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Note

Physical characterisation of three pseudopolymorphs of cyclopenthiazide

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Summary

Three solvates of cyclopenthiazide, an acetone solvate, ethyl acetate solvate and isoproprانol solvate were prepared and characterised by DSC, TGA, thermomicroscopy, X-ray powder diffraction, IR spectroscopy, intrinsic dissolution and powder dissolution. All three solvates were less soluble than polymorph I and all three reverted back to polymorph I during DSC.

Cyclopenthiazide [6-chloro-3-cyclopentylmethyl-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide] is a diuretic mainly used in conjunction with slow release potassium chloride. It is usually coated onto the potassium chloride cores of tablets. Ethyl acetate, isopropanol or acetone may be used during this coating process (during film coating) or may be used as solvent during synthesis of the drug or during recrystallisation.

This report deals with the preparation and physical properties of an ethyl acetate, isopropanol and an acetone solvate of cyclopenthiazide. Two polymorphic forms were mentioned by Kuhnert-Brandstätter (1971).

The three forms were characterised by differential scanning calorimetry, thermogravimetric analysis, thermomicroscopy, X-ray powder diffraction, infrared spectrometry, intrinsic dissolution and powder dissolution.

The acetone, isopropanol and ethyl acetate solvates were crystalised from the respective saturated solutions. The crystals were filtered off and dried under 600 mm vacuum at 40 °C for 24 h. The differential scanning calorimetry (DSC) thermograms of the different solvates and polymorph I were recorded on a Du Pont 910 DSC System equipped with a Du Pont Series 99 Thermal Analyzer programmer. The instrument was calibrated with an indium standard. The thermal behaviour was studied by heating 5 mg samples at a heating rate of 5 °C min^{-1} in a crimped pan with a crimped empty pan as reference. The study was conducted from 80 to 260 °C.

Differential scanning calorimetry (DSC) ther-

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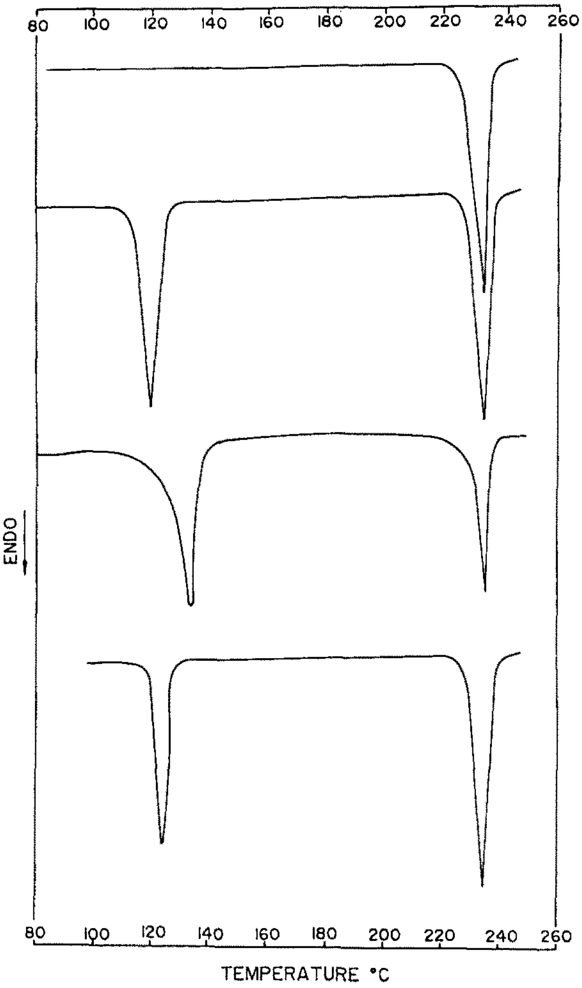

Fig. 1. DSC thermograms of polymorph I and the three solvates of cyclopenthiazide.

mograms for polymorph I and the three solvates are given in Fig. 1.

Each of the solvates gave two melting endotherms. The acetone solvate gave one at 120 °C and the second at 240 °C. The isopropanol solvate gave the first at 135 °C and the second at 236 °C. The ethyl acetate solvate gave the first at 125 °C and the second at 235 °C.

It is clear that all the solvates reverted to polymorphic form I described in the literature by Kuhnert-Brandstätter (1971).

Thermogravimetric analysis (TGA) were performed on a Shimadzu® DT40 TG apparatus to determine the mass loss of the samples at a heating rate of 10 °C min^{-1}.

The acetone solvate lost 6.25%, the isopropanol solvate 5.25% and the ethyl acetate solvate 4.00% of the respective solvents.

The thermal behaviour of the different solvates were studied with a Leitz® Laborlux K thermomicroscope equipped with a Leitz® model 350 heating block and a Goerz® 1200 thermocouple. The apparatus was calibrated with analytical grade acetanilide (melting point 115 °C). The heating rate was 5 °C min^{-1}.

The solvates showed the final melting points given under DSC (see Fig. 1). When carried out in oil no gas bubbles could be observed.

X-ray powder diffraction patterns of the different solvates were obtained by using a Phillips PW 1050/70 diffractometer system, CuK_α radiation (λ 1.5418 Å) and a scan speed of 0.5 2θ min^{-1}. The samples were lightly ground and packed into the aluminium sample container.

The X-ray data, i.e. I/I_0 vs 2θ, are compared in Fig. 2 to that of polymorph I. It is clear that the solvates differ from each other and from polymorph I.

IR spectra were recorded as potassium bromide discs (preliminary results showed no change during preparation of the discs). The apparatus used was a Nicolet® 5DX FT infrared spectrophotometer. The FTIR spectra of the three solvates showed significant differences from one another and also from polymorph I.

The intrinsic dissolution rates of the crystals were determined at 37 °C in 200 ml of a 10% v/v solution of ethyl alcohol in water as dissolution medium according to the method of Simonelli et al. (1969) and Sing et al. (1968). Five determinations were carried out for each form. The crystals were compressed into 13 mm discs in an evacuable die at 705 MN m^{-2} (10 ton). The dissolution medium was stirred at 150 rpm and the cyclopenthiazide dissolved was determined spectrophotometrically.

The least-square fit for a straight line through the dissolution points was calculated for each dissolution curve. The gradient, m, was taken as the

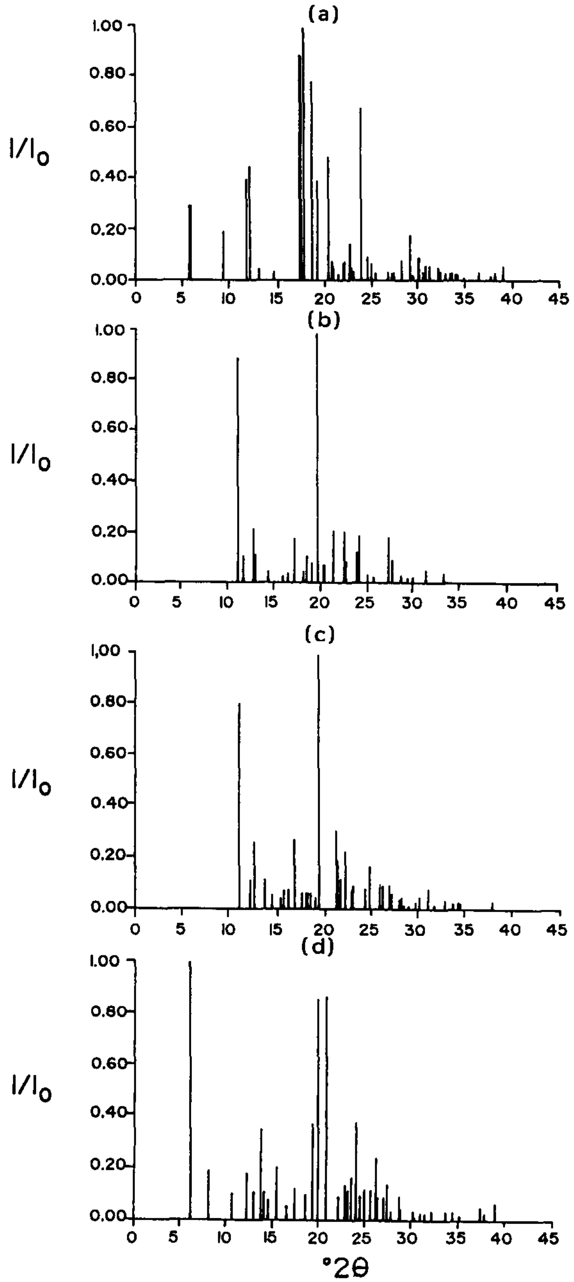

Fig. 2. X-ray powder diffraction patterns of the three solvates of cyclopenthiazide compared to that of polymorph I. (a) Polymorph I, (b) acetone solvate, (c) isopropanol solvate and (d) ethyl acetate solvate.

intrinsic dissolution rate. The intrinsic dissolution rates were compared using the Student-Newman-Keuls multiple range statistical test.

In 10% ethyl alcohol in water the ethyl acetate solvate is the best soluble of the three solvates studied. When their solubilities were however compared to the solubilities of polymorph I of cyclopenthiazide it was obvious that all the solvates were less soluble than polymorph I. Of the three solvates the ethyl acetate solvate had the highest solubility in 10% water in ethyl alcohol but lower than the solubility of the polymorph.

According to the intrinsic dissolution rates the solubility of the polymorph should be the highest. The polymorph gave the highest intrinsic dissolution rate and according to this result it must also be the best soluble in the solvent.

The intrinsic dissolution rate of polymorph I was significantly higher than the rates of any of the solvates (95% confidence level). The dissolution rate of the isopropanol solvate was significantly higher than the rate of the acetone or the ethyl acetate solvate. The dissolution rate of acetone and ethyl acetate solvates did not differ significantly.

Powder dissolution rates were determined by a modification of the method described by Lötter et al. (1983). The dissolution medium was 500 ml distilled water at 37 °C. Samples were passed through a 50 μm sieve and 50 mg of each form was then suspended in 50 ml of water on an ultrasonic bath. 1 ml of this suspension was added to the dissolution bath and stirred at 100 rpm. At each time interval 5 ml samples were withdrawn and the contents determined with a spectrophotometer at 225 nm. The particle size of the solvates used in this study were: ethyl acetate 23.69 μm, isopropanol 24.54 μm and acetone solvate 24.83 μm. The ethyl acetate solvate had the best solubility followed by isopropanol solvate and then the acetone solvate.

Differences in all methods employed could be detected between the three solvates and polymorph I of cyclopenthiazide.

When either the three solvents are used for recrystallisation of cyclopenthiazide or during granulation or coating of tablets care should be taken to make sure that the solvates are not formed or used per se because of their lower solubility, content uniformity problems when solvents are lost, or toxicity problems.

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