International Journal of Pharmaceutics 391 (2010) 197–202

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Crystallographic, thermal and spectroscopic characterization of a ciprofloxacin saccharinate polymorph

C.B. Romañuk[a], Y. Garro Linck[b], A.K. Chattah[b], G.A. Monti[b], S.L. Cuffini[c], M.T. Garland[d], R. Baggio[e], R.H. Manzo[a], M.E. Olivera[a,*]

[a] Departamento de Farmacia, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, 5016 Córdoba, Argentina and CONICET
[b] Facultad de Matemática, Astronomía y Física and IFFAMAF (CONICET), Universidad Nacional de Córdoba, 5016 Córdoba, Argentina
[c] Subsecretaria Ceprocor, Ministerio de Ciencias y Tecnología de la Provincia de Córdoba, Argentina and CONICET
[d] Departamento de Física, Facultad de Ciencias Físicas y Matemáticas and CIMAT, Universidad de Chile, Chile
[e] Departamento de Física, Comisión Nacional de Energía Atómica (CNEA), Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 26 November 2009
Received in revised form 17 February 2010
Accepted 1 March 2010
Available online 7 March 2010

Keywords:
Fluoroquinolone
Salts
Polymorphism
Solid-state characterization

ABSTRACT

A new polymorphic form of ciprofloxacin saccharinate (CIP-SAC II) is presented, and compared with CIP-SAC I, a different polymorph which we had previously reported. The characterization techniques used were single crystal and powder X-ray diffraction, differential scanning calorimetry, thermogravimetry analysis and infrared and ^{13}C solid-state nuclear magnetic resonance spectroscopy. The results obtained from these techniques are consistent. Differential scanning calorimetry and thermogravimetric analysis showed that the reaction between the precursors is completed and the crystalline forms of both salts obtained (I and II) are highly pure. Infrared spectroscopy gave clear evidence of a salt formation. Solid-state nuclear magnetic resonance spectroscopy would indicate some degree of qualitative similarity in the intermolecular interaction scheme in both polymorphs, while thermal analysis data might indicate a difference in quantitative terms. A thorough single crystal structure determination of the new form CIP-SAC II allowed disclosing the most important inter- and intramolecular interactions.

1. Introduction

Ciprofloxacin (CIP), 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-quinoline-3-carboxylic acid, is a widely prescribed, broad-spectrum oral fluoroquinolone antibiotic approved for the treatment of several types of infections (Clinical Pharmacology, 2007). It is active against both Gram negative and Gram positive bacteria (Hooper and Wolfson, 1993). In aqueous solutions CIP exists mainly in its zwitterionic form, due to the acid base interaction between the piperazine basic nitrogen and the carboxylic group. As a consequence the aqueous solubility of CIP at pHs close to 7 (isoelectric point of the molecule) is low (0.088 mg/ml) (Fallati et al., 1994; Romañuk et al., 2009). This property makes it difficult to formulate optimized liquid dosage forms such as parenteral, ototopic or ophthalmic solutions (Takács-Novák et al., 1990). Moreover, fluoroquinolones are characterized by a bitter taste (Pisal et al., 2004; Hee-Kim and Hoo-Kyun, 2004; Shirai et al., 1994), which is an additional complication for the oral administration of these compounds. Recent investigations have shown incomplete dissolution of CIP hydrochloride tablets at intestinal pH 6.8, due to its poor solubility (Breda et al., 2009). Also, it has been proposed that CIP bioavailability can be limited by both solubility and permeability (Breda et al., 2009). For active pharmaceutical ingredients (APIs) with solubility-limited bioavailability, a challenging task in the development of the product is to improve their solubility without compromising other performance. Indeed, a widely accepted approach to overcome poor solubility of an API is the preparation of their salt forms.

We have previously reported some saccharinate salts of a number of related fluoroquinolone antimicrobials (viz., ciprofloxacin, norfloxacin, enrofloxacin and ofloxacin) (Romañuk et al., 2009). Saccharin was selected as the counterion because of its sweet taste and its well known capability to form salts and cocrystals (Baran, 2005; Banerjee et al., 2005; Velaga et al., 2008). A significant improvement on aqueous solubility was observed for all the salt forms studied. In particular, for the CIP saccharin salt, (CIP-SAC) this improvement is maintained due to the ion-pair formation at pH 7 (Romañuk et al., 2009).

The aim of this work is to present a new polymorph of CIP-SAC (hereafter CIP-SAC II) and to compare it with the previously reported form CIP-SAC I (Romañuk et al., 2009). To this effect a thorough solid-state characterization of both forms have been accomplished, using techniques such as powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and infrared (IR) and solid-state nuclear

* Corresponding author. Tel.: +54 9 03514334127; fax: +54 9 03514334127.
E-mail addresses: meoliver@fcq.unc.edu.ar, miniolivera@yahoo.com.ar (M.E. Olivera).

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.03.007

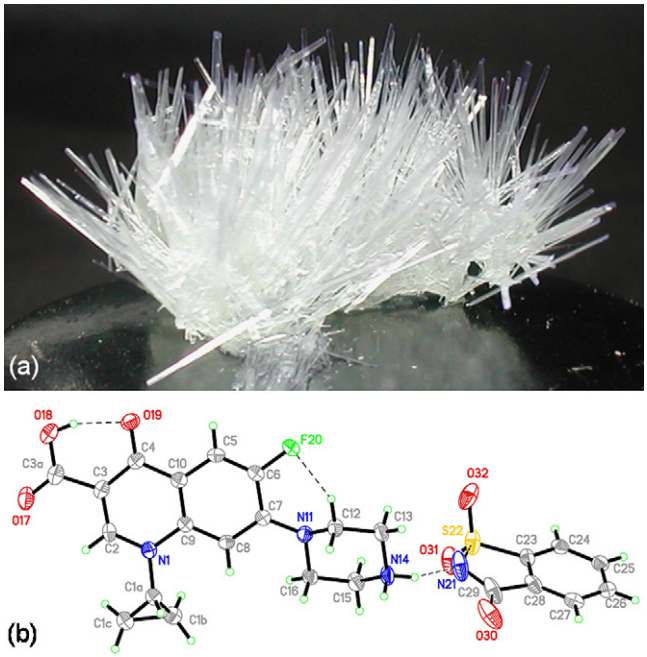

Fig. 1. (a) Single crystal of CIP-SAC II and (b) a view of CIP-SAC II asymmetric unit with some relevant intramolecular H-bonds.

magnetic resonance spectroscopy (SSNMR). The crystal structure of CIP-SAC (II) has also been determined by single crystal X-ray diffraction.

2. Experimental

2.1. Sample preparation and crystallization

CIP was obtained by neutralization of the hydrochloride salt (ciprofloxacin hydrochloride (CIP·HCl, USP, Neuland Laboratories Ltd.®), pharmaceutical grade). SAC was obtained by neutralization of the sodium salt (SAC-Na, Parafarm, China) and recrystallized from water; crystalline and anhydrous compounds were obtained and analyzed using DSC and powder X-ray diffraction techniques in order to control the reproducibility of different batches. CIP-SAC I was prepared as reported (Romañuk et al., 2009). CIP-SAC II was obtained by a slight modification of patent application P-060105581 (Manzo et al., 2009): appropriate quantities of CIP and SAC were dissolved in hot water and allowed to slowly cool in a dark place; acicular single crystals of CIP-SAC II were obtained after 2 or 3 days (Fig. 1a). These crystals were used to determine the crystal structure of the compound by X-ray diffraction and to carry on the analysis through the other techniques.

2.2. Analytical methodology

2.2.1. Single crystal and powder X-ray diffraction

Room temperature single crystal X-ray data collection was performed on a BRUKER SMART diffractometer, using SMART-NT with Bruker 2001 as the data collection driving software and SAINT-NT (Bruker, 2001) for data reduction and cell refinement. The structure was solved with SHELXS97 (Sheldrick, 2008) and refined using SHELXL97 (Sheldrick, 2008), with anisotropic displacement factors for non H atoms, and C–H hydrogen atoms stereochemically positioned, riding on their hosts. The O–H hydrogen was found in a difference map and refined with restrained O–H distance. XP in the SHELXTL-NT package was used for molecular graphics (Bruker, 2001).

Room temperature XRPD data were recorded on a RIGAKU diffractometer (Miniflex, Japon) using Cu Kα ($\lambda = 1.5417$ Å) radiation at 30 kV and 15 mA. Diffraction patterns were collected over a range of 5–50° 2θ at a scan rate of 0.01° 2θ min^{-1}.

2.2.2. Thermal analysis

The samples were subjected to differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), over a temperature range of 30–350 °C. The DSC standard cell of an A2920 MDSC (TA instruments) equipped with a data station (Universal Analysis, TA Instruments) was used to determine DSC curves. The temperature axis and the cell constant of the DSC cell were calibrated with indium (24 mg, 99.99% pure, peak maximum at 156.66 °C and heat of fusion 28.71 J/g, cell constant 1.2375). The samples (0.8–1.2 mg) were heated in crimped aluminum pans, under nitrogen flux (60 ml/min). Samples were run at 10°K/min ramps. A 2950 TGA HR thermogravimetric analyzer (TA Instruments) linked to a data station was used. The samples (0.8–1.5 mg) were placed in open aluminum pans and heated under the same conditions used in their respective DSC analysis.

2.2.3. IR and solid-state NMR spectroscopy

FT-IR spectra from 1% solid dispersions in KBr were recorded in a FT-IR Nicolet 5 SXC. High-resolution solid-state ^{13}C cross-polarization/magic angle spinning (CP/MAS) spectra for CIP-SAC I and II were recorded using a Bruker Avance II-300 spectrometer (300.13 MHz for ^{1}H and 75.46 MHz for ^{13}C). The samples were packed into a 4 mm rotor and spun with a rate of 10 kHz. The CP/MAS spectra were recorded employing a variable amplitude CP (2 ms contact time) (Harris, 1994). TPPM sequence was used for heteronuclear decoupling during acquisition with a proton field H_{1H} satisfying $\omega_{1H}/2\pi = \gamma_H H_{1H} = 60$ kHz (Bennet et al., 1995). The recycling time was 4 s. Different numbers of scans were recorded for each compound in order to obtain an adequate signal to noise ratio. The quaternary carbon edition spectra were recorded for all the samples. These spectra were acquired with the non quaternary suppression (NQS) sequence, in which the ^{1}H and ^{13}C r.f. fields are removed during 40 μs after CP and before acquisition (Harris, 1994). This experiment allowed us to identify quaternary carbon signals and methyl groups, and to perform the assignments in the solid-state. All the solid-state NMR experiments were performed at room temperature.

3. Results and discussion

3.1. X-ray diffraction techniques

Powder X-ray diffraction (PXRD) patterns of CIP-SAC polymorphs I and II presented clear differences (Fig. 2), confirming that they are different crystal forms and the technique appearing as a suitable tool for identification of both polymorphs not only during the crystallization process but also in the formulating development and manufacture.

Single crystal results: Table 1 presents some crystallographic data and refinement results for form II (CCDC, 2010), while Fig. 1b shows a view of the asymmetric unit, with the atom labelling used throughout this paper as well as the intramolecular H-bonds defining the two internal S_1^1 (6) loops hindering some torsional degrees of freedom (Bernstein et al., 1995). Bond distances and angles are normal, and the overall geometry does not deviate significantly from that on previously reported structures, as suggested by the least squares fit of the CIP unit in form II with, for instance, the one in the ciprofloxacin hexahydrate reported by Turel et al. (1997). The two molecules present a mean deviation as small as 0.21(1) Å (Fig. 3).