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POLYMORPH FORMATION FROM SOLVATE DESOLVATION
Spironolactone forms I and II from the spironolactone-ethanol solvate

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Spironolactone ($C_{24}H_{32}O_4S$) usually crystallizes into an orthorhombic phase, named Form II. Another orthorhombic phase, named Form I, is also known but seems difficult to obtain. Studies of the kinetics of desolvation of the ethanol solvate at room temperature showed that these two forms can be obtained through different mechanisms of desolvation.

Keywords: *kinetics, solvates, spironolactone, thermogravimetry, X-ray powder diffraction*

Introduction

The crystal structures of two spironolactone polymorphs (Forms I and II [1, 2]) are known, as well as the metrics and symmetry of several solvates [3–5]. However, despite several preparation methods of the crystalline forms have been proposed [3, 5, 6], Forms I and II, and even other forms or mixtures of forms, were obtained randomly after evaporating solutions in a large variety of solvents and different experimental conditions. In particular, it has to be kept in mind that crystals used for the structure determinations of Forms I and II were both obtained from solutions in acetone. Thus, even in this case, controlling polymorph crystallisation by means of specific solvents remains an open question.

After examining the available crystallographic data [1–5], it can be seen that the unit-cell metrics of Form I is very close to that of the ethanol solvate (Table 1). It was thus hypothesized that the desolvation of the solvate could lead easily to Form I if the molecular packings in the two structures are similar. In other words, Form I might be considered, according to Stephenson *et al.* [7], as an 'isomorphic desolvated form' i.e. made of about the same packing of the spironolactone molecules as in the solvate. To confirm this, the desolvation of the solvate was followed by X-ray diffraction as a function of time at constant temperature, and surprisingly, two mechanisms of desolvation were found, leading to Form I or Form II, respectively.

Experimental

Materials

Spironolactone

Spironolactone is known to show differences in bioavailability and aqueous solubility data for identical formulations of drug batches from different sources. Spironolactone powders were randomly obtained from (at least) 3 suppliers: Aldrich, Roussel, and Cooperation Pharmaceutique Française (CPF). These samples were characterized by X-ray powder diffractometry: experimental profiles were compared with the ideal profiles calculated from the published data, using the program Fullprof (2005) [8].

Pure Form I was not found in these commercial batches. White powder of crystallographically pure Form II was obtained from the Roussel batch. The Aldrich sample was made of a mixture of Form I and an unknown third form; the CPF sample was also found to be made of a mixture of Form I and traces of an unidentified fourth form.

Ethanol solvate

Needle-shaped crystals of the ethanol solvate were obtained by slow evaporation at room temperature of a saturated solution of commercial spironolactone Form II (Roussel) dissolved in ethanol (99.8% Carlo Erba), at 25°C. The so-obtained crystals were found to slowly lose their crystallization solvent, while standing at room temperature in air. Thus, they were stored in their mother liquor from which they were extracted just before starting data collections related to desolvation.

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Table 1 Lattice parameters of orthorhombic spironolactone-ethanol solvate, Form I and II

	Solvate single crystal [4]	Form I single crystal [1]	Form II single crystal [2]
Space group	P 2_1 2_1 2_1	P 2_1 2_1 2_1	P 2_1 2_1 2_1
a/Å	10.14	9.979	10.584
b/Å	36.21	35.573	18.996
c/Å	6.28	6.225	11.005
Unit-cell volume/Å^3	2306	2209.8	2212.6

Methods

X-ray powder diffraction

High resolution X-ray powder diffraction (XRPD) profiles were collected using an INEL diffractometer with a Curve Position angular Sensitive detector CPS 120 with steps of 0.029° in 2Θ degrees (incident radiation: λ CoK$_{\alpha_1}$=1.7889 Å, Debye–Scherrer geometry, transmission mode).

Specimens were introduced in 0.5 mm diameter Lindemann capillaries and allowed to rotate around their vertical axes during data collections. The needles of Form I or solvates were carefully in-capillary crushed in order to try and prevent prefered orientation effects.

Thermogravimetric analyses

In order to obtain dry solvates, isothermal thermogravimetric analyses (TG) experiments were run at 30°C, using a TGA50 thermobalance from TA-Instruments, with mixtures of mother liquor and solvate crystals in pierced pans under a nitrogen flow until a constant mass was recorded. Soon after the solvate specimens were dried, the desolvation-related mass losses were recorded at a 1 K min^{-1} heating rate. The mass losses were found to be 5.2%, i.e. close to the 5.24% ideal value for the (spironolactone:ethanol) 2:1 molar ratio, in agreement with the stoichiometry proposed by Agafonov *et al.* [4]. In addition, the XRPD profile of the solid recovered from 95°C was virtually the same as that of Form II.

Results and discussion

Desolvation was followed in situ by recording X-ray powder diffraction profiles as a function of time at 28±1°C. Two procedures were used. In both cases, the desolvation kinetics was followed by monitoring the intensities of selected reflections of XRPD profiles normalized to a constant exposure time.

In every case, peaks for suitable intensity measurements were carefully selected according to two criteria: intensity high enough at *t*=0, and unambigous ascription (overlapping peaks were discarded).

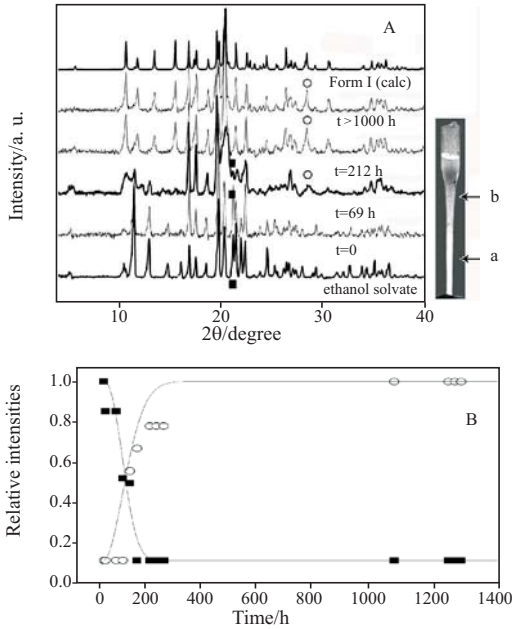

Fig. 1 Isothermal (28±1°C) desolvation of the ethanol solvate (initial conditions: a – mixture of solvate crystals and b – mother liquor, as shown by the left-hand side photograph). A – Selected XRPD patterns at different times (hours). B – Intensities of peak at 2θ=21.2° (filled squares) for the disappearing solvate and of peak at 2θ=28.4° for Form I (empty circles)

The first procedure consisted in introducing solvate crystals together with an excess of mother liquor in an open Lindemann capillary, with which XRPD profiles were recorded until complete desolvation into Form I. It is shown in Fig. 1 that the crystal solvate was transformed into Form I with no evidence of an amorphous intermediate step. In addition, at the half-life of the desolvation process, profiles exhibit peaks that can be ascribed to the solvate and to Form I (see profile at *t*=69 h in Fig. 1A).

The second method consisted in drying first the solvate crystals by running a preliminary isothermal thermogravimetry at 30°C. The solvate crystals, rid of solvent excess, were introduced straight away in an open Lindemann capillary, with which the desolvation process was followed with the same technique until complete desolvation into Form II. This revealed another desolvation kinetics likely consisting of a two-step mechanism (Fig. 2):

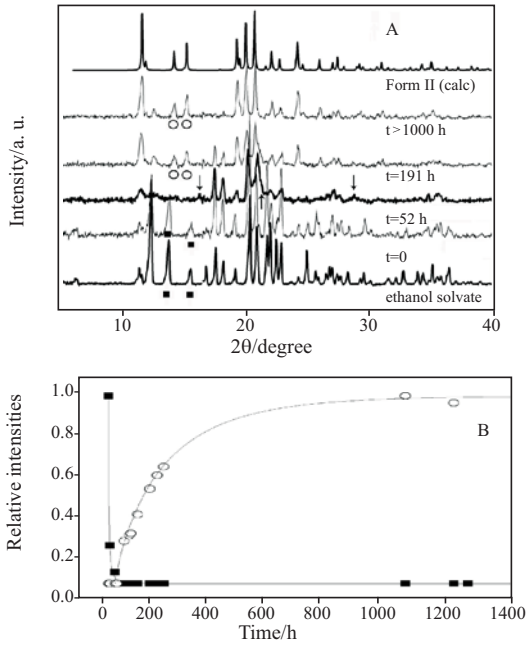

Fig. 2 Isothermal (28±1°C) desolvation of the ethanol solvate (already dried after standing to constant mass at 30°C). A – Selected XRPD patterns at different times (hours). B – Intensities of peaks at 2θ=12.9 and 14.8° (filled squares) for the disappearing solvate and of peaks at 2θ=13.4 and 14.5° (empty circles) for Form II. Arrows=peaks ascribed to a transiently forming phase

i) broadening and even disappearance of solvate-related peaks leading to an intermediate step that was found to be crystalline (profile at *t*=52 h in Fig. 2A), and *ii*) slow growth of Form II-related peaks.

As far as the mechanisms of these desolvation processes are concerned, attemps to describe structural mechanisms involved in desolvation can be found in the literature [9–14], and it was suggested [10] that periodically collected X-ray powder diffraction patterns could be of help to identify of phases during desolvation.

The kinetics results shown in Fig. 1 likely agree with the starting hypothesis according to which Form I should be an isomorphic desolvated form (it is here worth mentioning that solvate and Form I crystals both grow as needle-shaped crystals). This means that, when the solvent is lost from the original solvate crystal lattice, the new lattice is formed with virtually no change in the three-dimensional order of the spironolactone molecules (comparable cell parameters and identical space group [1–5]). Thus formation of Form I from the ethanol solvate may consist of a displacive process (according to the classification mentioned by Petit and Coquerel [10]), that has still to be related to either of type 1, type 2 and type 3 models Galwey [9] proposed for dehydration.

On the opposite, the mechanism of the process leading to Form II remains all the more somewhat unclear as the molecular packing of the solvate is still wanting. Nevertheless, it can be seen in Fig. 2A that a few peaks are transiently recorded (arrows on profile *t*=52 h), thus indicating that a stationary phase forms while desolvation goes on. Whether this phase is another solvate (for instance, spironolactone 0.25 ethanol) or an unstable polymorph has still to be checked. Anyway, it may tentatively be concluded that this process consists of a two-step process.

Conclusions

Although the mechanisms of desolvation of spironolactone solvates are still under investigation, the present results indicate that Form I can be obtained reproducibly from the ethanol solvate, insofar as it is allowed to lose very slowly its solvent molecules at room temperature with no preliminary drying by even moderate heating.

Nevertheless, Form I can also be obtained by desolvation according to a more complex mechanism, probably involving the preliminary formation of nuclei of an intermediate phase as a consequence of smooth drying through moderate heating.

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