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THERMAL BEHAVIOR OF ORTHORHOMBIC POLYMORPHS I AND II OF SPIRONOLACTONE

P. Espeau[1*], *B. Nicolai*[1], *R. Céolin*[1], *M.-A. Perrin*[1], *L. Zaske*[1], *J. Giovannini*[2] *and F. Leveiller*[2]

[1]Laboratoire de Chimie Physique, EA 4066, Faculté de Pharmacie, 4 av. de l'Observatoire 75006 Paris, France
[2]AstraZeneca R and D, 221 87 Lund, Sweden

Investigation into the thermal behavior of orthorhombic Forms I and II of spironolactone, by means of differential scanning calorimetry and high-resolution X-ray powder diffraction, showed that Form I melts then recrystallizes into Form II at 373–393 K, *i.e.* in the temperature range within which high resolution X-ray powder diffraction showed that Form I transforms into Form II. Refinements of the lattice parameters of the two forms indicated that Form I is denser than Form II in the range from 298 K up to the temperature at which it melts.

Keywords: *differential scanning calorimetry, spironolactone, polymorphism, X-ray powder diffraction*

Introduction

The crystal structures of two orthorhombic polymorphs of spironolactone (Forms I and II) were solved previously [1, 2]. Form II, the usual commercial phase, was found to melt at 483 K ($\Delta_{fus}H$(II)= 22.1 kJ mol^{-1}) and Form I was assumed to melt at 478 K ($\Delta_{fus}H$(I)=20.0 kJ mol^{-1}) according to previous differential scanning calorimetry (DSC) measurements [3]. However, X-ray powder diffraction studies as a function of temperature showed that Form I transforms into Form II at about 393 K [4], *i.e.* possibly conflicting with previous results [3]. In order to check whether the transition of Form I into Form II involves only crystalline phases, new investigations combining DSC measurements and X-ray powder diffraction studies as a function of the temperature were performed. Results are presented in the following.

Material and methods

A spironolactone sample of medicinal grade Form II from Roussel was used as such after checking its crystallographic purity. To determine the heat of the I–II transition, crystals of Form I were grown by slow desolvation of the ethanol solvate at room temperature.

DSC runs were performed at various rates (5 to 15 K min^{-1}) by means of a DSC 822^e thermal analyzer from Mettler-Toledo. Indium was used as a reference for calibrating temperatures and enthalpy changes. Samples were weighed with a microbalance sensitive to 0.01 mg then closed in aluminum pans.

X-ray powder diffraction (XRPD) data collection was carried out on solids placed in concave aluminum holders under nitrogen flow (250 mL min^{-1}) with a Siemens–Bruker D5000 diffractometer (parafocusing Bragg–Brentano (θ–θ)-type geometry) equipped with an Anton-Paar TTK heating chamber. The parallelism of the K$\overline{\alpha}$ (Fe-filtered) incident beam (λ CoK$_{\alpha_1}$=1.7890 Å and λ CoK$_{\alpha_2}$=1.7929 Å) was improved by means of Soller slits. A 1-mm collimator was used to reduce the diffusion from the anticathode (40 kV, 30 mA) to the diffracting area, which was kept constant by means of variable-divergence slits. The XRPD profiles were recorded with a Braun 50-M multichannel linear detector (10°(2θ)-wide detection window) at a 0.05 (2θ)° s^{-1} rate in the 1.5–50° (2θ)-range. Data were collected isothermally at 5 K intervals, with a heating rate in between data collection of 3 K min^{-1}, and lattice parameters values were refined using the FullProf suite [5].

Results and discussion

DSC runs on Form I crystals (Fig. 1) showed that transition I–II is not an enantiotropism-related solid-solid transition since an endothermic-exothermic sequence of peaks was recorded from about 373 to 393 K upon heating at 5 and 15 K min^{-1} rates, reminiscent of the thermal behavior previously reported by Florence and Salole [6]. It was concluded that the I–II transition occurs as a melting-recrystallisation process that was not 'seen' through previous X-ray diffraction experiments [4]. Such an outcome was confirmed by visual examination of the process using a Mettler FP51 hot stage (see insets in Fig. 1), as well as

* Author for correspondence: Philippe.Espeau@univ-paris5.fr

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Akadémiai Kiadó, Budapest, Hungary
Springer, Dordrecht, The Netherlands

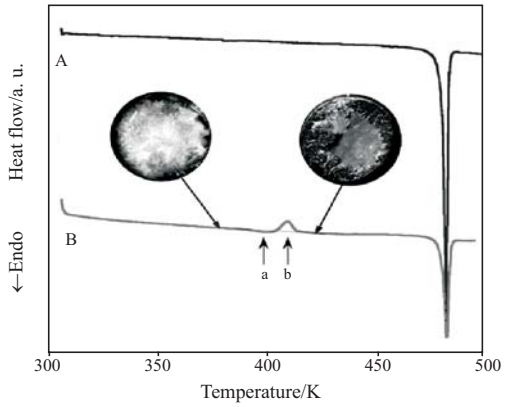

Fig. 1 DSC curves for spironolactone A – Form II and B – Form I.The endo-exothermic sequence (peaks 'a' and 'b') indicates that the fusion of Form I precedes the recrystallisation of the melt into Form II, as shown by visual examination of the process by means of a hot stage (see insets in which the arrows indicate the temperatures at which the photographs were taken)

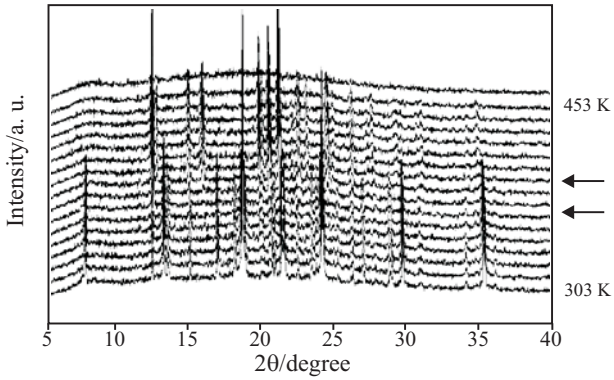

Fig. 2 High resolution X-ray diffraction profiles recorded as a function of the temperature starting with a sample of spironolactone Form I (interval between profiles: 10°). In spite of preferred orientations, the transformation of Form I into Form II is visible in the temperature range indicated by the horizontal arrows (about 373–393 K)

by an X-ray diffraction control of the recrystallized phase cooled from 423 K to room temperature.

The onset temperature of the melting of Form II, recorded at 480 K, and the related heat of fusion, $\Delta_{fus}H$(II)=22.9 kJ mol^{-1}, were found to be close to previous determination [3].

As far as the enthalpy change associated with the I to II transition is concerned, summing over the whole endo-exothermic effect gave values near 0 (0±0.8 kJ mol^{-1}), thus preventing from unambiguous conclusion as to the endo- or exothermic character of the transition. Nevertheless, such a result indicates that the melting enthalpy of Form I should be close to that of Form II at the temperature at which the event occurs.

X-ray powder diffraction profiles of Forms I and II recorded from 298 to 493 K showed the same results as those previously found with regard to the I–II transition [4]. The thermal behavior of Form I as a function of the temperature and its transition into Form II are shown in Fig. 2. In addition, specific volumes calculated from refined lattice parameters indicated that Form I is the denser phase in the T-range investigated. It came to: v(I)/cm^3 g^{-1}=0.75047+(0.00012983·T/K) (r^2=0.9917) and v(II)/cm^3 g^{-1}=0.75405+(0.00015647·T/K) (r^2=0.9978), indicating that the dependence of the specific volumes of these polymorphs on the temperature is virtually linear.

Conclusions

As far as the thermal behavior of Forms I and II are concerned, these studies performed using well-characterized samples unambiguously showed that Form I cannot melt at 478 K since it does at about 373–393 K.

It is also worth noting that the value for the melting enthalpy of Form II is smaller than the values usually found (33.3–50.0 kJ mol^{-1}) for a number of molecular drugs. This may be related to the lack of hydrogen bonds in orthorhombic packing, in which molecules are hold together by van der Waals interactions [1, 2]. Nevertheless, this does not explain why so great a difference in the melting temperatures is found.

With regards to the relative stabilities of these two polymorphs, it may provisionally be suggested that Form I is less stable than Form II at temperatures greater than 298 K, since it melts at a temperature far smaller than that of Form II, although it was the first phase isolated and characterized (thus erroneously named Form I) [1, 6].

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