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SULPHAPYRIDINE CRYSTAL FORMS

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Methods of preparation and characterization of two polymorphs, three solvates and amorphous form of sulphapyridine are described. Infrared spectroscopy, x-ray diffraction and thermal analysis data are given for the various forms. The qualitative and quantitative aspects of the transformation of metastable crystal forms under various conditions are described and kinetic parameters estimated. Heating all forms to 150° results in a change to a stable form suitable for identification purposes. The possible use of crystal forms of higher thermodynamic activity, apparent solubility and anticipated bioavailability in pharmaceutical preparations is discussed.

Biological availability, physical stability and identity of drugs have been shown to be greatly affected by their presence in various crystal forms[1-5].

Sulphapyridine was reported by Mesley and Houghton[3] to exist in one of six crystalline forms and the amorphous state. They described methods to prepare the crystal forms and used, but did not publish, infrared spectra for their characterization. Yang and Guillory[6] studied the incidence of polymorphism in various

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sulphonamides and reported methods of preparation, infrared spectra , differential thermograms, thermal data and x-ray powder diffraction data for five polymorphs and the amorphous form of sulphapyridine. Earlier, Castle and Witt[7] were able to isolate four out of five crystalline forms of sulphapyridine which were detected by thermomicroscopic techniques. They reported melting points varying from 175° to 192° for the various crystal forms. Kuhnert-Brandstatter and Wunsch[8] detected seven forms of sulphapyridine. Three of these forms were obtained in sufficient purity by thermomicroscopic techniques and were characterized by their infrared spectra[9]. Infrared spectra of one or more of the crystal forms of sulphapyridine were also published by Sheinker and Kuznetsova[10], Hayden[11] and in the Sadtler Pharmaceutical Collection. X-ray powder diffraction data were published by Lennox[12] for a crystal form of sulphapyridine.

The review of the previous reports indicated that the number and identity of sulphapyridine crystal forms is uncertain. Solvents used by various investigators for the preparation of apparently similar crystal forms were different. Inconsistencies in methods of preparation and characterization and lack of reproducibility in experimental findings were not uncommon. It appeared as though the abundance of experimental methods and results have made it difficult to make an objective assessment of the incidence of polymorphism and solvation of sulphpyridine.

The object of the present study was to present simple and reproducible methods of preparation and characterization of sulphapyridine crystal forms. The qualitative and quantitative aspects of the transformation of such crystal forms in various physical environments was also studied. Special attention was devoted to the dissolution behavior of metastable crystal forms. The latter are thought, as a result of higher thermodynamic activity, to be of higher apparent solubility and consequently bioavailability[4, 13-5].

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METHODS AND RESULTS

Materials and Apparatus

Sulphapyridine (Rhone Poulenc) was used as a starting material for crystallization during the course of the present investigation. The purity of the starting material and prepared crystal forms was checked by paper chromatography[16]. Solvents used for crystallization were of B.P. quality.

Infrared spectra were measured with a Perkin-Elmer double-beam grating infrared spectrophotometer model 237B. Determination of the concentration of sulphapyridine in solution was carried out using a Unicam SP 500 ultraviolet spectrophotometer. Mass spectra were determined using a Varian Mat 111 GC mass spectrometer.

X-ray powder diffraction measurements were made with a Norelco x-ray diffractometer (IC 2000 series, Philip Electronic Instruments Co.). Spectra were run in terms of 2 θ, Cu Kα radiation, 1°/min., 1° receiving slit and 1° diversifying slit.

Thermal analysis was carried out using a Perkin-Elmer differential scanning colorimeter DSC-1 B, with nitrogen as effluent gas at 40 cc/min., rate of heating 10°/min. and chart speed of 10°/inch. Thermogravimetric analysis was performed using a Cahn R-100 recording balance with a dupont 990 thermal analyzer at a heating rate of 10°/min. Nitrogen was passed at a rate of 75 cc/min. and the weight loss recorded.

Preparation of the Different Crystal Forms

The general procedure for the preparation of the different crystal forms involved crystallization from specific solvent. For this purpose, 0.2 g of the drug was dissolved in a suitable volume of an appropriate solvent to form a saturated solution at the boiling point of that solvent. The solution was allowed to cool slowly at room temperature. The crystals which separated were then filtered on sintered glass disc (Jene 39 G 3), dried in a current of air at room temperature (25°C) and stored in a desiccator[17]. Conditions for the preparation of each of the crystal forms are summarized as follows:

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Form I was prepared by crystallization from a wide range of solvents including water, methanol, ethanol, various hydroalcholic solvents or by precipitation from a solution in sodium hydroxide by the addition of hydrochloric acid. However, optimum conditions for the preparation of Form I in a reproducible manner involve crystallization from water or heating any other crystal form to 150°.

Form II was prepared by crystallization from isopropanol.

Form III was prepared by crystallization form acetone.

Form IV was prepared by crystallization from chloroform.

Form V was prepared by crystallization from dioxane.

An amorphous form was also prepared by melting any of the crystal forms and slow cooling of the melt.

Characterization of the Crystal Forms

The infrared spectra of Forms I-V and the amorphous form in Nujol mulls are shown in Fig 1. X-ray powder diffraction patterns of the same crystal forms are shown in Fig 2. Differences observed in the infrared spectra and x-ray patterns are sufficiently distinct to characterize the various crystal forms.

Differential thermograms of sulphapyridine crystal forms are shown in Fig. 3. Thermal data of these forms are given in Table 1. Thermogravimetric analysis, used to calculate the percentage weight loss accompanying various thermal transitions and especially loss of solvent from solvated forms, gave the results in Table 2. Mass spectroscopy and ultraviolet absorptivity measurements were carried out to confirm the presence of specific solvents in various crystal forms and determine the quantity of such solvents. The results are also shown in Table 2.

Interconversion of the Crystal Forms

(a) Crystallization. Sulphapyridine crystal form were interconvertible to one another by crystallization from the appropriate solvents as descrived under "Preparation of the different crystal forms."

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(b) Heating. Heating any of the crystal forms to 150° resulted in a transformation to Form I.

(c) Suspension in water. Suspension of all crystal froms in water also resulted in a transformation to Form I.

(d) Grinding. Dry grinding produced a transformation of all crystal forms to Form I. The transformation of Forms II, III and IV was, however, faster than that of other forms. Grinding under water was found to accelerate the transformation to Form I. Various treatments appeared to be synergistic in effecting transformation of all crystal forms to Form I.

Dissolution Rate Studies

The procedure adopted for measuring the dissolution rates of the different forms was essentially similar to that previously used for sulphamethoxydiazine crystal forms[17]. Excess quantities of the solid (screened to a particle size of 80-90 μm) were suspended in 50 ml aliquots of 0.01 N HCl in 100 ml glass-stoppered flasks. The flasks were rotated at 48 rev/min in a constant temperature water-bath maintained at 37° ± 0.1°. At measured time intervals, 1 ml aliquots were withdrawn using 1 ml pipettes fitted with suitable filter adapters, 1 ml of 0.01 N HCl at 37° was replaced in each flask. Appropriate dilutions were made and the concentration of sulphapyridine in the various samples was determined by measuring the ultraviolet absorbance at 240 nm, referring to a standard curve ($E^{1\%}_{1\ cm}$ determined in the present study = 471.4).

Results of the dissolution rate measurements of some crystal forms are shown in Fig. 4.

Kinetics of Transformation of Form II to Form I

The transformation of sulphapyridine Form II to Form I is particularly important, since the use of Form II in the formulation of dosage forms could be favored on basis of its high apparent solubility and, consequently, anticipated increase in bioavailability. The stability of Form II under different conditions of temperature and humidity was, therefore, studied.

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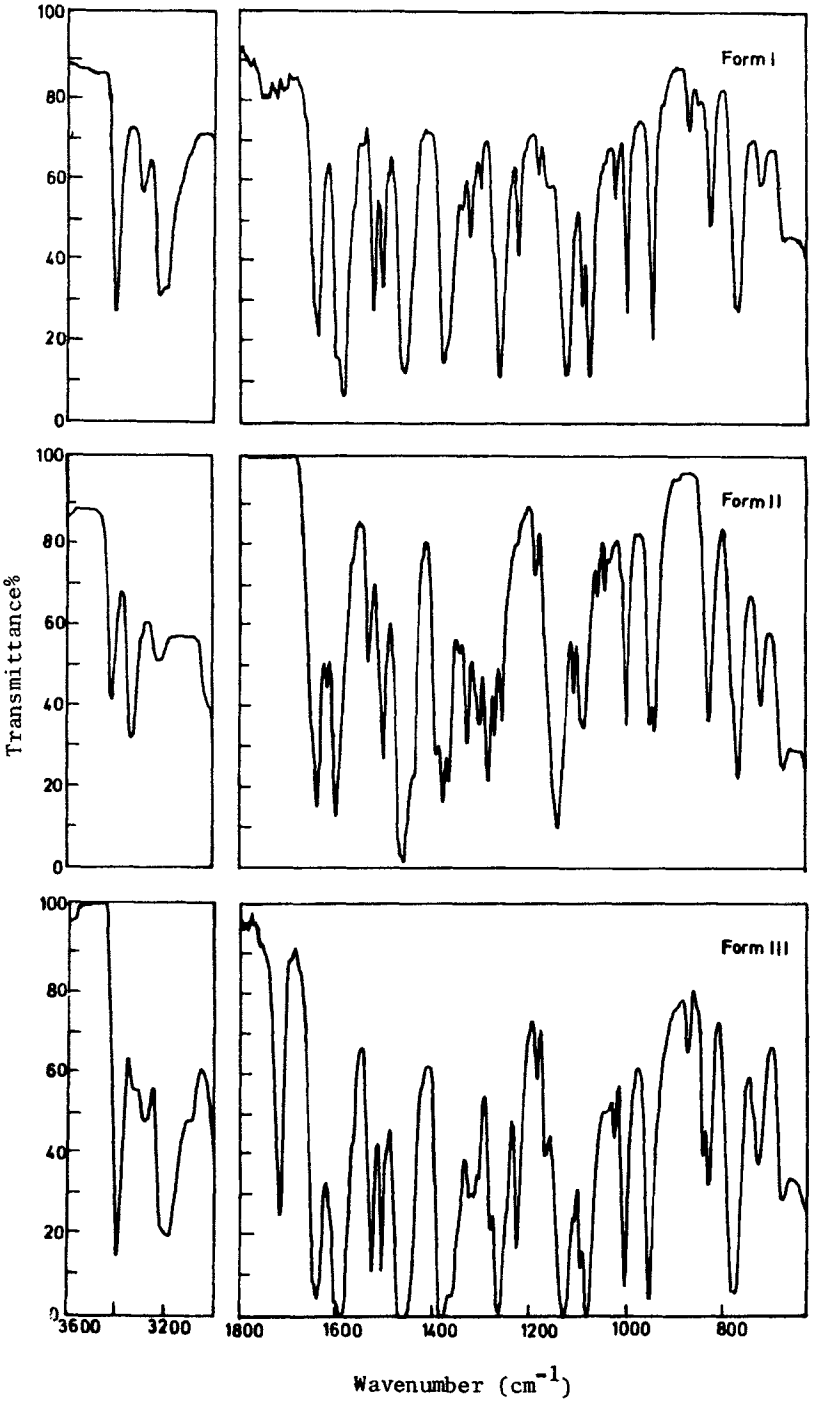

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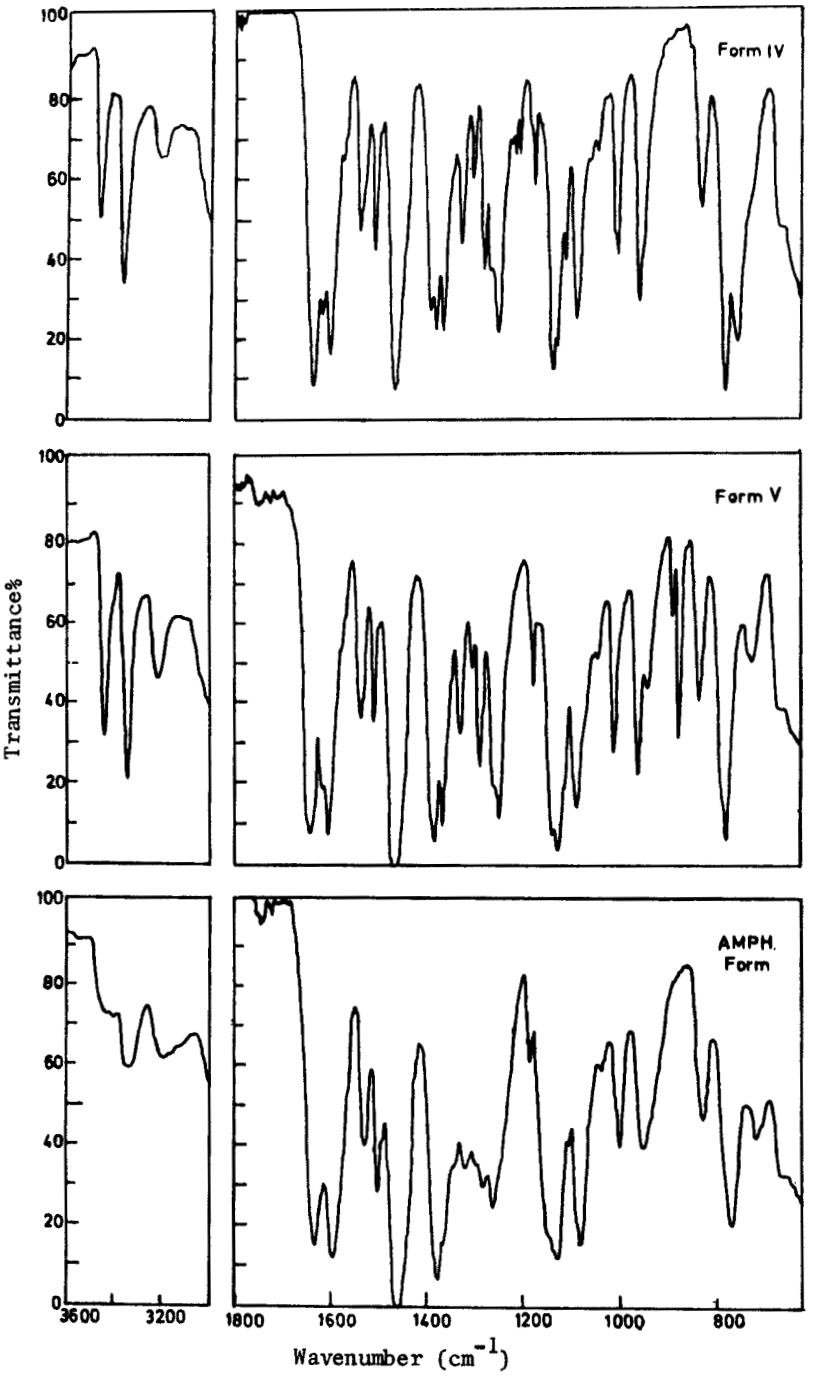
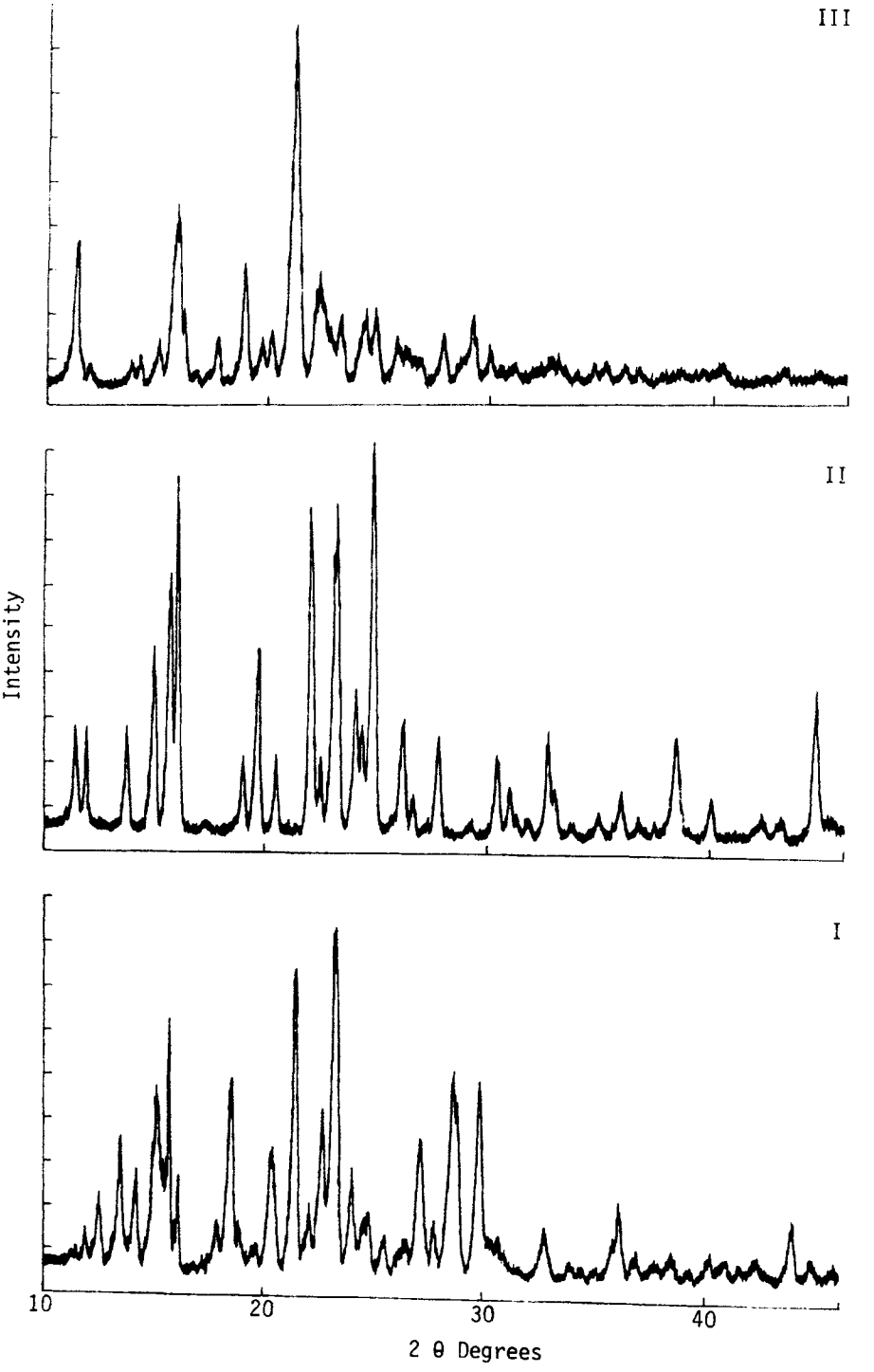


FIGURE 1

Infrared spectra of sulphapyrdine crystal forms in Nujol mulls.



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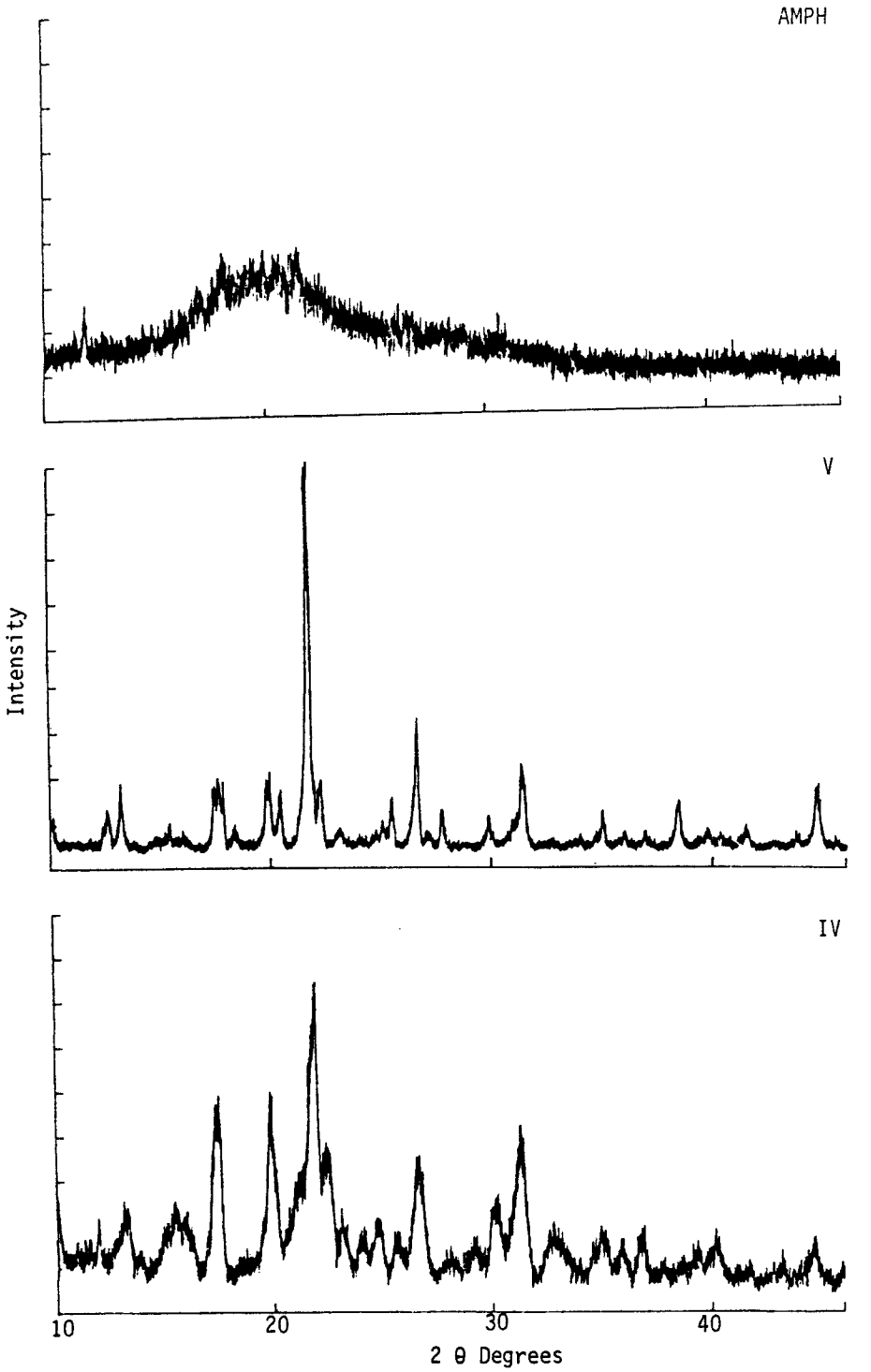

FIGURE 2

X-ray diffraction data of sulphapyridine crystal forms.

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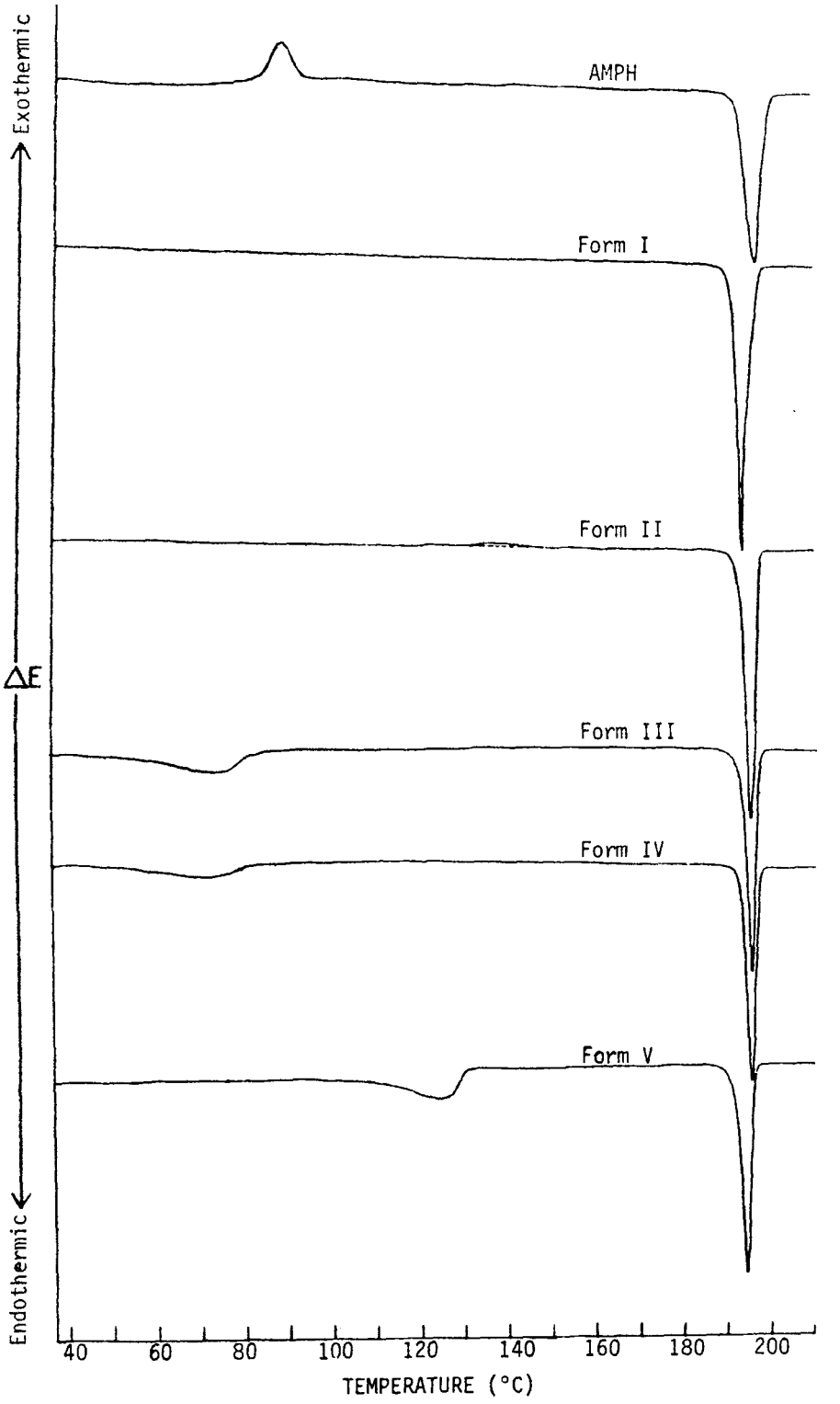

FIGURE 3

Differential thermograms of sulphapyridine crystal forms.

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TABLE 1

Thermal Data of Sulphapyridine Crystal Forms

Form	Temp at peak max of transition curve °K	Heat of transition cal/mol	Temp at peak max of melting curve °K	Heat of fusion*, cal/mol	
				Exptl	corrected to its equivalent of non-solvated form
I	-	-	466	9,400	-
II	411	-770	467	9,150	-
III	348	+	468	+	-
IV	345	+	469	+	-
V	398	6,880	468	6,910	8,950
Amorphous	361	+	469	+	-

*Average of three determinations --- +Not determined

TABLE 2

Solvent Determination in Sulphapyridine Crystal Forms

Form	Expected solvent	Test for specific solvent by mass spectroscopy	% weight loss in TGA		Moles of solvent/mol of drug	
			Exptl	Calc for assumed solvate	Based on absorptivity measmt	Based on wt loss in TGA
I	water	negative	none	-	-	-
II	isopropanol	negative	none	-	-	-
III	acetone	positive	16.7	18.9	0.5	1.0
IV	chloroform	positive	29.7	32.4	1.0	1.0
V	dioxane	positive	26.1	26.2	1.0	1.0
Amorphous	none	-	none	-	-	-

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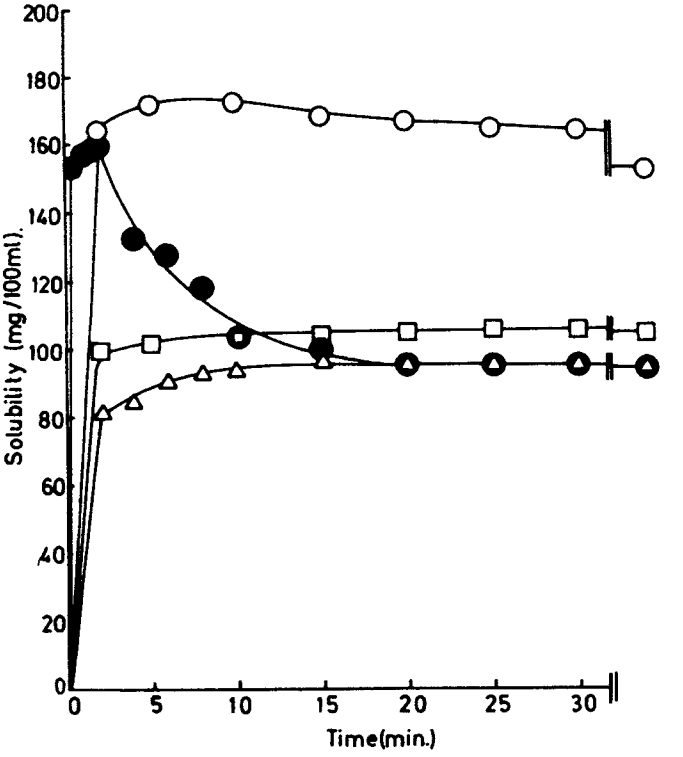

FIGURE 4

Dissolution rates of sulphapyridine crystal forms. △ Form I, ● Form II, □ Form V, ○ amorphous form.

A quantitative Nujol mull infrared technique similar to that previously used to study the kinetics of transformation of sulphamethoxydiazine[19] and succinylsulphathiazole[5] crystal forms was employed. The technique is based on the application of an absorbance ratio procedure[20] in which the absorbance of specific bands characteristic of the crystal forms being examined is measured relative to an appropriate internal standard band in the infrared spectra. Such absorbance ratios are constant and characteristic for specific crystal forms. Calibration curves relating measured

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absorbance ratios of specific crystal forms to the percentage composition in mixture prepared therefrom are established and subsequently used to find out the concentration of a particular crystal form in a mixture of crystal forms of unknown composition. Application of this method to the analysis of mixtures of Forms I and II of sulphapyridine was feasible thanks to the presence of a prominent band at 1225 cm^{-1} in the infrared spectrum of Form I which is almost absent from the spectrum of Form II.

Samples of Form II were placed in hot air ovens at 70, 90 and 100° ± 0.1°. At various time intervals, a few milligrams of each sample were taken and analyzed by quantitative infrared spectroscopy for their content of Form I. The concentration of Form II was found by difference. Results of the transformation of Form II to Form I at various temperatures are shown in Fig 5.

The effect of humidity on the rate of transformation of sulphapyridine Form II to Form I was studied by placing samples of Form II in desiccators over salt solutions providing relative humidities of 50, 70, 80, 90, and 100% at 25° ± 0.1°. Rate constants calculated from log concentration of Form II-time plots at various relative humidities are shown in Table 3.

TABLE 3

Effect of Humidity on the Rate of Transformation of Sulphapyridine Form II to Form I at 25°

Relative Humidity %	Rate of constant K x 10^4 hr^{-1}
100	431.8
90	129.5
80	62.4
70	27.8
50	8.73

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DISCUSSION

Sulphapyridine is shown to exist in five, or possibly more, crystal forms in addition to an amorphous form. Forms I and II represent true polymorphs of sulphapyridine whereas Forms III, IV and V represent solvates of acetone, chloroform and dioxane respectively. Mass spectroscopy, thermogravimetric analysis and ultraviolet absorptivity measurements confirm the presence of these solvents in a ratio of approximately one molecule of solvent per molecule of sulphapyridine. Solvents probably exist in an adduct or clathrate form, from which they are given off on heating at temperatures above the boiling point of the solvent and below the melting point of the crystal form. The solvent content of various crystal forms is not necessarily constant and depends on details of the method of preparation and the time and conditions under which the crystal forms are stored. For example, the acetone solvate (Form III) was found to have 0.5-1 mole of solvent bound to each mole of the drug (Table 2). The formation of solvates, other than those reported in the present study, is not unlikely especially when a wide range of solvents is used for the crystallization of sulphapyridine.

Lack of detailed information and the use of different techniques of preparation and characterization of sulphapyridine crystal forms in the literature[3, 6, 9] have made comparisons of various results rather difficult. However, the present investigation has presented simplified and reproducible methods of preparation and characterization of sulphapyridine crystal forms. The resulte reveal that most of the crystalline modifications of sulphapyridine likely to be encountered are actually solvates and not true polymorphs[6]. The number of solvates and the type and amount of solvent contained in them are not important from a pharmaceutical viewpoint since their use in dosage forms would be very much limited by the safety of administration of the solvents contained therein.

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From a comparison of infrared spectra, there seems to be almost a complete agreement of the identify of Form I in various reports[6, 9, 11]. Results of the present report would suggest, in agreement with Mesley & Houghton's recommendation[3], that heating any crystal form of sulphapyridine to 150° would be satisfactory prerequisite to the determination of the infrared spectrum for identification purposes. Such a procedure was shown to effect transformation of all crystal forms to Form I. Thermal analysis data (Fig. 3 and Table 1) revealed that all crystal forms melt at 193-196°. No evidence could be found to explain the differences in melting points reported by Castle & Witt[7] for four of their sulphapyridine crystal forms. On the contrary, the present results agree with previously reported findings[17], that crystal forms change to one and the same crystal form before melting and have, therefore, similar melting points. Forms I and II did not show any transitions before melting, except for a small exothermic transition at ≈ 138° in Form II. The amorphous form showed an exothermic transition at ≈ 88° which probably accompanied recrystallization from a glass state to crystal Form I. Forms III, IV and V exhibited endothermic transitions associated with loss of solvent and transformation to Form I. The heats of fusion calculated from differential scanning calorimetry for crystal forms I and II were similar, withing acceptable experimental errors. Heats of fusion reported by Yang and Guillory[6] for sulphapyridine crystal forms were somewhat lower than those calculated in the present study. Differences in heat of fusion could be due to variation in factors such as rates of heating, particle size and thermal conducting qualities of the crystal forms.

Dissolution rate studies of the various crystal forms (Fig. 4) revealed that Form II and the amorphous form had apparent solubilities which were 1.7-1.8 times greater than that of Form I. Solvates (represented in Fig. 4 by Form V which is a dioxane solvate) had apparent solubilities which were only slightly higher than that of Form I.

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The use of Form II or the amorphous form in pharmaceutical preparations obviously depends on the time during which such metastable forms maintain their identity and consequently higher solubility. Kinetic parameters of the transformation of Form II, calculated in the present investigation, are therefore important in deciding the possible utilization of such a crystal form. Rate constants calculated for the transformation of Form II to Form I at various temperatures (Fig. 5) were used to draw an Arrheniustype plot from which the data in Table 4 were obtained. A half-life of slightly over six weeks at room temperature was estimated for the transformation. Because various physical factors are complimentary in affecting the transformation of Form II to Form I (as described under Interconversion of the crystal forms), the effect of humidity on the rate of transformation is also a determining factor. The results if Table 3 reveal that

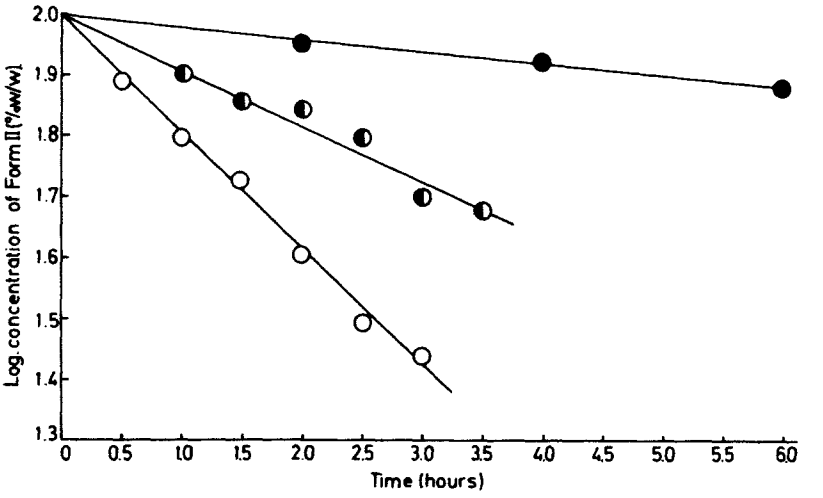

FIGURE 5

Transformation of sulphapyridine Form II to Form I in the solid state at various temperatures. ● 70°, ◐ 90°, ○ 100°.

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TABLE 4

Kinetic Parameters of the Transformation of Sulphapyridine Form II to Form I

Rate constant $K \times 10^2$ hr^{-1}			$K_{25°}^{*} \times 10^4$ hr^{-1}	$t_{½}(25°)$ days	E_a Kcal/mol
70°	90°	100°			
4.61	21.9	44.2	6.31	46	19.4

*by extrapolation.

water vapor is a very important factor in affecting transformation of Form II to Form I. The rate constant of the transformation was increased by about 50-fold when the percentage relative humidity was increased from 50 to 100. These results should help to establish optimum conditions for the formulation and storage of sulphapyridine Form II in dosage forms.

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