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Sulphamethoxydiazine crystal forms

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Methods of preparation of three polymorphs, two solvates and an amorphous modification of sulphamethoxydiazine are described. Infrared spectroscopy and X-ray diffraction data are given for the characterization of the various forms. The interconversion of these forms under various conditions of heating, suspension in water and grinding is studied. The dissolution behaviour of the different forms is also discussed. All forms on heating to 150° change to the same form and on suspension in water change to another water-stable form.

Physical stability and biological availability have been shown to be greatly affected by polymorphism and solvation of drugs (Higuchi, 1958; Frederick, 1961; Higuchi, Lau & others, 1963; Shefter & Higuchi, 1963; Aguiar, Krg & others, 1967). The pharmaceutical applications of polymorphism have been recently reviewed by Haleblian & McCrone (1969). These papers suggested that physical chemical studies of solid drugs are essential before their formulation in different dosage forms.

Sulphamethoxydiazine was reported by Svatek, Knobloch & Budesinsky (1966) to be dimorphic. Methods of preparation of the two crystal forms were described. Later, Mesley & Houghton (1967) described methods for the preparation of one amorphous and three crystalline forms of the same compound. Because of the different number of polymorphs, and the difficulty of correlating their preparation and characterization, more thorough investigation of this polymorphic system seemed necessary.

We have examined the preparation, characterization, interconversion and dissolution behaviour of the various crystal forms of sulphamethoxydiazine.

METHODS AND RESULTS

Materials and apparatus

Sulphamethoxydiazine was supplied by courtesy of Alexandria Co. for Pharmaceuticals and Chemical Industries, U.A.R. The purity of the starting material and products of crystallization from different solvents was checked by paper chromatography using the solvent system described by Steel (1951). Solvents used for crystallization were of B.P. quality.

Infrared spectra were measured with a Perkin-Elmer double-beam grating infrared spectrophotometer model 237B and the concentration of sulphamethoxydiazine during dissolution rate studies was followed by ultraviolet spectrophotometry. X-ray diffraction measurements were made with a General Electric XRD-6 diffractometer with variables: 3° beam slit and 0·2° detector slit; CuK_{α} radiation, 45 KV, 11 mA, Ni filtered.

Preparation of the different crystal forms

The general procedure for the preparation of the different crystal forms involved

crystallization from specific solvents. For this purpose, about 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 and stand at room temperature, except for Form II, for 24 h. The crystals which separated were then filtered on a sintered-glass disc (Jena 39 G 3), dried in a current of air at room temperature (25°) and stored in a desiccator. Optimum conditions for the preparation of the different crystal forms are summarized as follows:

Form I was prepared by crystallization from boiling water or by heating any other form to 150°.

Form II was prepared by rapid cooling in a refrigerator of a saturated solution in ethanol.

Form III was prepared by crystallization from any of the following solvents: methanol, isopropanol, ethyl acetate or by precipitation from a solution in acetone by the addition of water.

Forms IV and V were prepared by crystallization from dioxane and chloroform respectively.

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

Characterization of the different crystal forms

The main differences observed in infrared spectra of Forms I–V and the amorphous form in Nujol mulls are summarized in Table 1. The X-ray diffraction patterns of the various crystal forms are shown in Fig. 1, A–E. Such patterns show distinct differences that can be used for their characterization.

Interconversion of the different crystal forms

(a) *Crystallization.* Any form can be converted to another by crystallization from the appropriate solvent as described under "Preparation of the different crystal forms".

Table 1. *Characterization of sulphamethoxydiazine crystal forms by infrared spectroscopy*[a].

Form	800–875 cm^{-1}	900–970 cm^{-1}	1550–1600 cm^{-1}	3000–3500 cm^{-1}	Other characteristic bands and absorbance ratios (r)
I	b (838) & 2s§	b (927) & 2s§	2b (1567, 1595)	2b (3345, 3458)	Consistent s (1640) A 943/A 785 = 1·72 A 1320/A 1345 = 1·82
II	doublet (835, 852)	2b (922, 950)	doublet (1580, 1595)	2b (3275, 3365)	Relatively strong b (922) A 922/A 950 = 0·53 A 1580/A 1595 = 0·98
III	b (845) & 2s§	2b (903, 935)	2b (1567, 1595)	broad b (3190), b (3315), b (3398) & 2s§	b (980) A 980/A 785 = 0·43 A 1310/A 1323 = 0·69
IV	2b (830, 873)	b (944) & s	b (1595) & s	2b (3343, 3453)	b (1120) Relatively strong b (1253) A 830/A 873 = 0·66 A 1253/A 785 = 1·60
V	b (832) & s	b (940) & 2s*	b (1595) & 2s*	2b (3350, 3455)	Strong b (755) A 755/A 785 = 3·29 A 832/A 862 = 1·75
Amorphous	b (830) & s	broad b (935)	2b (1567, 1595)	2b (3335, 3438)	—

(a) Figures between brackets denote the frequency in wavenumbers at peak maxima; (b) = band; (s) = shoulder, § on either side of the band, * on one side of the band; (r) = ratio of absorbance (A) of the specified bands.

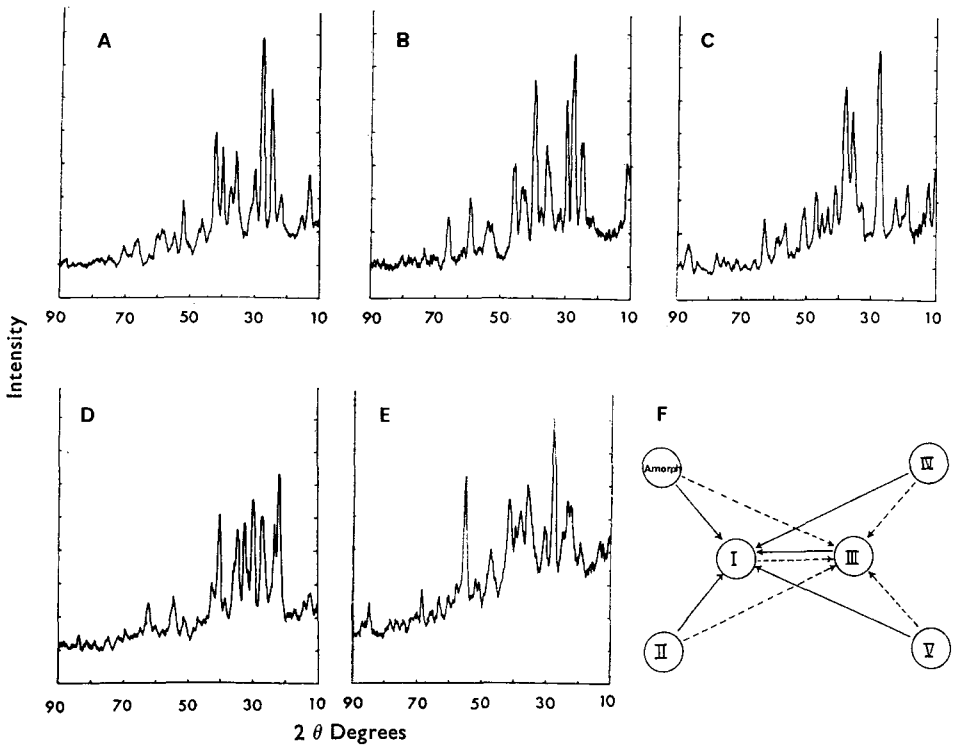

FIG. 1. A–E. X-ray diffraction data of sulphamethoxydiazine crystal forms.
F. Interconversion of sulphamethoxydiazine crystal forms. —— heating to 150°, - - - - grinding or suspension in water.

(b) *Heating.* Heating to 150° was found to effect transformation from any form to Form I. A similar procedure was suggested by Mesley & Houghton (1966) for identification purposes.

(c) *Suspension in water.* Suspension of all forms in water resulted in transformation to Form III. The time necessary to achieve such a transformation varied according to the sample source and particle size. Forms IV, V and the amorphous form were found to change initially to Form I; prolonged suspension, however, completed the transformation to Form III. Form II, on the other hand, changed in a relatively short time to Form III.

(d) *Grinding.* Dry grinding converted all forms to Form III. Form I was detected as an intermediate in all cases. Grinding under water was found to accelerate the transformation to Form III.

A summary of the course of interconversions is illustrated in Fig. 1F.

Dissolution rate studies

The procedure adopted for measuring the dissolution rates of the different forms consisted in suspending excess quantities of the solid (screened to a particle size of 80–90 μm) in 200 ml of 0·1N HCl in a 250 ml glass stoppered flask. The flask was then rotated at 70 rev/min in a constant temperature water-bath maintained at 30° $\pm$0·1°. At measured time intervals, 3 ml aliquots were withdrawn and immediately filtered through a Jena 39 G 3 sintered-glass funnel, 3 ml of 0·1N HCl were replaced

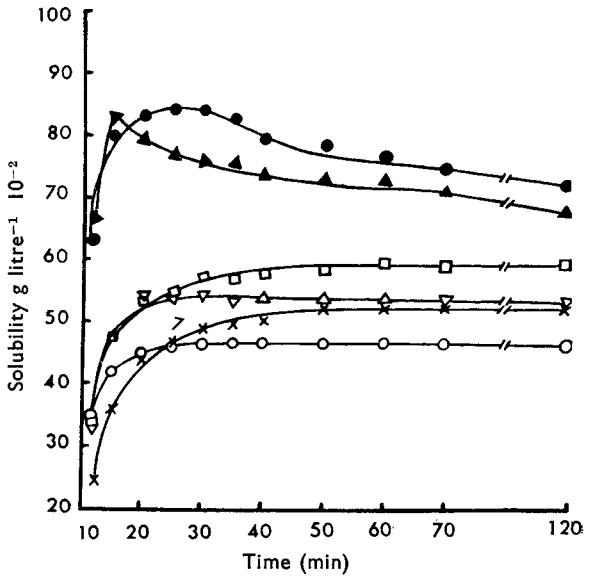

FIG. 2. Dissolution rates of sulphamethoxydiazine crystal forms. ×—× Form I, ●—● Form II, ○—○ Form III, □—□ Form IV, △—△ Form V, ▲—▲ amorphous form.

in the flask. Appropriate dilutions were made and the concentration of the drug in the various samples was determined by measuring its ultraviolet absorbance at 228 nm and referring to a standard curve. Results of the dissolution rate measurements of the various forms are shown in Fig. 2.

DISCUSSION

Sulphamethoxydiazine exists in the solid state in one of five or more crystal forms or in an amorphous state. Forms I, II and III represent a true polymorphic system, whereas Forms IV and V are probably solvates of dioxane and chloroform respectively.

We found the methods of preparation of sulphamethoxydiazine crystal forms (Svatek & others, 1966; Mesley & Houghton, 1967) in many cases difficult to reproduce. Crystallization from aqueous ethanol, reported by Mesley & Houghton (1967) to produce Form A gave Form III. Crystallization from aqueous solution reported by the same authors to produce Form B in our hands resulted in Form I. Had Mesley & Houghton (1967) suggested that their Form A changed to Form B by heating this would have matched the change we found from Form III to Form I; unfortunately the contrary was reported. The procedure of precipitating sulphamethoxydiazine from acetone solution by the addition of water or from a solution in an alkali by the addition of an acid gave Form III. This too was contrary to the findings of Mesley & Houghton (1967) who reported the production of a third Form C. We found their procedure in most cases to result in mixtures of crystal forms and amorphous material.

Form α (m.p. 212°) prepared by Svatek & others (1966) by "rapid motion crystallization from warm aqueous solutions" was found to match Form I on basis of similarity of their infrared spectra. Their β form (m.p. 197°) was prepared from "saturated aqueous solutions at room temperature". They also recommended crystallization

from acetone for the preparation of the pure β form. This latter procedure was found to give Form III. The infrared spectrum published for the β form is identical with that of our Form III.

All forms had a melting point of 212–214°. No other transitions were observed below the melting point except when solvent was given off; e.g. Forms IV and V in which case the crystals turned opaque. This is not in agreement with the finding of Svatek & others (1966) who reported a m.p. of 197° for their β-form. The change to the α-form by heating to 197° (described as melting of the β-form and slow cooling of the melt) was matched in the present study by a change to Form I. However, the description of this temperature (197°) as a melting point of the β-form does not agree with our finding that all forms change to Form I at 150° and consequently should have the same melting point. Evidence is gradually accumulating against the general belief reported by Haleblian & McCrone (1969), that polymorphs have different melting points. Among several drug systems recently studied, e.g. cortisone acetate (Carless, Moustafa & Rapson, 1966), some sulphonamides (Mesley & Houghton, 1967; Moustafa & Carless, 1969) and the antiviral compound SK & F 30097 (Ravin, Shami & Rattie, 1970), all polymorphs were found to change to one and the same form before melting and therefore to have the same melting point.

Infrared spectra of the various forms in Nujol mulls could be used conveniently in their characterization. Comparison of these spectra suggest that the most probable type of association characterizing the various crystal forms is that involving intermolecular hydrogen bonding. This is likely to take place between the aromatic amino-group of one molecule and the oxygen of the sulphonamide linkage of another. Evidence supporting this suggestion is manifested by a lowering of frequency of the NH stretching vibrations which is particularly obvious in the infrared spectrum of Form II (Bellamy, 1964). The absorption bands corresponding to these vibrations appear at the lower frequencies of 3275, 3365 cm^{-1} in the infrared spectrum of Form II as compared to 3345, 3458 cm^{-1} in case of Form I.

A relatively strong band at 1253 cm^{-1} with another band at 1120 cm^{-1} and a strong band at 755 cm^{-1} in the infrared spectra of Forms IV and V suggest their presence as solvates of dioxane and chloroform respectively (Cross, 1960). A similar observation was described by Mesley (1965) and Cords (1953) for chloroform adducts of certain steroids.

Many of the differences in the infrared spectra of the crystal forms appear in the Fingerprint region. Correlation of such differences to the mode of association between molecules in the crystal lattice of the various forms is rather difficult. However, the evidence available so far in this study confirms the opinions of Mesley & Houghton (1967) and Svatek & others (1966) who excluded amide-imide tautomerism as an explanation of the differences observed in the infrared spectra of sulphamethoxydiazine crystal forms.

Dissolution rate studies of the various crystal forms (Fig. 2) showed obvious differences in solubility and dissolution rate between Forms I, III, IV and V on one hand and Form II and the amorphous form on the other. The latter forms showed an apparent equilibrium solubility (viz. peak of the dissolution rate curve) which is about 1·8 times that of the water-stable Form III. However, longer periods of contact of the solid with the dissolution medium was found to result, as expected, in a decrease in solubility to a value corresponding to that of the water-stable Form III. Infrared determinations confirmed the transformation of the various forms to

Table 2. *Thermodynamic values calculated for Forms II and III of sulphamethoxydiazine*

Crystal form	Trans. temp. °C	Heat of solution ΔH cal/mol	ΔG_{303} cal/mol	ΔS_{303} e.u.	ΔS e.u.
III	—	−6530	—	—	—
II	104	−5111	−291	−3·7	−3·8

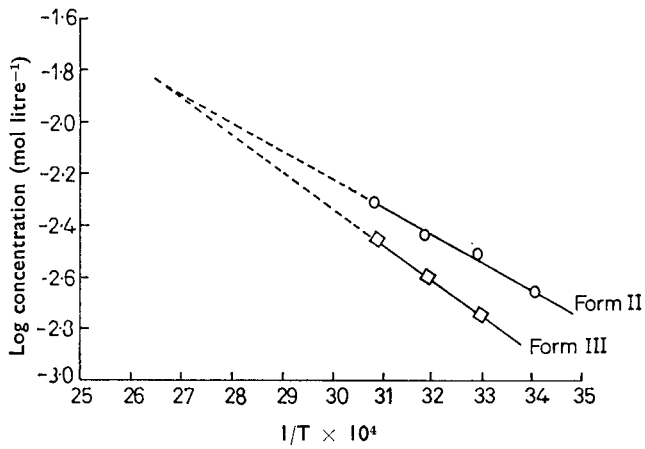

FIG. 3. The van't Hoff-type plot for Forms II and III of sulphamethoxydiazine. ○—○ Form II, □—□ Form III.

Form III. The apparent solubilities of Forms II and III determined at various temperatures were plotted according to the classical van't Hoff plot (Shefter & Higuchi, 1963; Higuchi & others, 1963; Aguiar & others, 1967; Poole & Bahal, 1970). Results of this treatment are shown in Fig. 3 and Table 2. The observed entropy difference might be related to the possible association by intermolecular hydrogen bonding as already outlined. The thermodynamics of the solid state transformation of Form II to Form III is particularly important since Form II has the highest solubility of all crystal forms and would therefore be the one favoured for pharmaceutical use. Its transformation to the least soluble water-stable Form III is an important factor in deciding its physical stability and biological availability from various dosage forms.

From the previous discussion, it could be suggested that Form I is a suitable reference material for the identification of sulphamethoxydiazine. Heating any form to 150° would be the only prerequisite.

In four commercial preparations (tablets and suspensions) of sulphamethoxydiazine, Form I or mixtures of Forms I and III were encountered. Results of the present investigation would recommend the use of Form II in pharmaceutical preparations provided that adequate measures are taken to keep it in this metastable state.

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