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THERMAL STUDY OF PREDNISOLONE POLYMORPHS

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ABSTRACT

Prednisolone, a commercial product (polymorph 1), when crystallized from a methanol–water mixture, gives polymorph 2. By heating form 2, polymorph 3 has been isolated. The thermal behaviour of the three forms has been studied.

INTRODUCTION

The existence of polymorphism in drugs is a very important factor in pharmaceutical technology due to the fact that one polymorph can be active and, therefore, another polymorph can be inactive.

The polymorphs of a drug can be studied by differential thermal analysis, or by differential scanning calorimetry. The determination of various polymorphs and the study of the heat of solid–solid transition to methyl prednisolone has been reported by Guillory [1] using differential thermal analysis. The thermal behaviour of various polymorphs of sulfathiazole has been studied by a number of workers [2–6] using differential scanning calorimetry.

Prednisolone has been used extensively as a model drug in research works in recent years; it was found necessary to conduct an investigation of prednisolone polymorphism to see whether or not this drug exists in more than one crystalline form.

This paper reports the isolation and the thermal study of three polymorphs of prednisolone by differential scanning calorimetry and thermogravimetry.

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EXPERIMENTAL

Materials

Prednisolone form 2 was prepared by slow recrystallization of commercial prednisolone BP/USP (form 1) in a methanol–water mixture.

Prednisolone form 3 was prepared by heating form 2 at 130°C for 24 h.

IR spectroscopy, X-ray powder diffraction and scanning electron microscopy were used to identify the three forms [7].

Methods

Thermal measurements were performed using a Mettler TA 3000 system with a differential scanning calorimeter (model DSC 20) and a TGS-2 thermobalance with a TADS-3000 and TAC 7/4 system.

Samples were ~ 5 mg to render the degree of temperature non-uniformity within the sample insignificant. An aluminium pan was used under a dry nitrogen atmosphere at a flow rate of 20 ml min^{-1}. The scanning rate used was 2°C min^{-1} and the instrument calibration was checked periodically with standard samples of indium (purity 99.99%), since its heat of melting is well documented [8].

RESULTS AND DISCUSSION

The DSC and TG results of the three polymorphs of prednisolone are summarized in Table 1, and their DSC and TG curves are shown in Figs. 1–3.

The DSC curve for prednisolone form 1 exhibits one endothermic peak, which represents the melting at 239.1°C. The area under the peak was measured and ΔH melting was calculated. The calculated heat of melting was found to be 33140 ± 80 J mol^{-1}. The purity of form 1 was also

TABLE 1

Thermal data of prednisolone polymorphs

	Form 1	Form 2	Form 3
Dehydration temp. (°C)	–	30–115	–
% $\Delta m/m$ (weight loss)			
calc.	–	6.51	–
found	–	6.65	–
Melting point (°C)	239.1	245.3	243.0
ΔH melting (J mol^{-1})	33140 ± 80	28080 ± 956	23670 ± 108
Purity (%)	99.00 ± 0.7	92.59 ± 4.0	98.72 ± 2.5

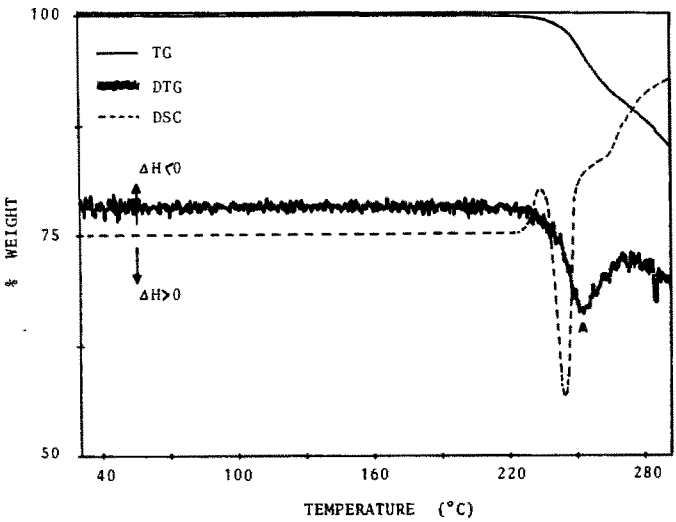

Fig. 1. DSC, TG and DTG curves of prednisolone form 1.

calculated by Van't Hoff's law [9,10]. This purity was found to be 99.00 ± 0.7%.

The TG and DTG curves for prednisolone form 1 do not show any weight loss between 30 and 220°C.

The DSC curve for prednisolone form 2 shows two endothermic peaks at 120 and 245.3°C. The first one can be attributed to the loss of 1.5 moles of water. This endothermic process gives, on the TG and DTG curves, one

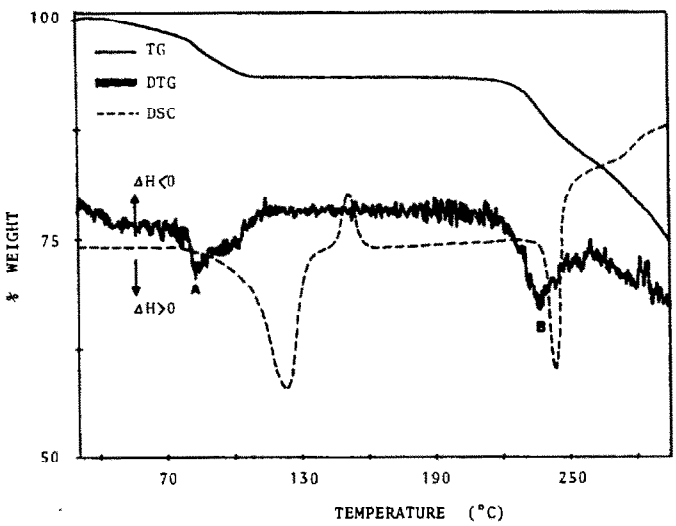

Fig. 2. DSC, TG and DTG curves of prednisolone form 2.

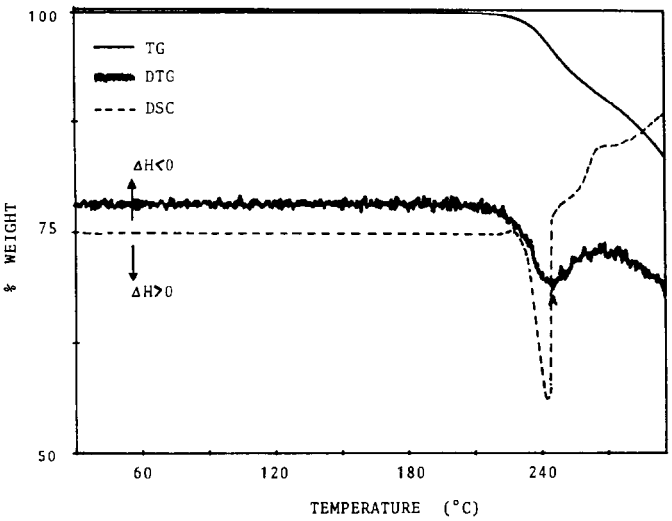

Fig. 3. DSC, TG and DTG curves of prednisolone form 3.

weight loss between 30 and 115°C (6.65%) which corresponds to the calculated weight loss of 1.5 moles of water. The second peak in the DSC curve at 245.3°C represents the melting prednisolone form 2. The calculated heat of melting was found to be $28\,080 \pm 956$ J mol^{-1}. A large value of ΔH with a very large standard deviation was obtained for prednisolone form 2. This is an indication of the non-uniformity of samples after the water loss or, in other words, the samples taken consist of various proportions of the dehydrated prednisolone which contribute to this great variation. The TG and DTG curves of prednisolone form 2 do not show any weight loss between 115 and 213°C. The DSC curve of prednisolone form 2 shows another exothermic peak at 146°C; this exothermic process can be attributed to some crystallization of the sample after the water loss. This was confirmed by the microscopic examination, as well as by visual observation of one open pan while scanning.

The calculated purity by Van't Hoff's law of prednisolone form 2 was found to be $92.59 \pm 4.0\%$. The large variation of purity values which was observed in prednisolone form 2 is probably due to an incomplete crystallization of the melting species.

The DSC curve of prednisolone form 3 shows one endothermic peak at 243.0°C which corresponds to its melting. The values for ΔH of melting obtained from ten runs gave a calculated average of $23\,670 \pm 108$ J mol^{-1}. No weight loss was observed in the TG and DTG curves for this endothermic process between 30 and 212°C.

The purity of prednisolone form 3 was found to be $98.72 \pm 2.5\%$.

The scanning rate was found to have little or no effect on the values of ΔH for the three prednisolone forms. In this study, it was found that there is

a difference of about 3% in ΔH values of prednisolone polymorphs scanned at 2 and 40°C min^{-1}. This is the same difference observed when the calibration substance was scanned at both rates.

The results of this study preclude the existence of three forms of prednisolone.

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