermograms of phenylbutazone crystal forms.

Some workers report the maximum peak temperatures as melting points (see Table 1) and this procedure is open to criticism since at this temperature about half the sample will have melted. It seems more satisfactory to define the melting point as being the point of intersection between the base line and the linear section of the ascending endothermic curve, as this is the onset of melting (Wendlant (1974).

The effects of grinding and compression pressure on the thermal properties of phenylbutazone crystal forms were also studied. With Forms A and B the only effect observed was a lowering of melting point when grinding was done at high amplitude or when the forms were compressed at high pressures in a tablet die. However, Forms C, D and E appeared to be partially converted to Form A on grinding or compression at high pressures. Form C showed transformation to Form A at 86·7 MN m^{-2} compression pressure, while Forms D and E transformed at 173·4 MN m^{-2} pressure. The effect of grinding for 10 min is shown in Fig. 2 and that of compression in a tablet die is shown in Table 4.

Long-term storage tests of the phenylbutazone crystal forms were carried out by storing crystals in

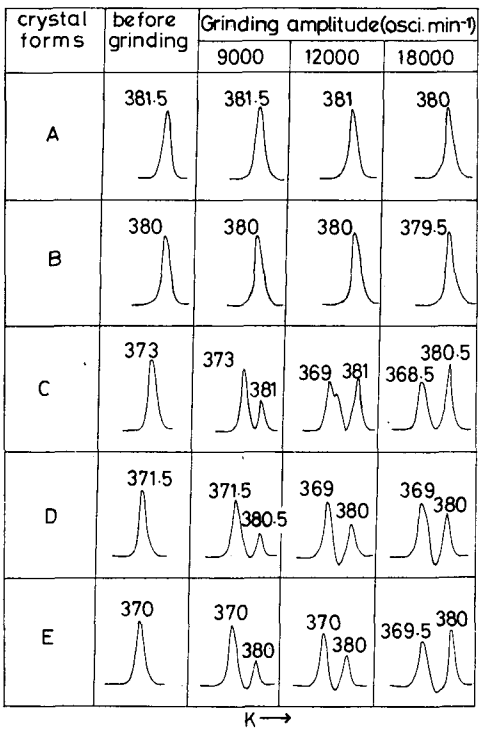

FIG. 2. Thermograms (32 °C min^{-1}) of phenylbutazone crystal forms before and after grinding at different amplitudes for 10 min.

Table 4. Effect of compression pressure on conversion of Forms C, D and E to Form A. (Compression in 12 mm stainless steel tablet die.)

Compression pressure MNm^{-2}	% Form A present in C	D	E*
43	—	—	—
86	1·3	—	—
130	2·3	—	—
173	3·2	1·0	1·0
216	5·6	2·2	1·8

* Means of 3 determinations.

an oven at 40 °C. The amount of Form A in each form was calculated from the thermogram peak areas and is shown in Table 5. Forms A and B remained unchanged but Forms C, D and E were found to transform partially into Form A after storage for about two months. The amount of Form A increased with time of storage. The stability of crystal forms on the basis of amount of Form A formed are in order of Form A> Form B> Form D> Form E> Form C. This result is similar to that obtained with the study of effects of grinding and compression pressure.

Table 5. Stability of the different crystal forms of phenylbutazone, after storage at 40 °C.

	% of Form A formed after storage (months)					
Form	1	2	4	5	6	12
A	*	*	*	*	*	*
B	*	*	*	*	*	*
C	*	2·5	4·0	5·0	17·5	60·2
D	*	1·5	2·0	2·0	2·9	6·2
E	*	2·0	3·0	3·2	10·5	14·4

* No change in thermogram and max. peak temperature.

The solubility measurements of the crystal forms showed the equilibrium solubility of Forms A, B, D and E were achieved after about 24 h but the solubility of Form C was found to be increasing even after 144 h. The longer time required for Form C to achieve the equilibrium solubility could have been due to the poor wetting of the crystals, so the measurements were repeated in the presence of the wetting agents, polyethylene glycol 300 (2·25%) and Tween 80 (0·05%) (Table 6).

The equilibrium solubility of the crystal forms was increased and achieved more quickly in the presence of the PEG 300 but was decreased when Tween 80 was present. This adverse effect may be due to the adsorption of Tween 80 on the crystal surface.

Table 6. Equilibrium solubility of phenylbutazone crystal forms (mg/100 ml).

	Form				
	A	B	C	D	E
0·2 M phosphate buffer pH 7·5	480	510	490	515	535
Solubility ratio*	1	1·06	1·23	1·07	1·11
Buffer with 0·05% Tween 80	450	485	552	495	510
Solubility ratio*	1	1·07	1·23	1·10	1·13
Buffer with 2·25% PEG 300	352	577	672	585	615
Solubility ratio*	1	1·08	1·26	1·09	1·15

$$* \text{ Solubility ratio} = \frac{\text{Solubility of Form A}}{\text{Solubility of polymorph}}$$

Although the presence of the wetting agents affected the solubility of crystal forms, the ratio of equilibrium solubility of Form A to equilibrium solubility of other forms in each solution was found to be similar (Table 7), which indicates that the difference in equilibrium solubility of the phenylbutazone crystal forms is due to the difference in their crystal structure. The equilibrium solubility of the phenylbutazone crystal forms was in order of Form C< Form E< Form D< Form B< Form A, which would be expected from the stability of stored samples.

A comparison between the dissolution rates of the different crystal forms is shown in Fig. 3. Form C showed a maximum dissolution rate about 55% higher than that of the stable Form A. The new Forms B and E have about 20% and 35% higher dissolution rate respectively than Form A. The dissolution rates of crystal forms are in order of Form C> Form E> Form B> Form D> Form A.

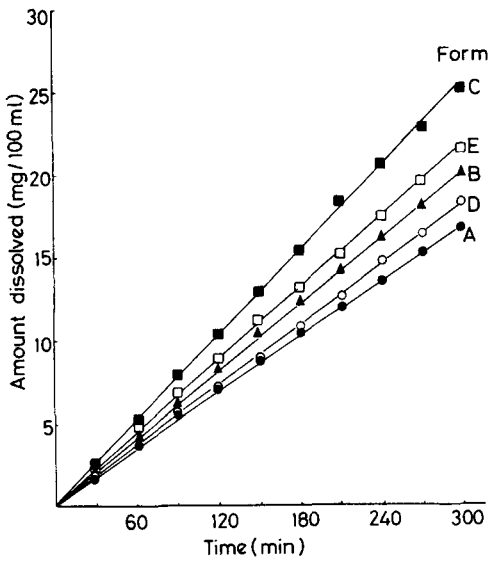

FIG. 3. Comparison of dissolution rates of phenylbutazone crystal forms in 0·2 M phosphate buffer pH 7·5 at 37 °C and 100 rev min^{-1} Form A ●, Form B ▲, Form C ■, Form D ○ and Form E □.

Table 7. The dissolution rate (DR) and solubility of phenylbutazone crystal forms in 0·2 M phosphate buffer of pH 7·5 at 37 °C.

Form	DR μg cm^{-2} s^{-1}	DR ratio	Equilib. sol. mg/100 cm^3	Sol. ratio
A	3·96	1	480	1
B	4·76	1·20	510	1·06
C	6·10	1·54	590	1·23
D	4·70	1·18	515	1·07
E	5·37	1·35	535	1·11

* Mean of 3 determinations.

In a transport controlled dissolution process, when diffusion from the solid is the rate determining step, the dissolution process can be represented by the general Noyes-Whitney equation:

$$\frac{dc}{dt} = K\frac{S}{V}(c_0 - c) \qquad (1)$$

where c = the concentration at time 't', c_0 = the saturated concentration, K = the apparent dissolution rate constant, S = the surface area of solid and V = the volume of solution.

i.e.
$$\frac{dc}{dt} \alpha\ C_0 \qquad (2)$$

where S remains constant.

The dissolution rate of each form should then be in the ratio of their equilibrium solubilities. Table 7 shows the dissolution rate of each form and their equilibrium solubilities. From this it is evident that the dissolution process of phenylbutazone crystal forms does not follow this simple model.

The Noyes-Whitney model assumes that there is an instantaneous reaction at the crystal surface to give a saturated solution. Berthoud in 1912 showed that the reaction at the surface was not instantaneous but that finite time was needed for transfer of the dissolving species from the solid to the liquid phase and this additional rate controlling process was necessary to explain the dissolution phenomena. The dissolution process could thus be regarded as an interfacial controlled phenomenon.

Wurster & Taylor (1965) applied the Berthoud

modification of the Noyes-Whitney equation in the following form:

$$\frac{dc}{dt} = \frac{S}{V} \frac{k_r kt}{k_r + k_t}(C_0 - C) \quad (3)$$

where k_r = the rate constant of the interfacial reaction, k_t = the rate constant of the transport process and thus the experimentally derived rate constant K is a hybrid rate constant in equation 1.

Levich (1962) developed a mathematical model to evaluate 'k_t' for a solely diffusion controlled process during dissolution of a rotating disc. The diffusion rate constant was given by:

$$k_t = 0.620\, D^{2/3}\, \nu^{1/6}\, \omega^{1/2} \quad (4)$$

where D = diffusion coefficient; ν = kinematic viscosity; ω = angular velocity of the disc. This equation has been used by Summers (1972) and Carless & Jordan (1974) in conjunction with equation 3 to calculate the relative contribution made by k_r to the dissolution of compressed discs of aspirin and sulphathiazole. With the same procedure the values of k_r and k_t were determined for the polymorphs A to E (Table 8).

Table 8. Dissolution rate constants for the dissolution of phenylbutazone crystal forms.

Form	Diff. coeff. $\times 10^6$ cm^2 s^{-1}	K $\times 10^3$ cm min^{-1}	Calc. $k_r \times 10^3$ cm min^{-1}	Calc. $k_t \times 10^3$ cm min^{-1}
A		54	108	
B		58	125	
C	7·8	63	151	108
D		52	100	
E		57	120	

The values of K and k_t are significantly different for all the crystal forms, which suggests that the interfacial process is the dissolution controlling step for phenylbutazone crystal forms A, B, C, D and E.

Piccolo & Tawashi (1970) and Carless & Jordan (1974) have shown that the presence of the dye reduced the dissolution rate of sulphathiazole, which was controlled by the interfacial reaction. Since the dissolution process of the phenylbutazone crystal forms is controlled by a partial interfacial reaction, it is likely that the presence of materials such as tablet excipients could affect the dissolution rate to a greater extent than for a diffusion controlled process. Table 9 shows the effects of various materials dissolved in the dissolution medium on the dissolution rate and rate constant of the phenylbutazone Form A.

The presence of materials like polyvinylpyrrolidone, gelatin and hydroxypropylmethylcellulose reduced the dissolution rate significantly, while materials such as lactose and acacia had only little effect. This result is similar to results obtained by Lovering & Black (1974) in their study of the effect of various substances on the permeability coefficient of phenylbutazone through membranes of polydimethylsiloxane and everted rat gut. They found phenylbutazone permeation rates in one or both membranes decrease in the presence of gelatin, polyvinylpyrrolidone, methyl cellulose, polysorbate 80, while lactose, acacia, sucrose, starch and talc have no apparent effect. The decrease in the dissolution rate of phenylbutazone observed in the above studies may be due to the interference on the interfacial reaction of the phenylbutazone by the materials absorbed in the membrane/tablet surface. For example, an increase in lactose concentration is accompanied by a decrease in k_r but with polyvinylpyrrolidone (which decreases the dissolution rate) the reverse is the case.

Table 9. Dissolution rate (DR) constant for the dissolution of phenylbutazone Form A in 0·2 M-phosphate buffer with various materials dissolved in it.

Dissoln. medium	DR μg cm^{-2} s^{-1}	s.d.	K $\times 10^3$ cm min^{-1}	$k_t \times 10^3$ cm min^{-1}	kr $\times 10^3$ cm min^{-1}
Buffer soln.	4·28	0·141	54	108	108
+ 0·1% Acacia	3·89	0·085	58	107	87
+ 0·1% Lactose	3·99		50	108	92
+ 0·5% Lactose	3·80	0·159	49	106	91
+ 0·1% NaCMC	3·78	0·043	47	101	88
+ 0·1% Gelatin	3·44	0·034	42	106	69
+ 0·1% PVP	3·13		39	107	61
+ 0·5% PVP	3·11	0·088	39	105	62
+ 0.025% HPMC	3·05	0·062	38	106	59

Any attempt to correlate the polymorphic forms found with those of other workers is made difficult by the lack of published data but from the available evidence it could appear that our forms A, C and D are equivalent to Müller's forms δ, β and α respectively.

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REFERENCES

Berthoud (1912) J. Chem. Phys. 10: 624

Cadman, A. D., Fleming, R. Guy, R. H. (1981) J. Pharm. Pharmacol. 33: 121–123

Carless, J. E., Jordan, D. (1974) Ibid. 26: 85P

Ibrahim, H. G., Pisano, F., Bruno, A. (1977) J. Pharm. Sci. 66: 669–673

Levich, V. G. (1962) Physico-Chemical Hydrodynamics. Prentice Hall Inc.

Lovering, E. G., Black, D. B. (1974) J. Pharm. Sci. 63: 671–676, 1399–1402

Matsunaga, J., Nambu, N., Nagai, T. (1976) Chem. Pharm. Bull. 24: 1169–1172

Müller, B. W. (1978) Pharm. Acta. Helv. 53: 333–340

Piccolo, J., Tawashi, R. (1970) J. Pharm. Sci. 59: 56–59

Summers, M. P. (1972) Ph.D. Thesis University of London

Tuladhar, M. D. (1982) Ph.D. Thesis, University of London

Wood, J. H., Syarto, J. E., Lotterman, H. (1965) J. Pharm. Sci. 54: 1068

Wendlant, W. W. (1974) Thermal methods of analysis. John Wiley & Sons

Wurster, D. E., Taylor, P. W. (1965) J. Pharm. Sci. 54: 670–676