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Effect of crystal form on the oral absorption of phenylbutazone

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Phenylbutazone, in spite of its relatively high toxicity, is still used in many countries as a potent anti-rheumatic drug. It possesses strongly hydrophobic characteristics (Lerk et al., 1977) and is almost insoluble in acidic pHs. Although a number of workers have reported upon the occurrence of polymorphs in phenylbutazone (Matsunaga et al., 1976; Ibrahim et al., 1977; Matsuda et al., 1980), assessment of the difference, if any, in absorption from the polymorphs has not been reported so far. Since this drug has a potential for incomplete bioavailability (Chodos and Disanto, 1974), the present authors studied the solubility, dissolution rate and oral absorption of two samples of phenylbutazone obtained by recrystallization from ethanol and chloroform. It was observed that the sample obtained from chloroform possessed significantly better in vitro and in vivo characteristics due to difference in crystal form.

Phenylbutazone B.P. obtained through commercial source was classified through B.S.S. 200. It conformed to form I, m.p. 103°C (Matsunaga et al., 1976). All other reagents used were of reagent grade. Ethanol was purified by refluxing with KOH-Zinc dust and distillation.

A 5 g portion of the drug was dissolved in 50 ml of solvent (chloroform or ethanol) in the flask of a rotary flash evaporator (Remi). The solvent was removed at 60°C under vacuum. After complete removal of the solvent the drug powder material was classified through sieve no. 200 and stored in a vacuum desiccator. The drug material obtained from ethanol (sample x) and chloroform (sample y) were subjected to TLC as described by Beckstead et al. (1968); no decomposition was detected in any sample. Experiments on the hot-stage microscope and elemental analysis ruled out any possibility of solvate formation.

The melting point of the samples was determined on a Silicone Bath Melting Point Apparatus (Campbell Electronics, Bombay) and are corrected. Quantitative

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I.R. spectra of the samples were recorded in nujol mull (Perkin-Elmer, model 29). The nujol mulls were prepared, in each case, with 5 mg of the drug sample and 0.1 ml of nujol, using a minimum amount of friction to avoid reversal of the crystal form. X-Ray diffraction patterns were recorded on model Philips PW 1010, using Cuk-alpha radiation and Ni filter.

The solubility of the samples was determined in pH 7.2 phosphate buffer in triplicate by a standard method (Miyazaki et al., 1979). Dissolution rate was determined in triplicate by the method of Kaneniwa and Watari (1974). For samples x and y the excess drug material remaining in the dissolution vessel was collected, dried in a vacuum desiccator and the m.p. and I.R. spectra were recorded. All in vitro samples were assayed for drug content by the method of Clarke (1969).

Each crystal sample was tested in 5 dogs, in a cross-over manner, with a 2-week wash-out period between drug administrations. Fasted, healthy mongrel dogs of either sex (12–15 kg, maintained on a standard dog diet) received 200 mg of each drug crystal orally, washed down with 50 ml of luke-warm tap water. The animals were observed constantly to make sure that there was no vomiting of the drug. Plasma was separated from heparinized blood samples (5 ml) collected at 0.5, 1, 2, 3, 4, 5, 6 and 8 h after drug administration and stored at −10 °C. For the calculation of relative bioavailability the same animals received 200 mg phenylbutazone as a bolus intravenous injection over 30 s in a fast-running normal-saline solution. Phenylbutazone levels were determined in duplicate by the method described by Jahnchen and Levy (1972). This method eliminates interference by the metabolites of phenylbutazone (oxyphenbutazone and side-chain hydroxylated phenylbutazone).

The difference in crystal form between the samples x and y was observed from the differences in m.p., X-ray diffraction patterns, I.R. spectra (Fig. 1) and solubilities.

The form y first fused at 80–80.5 °C, the smectic material then recrystallized around 81 °C and again melted at 101–101.5 °C. Clearly this is a mixture of already reported forms II and III (cf. Matsunaga et al., 1976) and a new form. Form x melts sharply at 103 °C, thus this sample is probably similar to the original form I. The solubility of the different forms were observed to be: form I, 215 mg%; form x, 234 mg% and form y, 286 mg%.

The dissolution rates of the three samples (Table 1) show that form y has a faster dissolution rate (50% more) than that of form I, with form x having a non-significant difference. The X-ray diffraction pattern and I.R. spectra of forms I and x are identical, but differ from that of form y. A study of Fig. 1 reveals that although both the forms x and y exhibit their principal peaks at the same wave numbers, their pattern and intensity vary. Shifts in minor peaks are also observed. These variations indicate differences in crystal form.

The bioavailability parameters of phenylbutazone crystal forms are listed in Table 2. It is observed that although the rate of absorption is identical for both crystal forms, the maximum drug concentration is significantly ($P < 0.001$) higher for form y. There is no significant difference in bioavailability between the commercial sample and form x, both being of the same crystal form. The correlation coefficient between dissolution rate at 40 min and peak plasma level was found to be +0.709 (significant at 0.01% level).

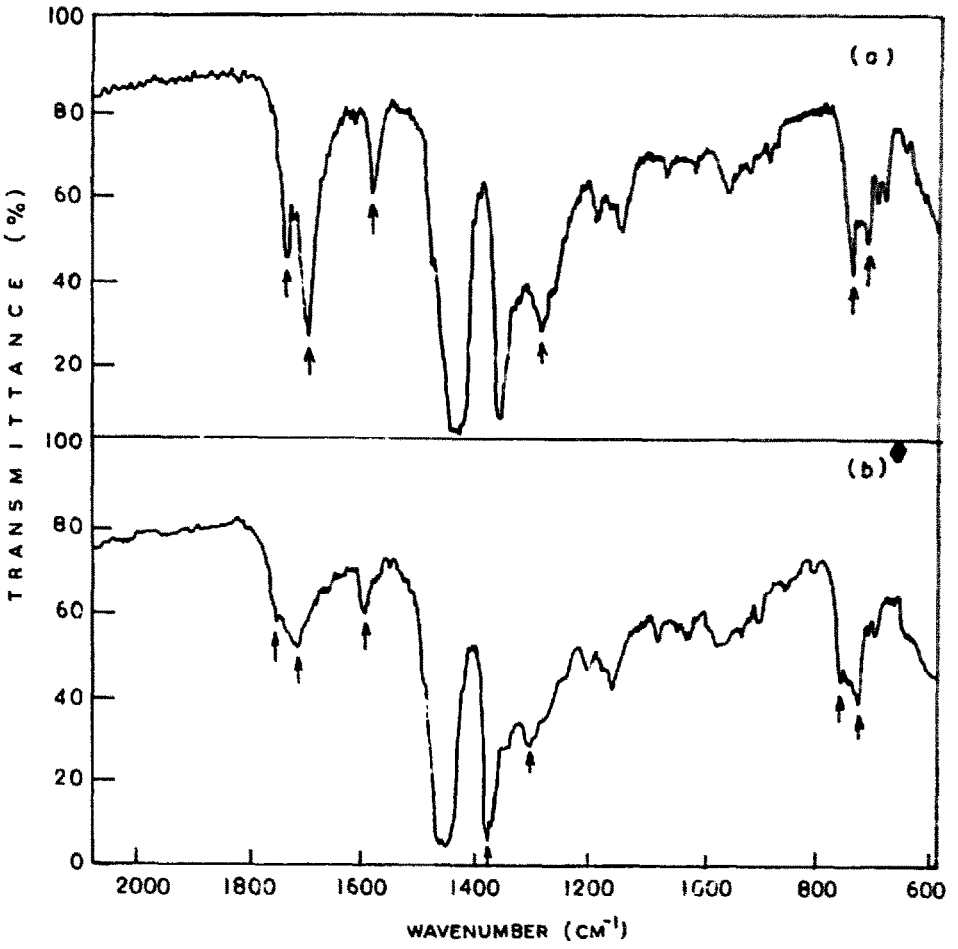

Fig. 1. I.R. spectra of phenylbutazone crystallized from ethanol (a) and chloroform (b). Arrows show differences in the peak pattern of the crystal forms.

The I.R., X-ray diffraction and m.p. data were re-examined for all the varieties after a period of 6 months. Also, the materials recovered from the dissolution media were examined. It was observed that there were no detectable differences in the data before and after the storage period.

TABLE 1

DISSOLUTION RATES OF DIFFERENT PHENYLBUTAZONE CRYSTALLINE FORMS IN DISTILLED WATER

Sample	Average amount [1] of phenylbutazone dissolved in: (mg/500 ml)					
	10	20	30	40	50	60 (min)
Form I	16.50(±0.208)	17.15(±0.104)	17.76(±0.158)	17.83(±0.158)	18.67(±0.104)	20.32(±0.104)
Form x	20.20(±0.104)	20.83(±0.134)	21.23(±0.350)	21.53(±0.104)	22.48(±0.120)	23.02(±0.104)
Form y	24.86(±0.104)	25.06(±0.104)	25.37(±0.120)	25.68(±0.104)	26.04(±0.104)	26.68(±0.104)

[1] Results were determined in triplicate. Values in parentheses are S.D. of mean. * $P < 0.001$ in comparison to Form I.

TABLE 2

AVERAGE VALUES[1] OF BIOAVAILABILITY PARAMETERS OF DIFFERENT PHENYLBUTAZONE CRYSTAL FORMS IN THE DOG

Crystal form	C_{max} ± S.D. (mg/litre)	T_{max} (h)	AUC 0–8 h (mg·h/litre)	Relative availability (%)	Availability (%) relative to i.v. dose
Form I	74.6 ± 1.18	3	107.4	100	57
Form x	81.2 ± 2.92	3	109.0	101.8	56
Form y	94.7 ± 3.9	3	147.0	136.2	76.9
i.v. dose	125.0 ± 2.82	0.5	191.7		100.0

[1] Results were determined in triplicate.* Each crystal sample was tested in 5 dogs in a cross-over manner (see text for details).

The potential of using crystal form y for human treatment is currently under investigation in our laboratory, the results of which will be communicated later.

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