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Revisiting the Solid State of Norfloxacin

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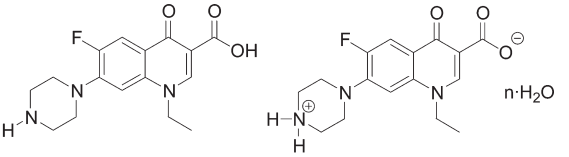
ABSTRACT: The crystal polymorphism of Norfloxacin and its hydrates has been revisited in order to update the knowledge about the solid state behavior of this active pharmaceutical ingredient. We have re-examined the crystal structure of anhydrous Form A and clarified some ambiguities previously published, confirming that one of the two previously reported anhydrous forms A is in fact a sesquihydrate form. Moreover, the structures of two new polymorphs of the sesquihydrate have been determined by means of single crystal X-ray diffraction, and their thermodynamical relative stability has been established.

Introduction

The solid state properties of active pharmaceutical ingredients (APIs) are of great importance in the pharmaceutical/generic field because the delivery of an API with the most suitable solubility, bioavailability, and stability profiles depends on which crystal form of the drug is present. Many marketed drugs are polymorphic;[1] thus, the knowledge of the factors favoring a particular crystal form can be vital during the development of a pharmaceutical formulation.

In this sense, pharmaceutical hydrates are important due to the presence of water molecules in so many pharmaceutical drugs, which affects a variety of physical and chemical properties, such as the stability, solubility, and dissolution rate. Usually, hydrates are less soluble than their anhydrous forms because the interaction between the compound and the water molecules confers an extra thermodynamical stability.[2] Norfloxacin is an example that contradicts that general rule because the hydrated forms are more soluble than the anhydrous one. This implies that the hydration process plays an important role in influencing the bioavailability of Norfloxacin, and it has made its hydrates an interesting object of study.

Norfloxacin (1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, NF; Figure 1) is a synthetic broad antibacterial fluoroquinolone compound used in the treatment of various infectious diseases, such as gonorrhea and prostate and urinary tract infections.[3] The crystal chemistry of NF has been extensively explored: in particular, three anhydrous forms,[4] several hydrates (1.125 hydrate, 1.25 hydrate,[5] sesquihydrate,[6] dihydrate,[7] hemipentahydrate, trihydrate, and pentahydrate[8]), an amorphous form, a methanol hydrate,[9] and a variety of salts and cocrystals[10] have been reported. Moreover, two X-ray crystal structures for anhydrous NF have been published. Both structures are referred to as Form A, although the crystallographic system, cell parameters, and crystal packing are different, with one structure being triclinic[10] and the other one monoclinic.[4c] On the other hand, among the numerous NF hydrates, the dihydrate[7] and the 1.25 and the 1.125 hydrates[5] have been characterized by single X-ray diffraction. These three X-ray crystal structures confirm the zwitterionic state of NF in all hydrated forms. Water-induced proton transfer in NF from anhydrous (neutral) to zwitterionic hydrates had been postulated from IR data and was confirmed later by X-ray diffraction.[11] However, the monoclinic NF anhydrous form reported by us with zwitterionic hydrogen bonding contradicted the aforementioned findings. Thus, taking into account all these observations, we decided to reinvestigate the monoclinic NF polymorph in order to clarify these contradictions with respect to Form A by obtaining new crystals of this polymorph.



Neutral Anhydrous Norfloxacin Zwitterionic Hydrate Norfloxacin

Figure 1. Neutral and zwitterionic forms of Norfloxacin.

In this contribution, we demonstrate that the monoclinic anhydrous Form A previously published by us is instead a sesquihydrate. This fact is in agreement with the postulated model of water mediated proton-transfer in NF hydrates. Single crystal structure determination of crystals of the previously described monoclinic Form A, at room temperature and at 150 K, confirms that the composition is a sesquihydrate (Form I at room temperature)[12] that transforms to another polymorph (Form II) at low temperature. With this correction, we review and summarize the known crystal forms of NF.

Experimental Section

Materials. Norfloxacin was purchased from Sigma-Aldrich (ref. N9890).

Crystallization of the Sesquihydrate Form I of Norfloxacin. Single crystals were grown as yellow polyhedral crystals by vapor diffusion of MTBE into a DMF solution (0.5 mL) of Norfloxacin (20 mg) at room temperature.

X-ray Powder Diffraction. Powder X-ray diffraction patterns (PXRD) were obtained on a PANalytical X'Pert PRO MPD diffractometer with Cu Kα radiation (λ = 1.5418 Å), in transmission geometry with the samples introduced in glass capillaries of 0.5 mm diameter, using an incident beam elliptic focalizing mirror and a PIXcel detector with an active detection length of 3.347°. The analyzed samples were scanned from 2 to 60° in 2θ with a step size of 0.026° and a total measuring time of 30 min.

The temperature dependent X-ray powder diffraction experiment was performed in the same experimental device with an

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Oxford Cryosystems 700 Series Cryostream Cooler temperature system installed. The analyzed sample was measured at 292, 273, 223, 173, and 123 and again at 292 K using heating and cooling rates of 6 K/min.

Single Crystal X-ray Diffraction. Form I: A prismatic crystal (0.1 mm × 0.1 mm × 0.2 mm) was selected and mounted on a Enraf-Nonius CAD4 four-circle diffractometer. Unit-cell parameters were determined from automatic centering of 25 reflections ($12° < \theta < 21°$) and refined by a least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation, using an $\omega/2\theta$ scan-technique. 5030 reflections were measured in the range $2.43 \leq \theta \leq 30.08$, 4765 of which were nonequivalent by symmetry (R_{int}(on I) = 0.015). 3027 reflections were assumed as observed applying the condition $I > 2\sigma(I)$. Three reflections were measured every two hours as orientation and intensity control; significant intensity decay was not observed. Lorentz-polarization and absorption corrections were made. The structure was solved by direct methods, using the SHELXS computer program (Sheldrick, G.M. (1997)), and refined by a full-matrix least-squares method with the SHELX97 computer program (Sheldrick, G.M. (1997)), using 5030 reflections (very negative intensities were not considered). Two H atoms were located from a difference synthesis and refined with an isotropic temperature factor, and 16 H atoms were computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 times the equivalent temperature factor of the atom to which they are linked. H atoms corresponding to water molecules could not be located. CCDC 720746. Form II: Single-crystal X-ray diffraction data were collected on a Bruker Smart CCD area detector with an Oxford Cryosystems low temperature system. The crystal structure was refined again using the same method as Form I. Eighteen H atoms were computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 times the equivalent temperature factor of the atom which is linked; however, H atoms corresponding to water molecules could not be located (CCDC 720747).

Differential Scanning Calorimetry (DSC). Differential scanning calorimetry was carried out by means of a Mettler-Toledo DSC-822e calorimeter and a Mettler-Toledo DSC30 calorimeter. Experimental conditions: aluminum crucibles of 40 μL volume, atmosphere of dry nitrogen with a 50 mL/min flow rate, heating rate of 10 °C/min and 20 °C/min. Both calorimeters were calibrated with indium of 99.99% purity.

Thermogravimetric Analysis (TGA). Thermogravimetric analyses were performed on a Mettler-Toledo TGA-851e thermobalance. Experimental conditions: alumina crucibles of 70 μL volume, atmosphere of dry nitrogen with 50 mL/min flow rate, heating rate of 10 °C/min.

Hot-Stage Microscopy (HSM). A Nikon polarization microscope (Nikon Eclipse 50i) equipped with a Linkam LTS350 hot stage and digital video recorder facilities was used.

Results and Discussion

Norfloxacin Sesquihydrates. Attempts to grow higher quality crystals of NF Form A by repeating the procedure of vapor diffusion of MTBE into a not totally anhydrous DMF solution of NF resulted in the crystallization of Form I NF sesquihydrate.[12] The room temperature crystal structure, determined here, is shown in Figure 2. The ORTEP diagram of the molecule and associated water molecules is presented in Figure 2.

Thermogravimetric analysis of this hydrate (Figure 3) shows a weight loss of 7.9%, which corresponds to 1.5 molecules of water (the calculated weight loss for 1.5 hydrate is 7.8%).

Moreover, the DSC curve (Figure 4) shows a first endotherm at 97 °C due to the loss of bound water from the crystal lattice followed by an endotherm at 221 °C attributable to the melting of anhydrous NF Form A. A sample of NF sesquihydrate has been dehydrated by heating it until 190 °C, and its PXRD has been measured, confirming that NF sesquihydrate converts into Form A of NF anhydrous

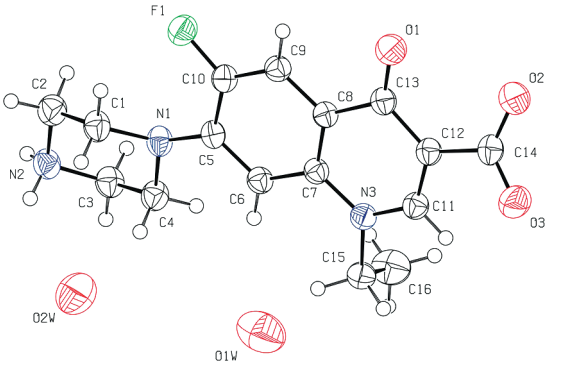

Figure 2. ORTEP representation of NF sesquihydrate Form I, showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level, and the H atoms are drawn as arbitrary radii. One water molecule (O2W) shows 0.5 site occupancy in the asymmetric unit.

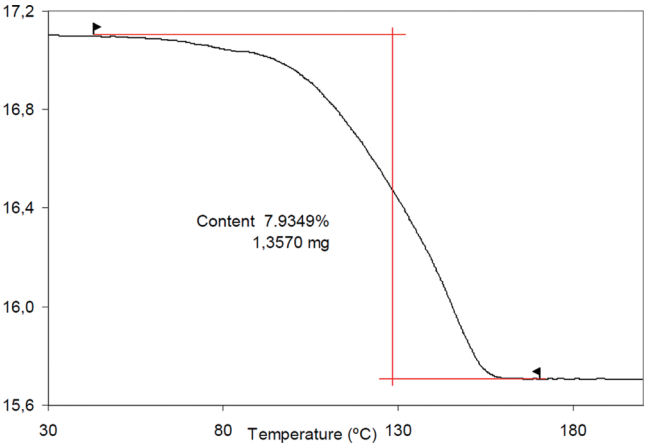

Figure 3. Thermogravimetric analysis of NF sesquihydrate.

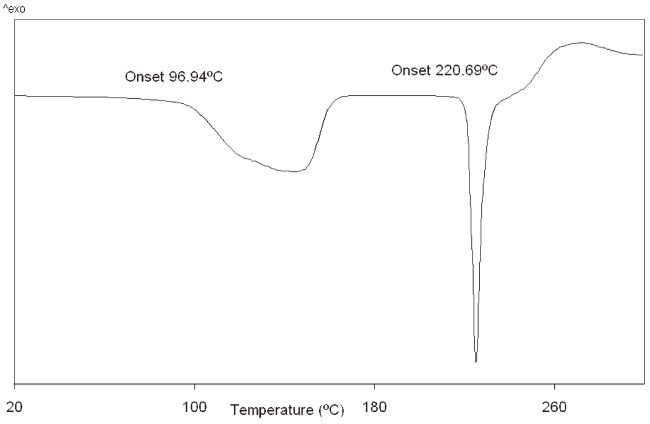

Figure 4. DSC analysis of NF sesquihydrate.

after losing the water molecules (see Figure 1 in the Supporting Information).

The loss of bound water of Norfloxacin sesquihydrate has also been observed by thermomicroscopy (Figure 5). While heating NF sesquihydrate on a hot stage at a rate of 10 °C/min, the first bubbles of dehydration were observed around 140 °C (Figure 5c). The crystals darkened during the dehydration process (Figure 5c–j), as temperature was increased.

In view of the difficulty in crystallizing again the targeted polymorph, we decided to re-examine the original single

X-ray diffraction data obtained by us. The aim was to explore the possibility that the monoclinic Form A previously reported was actually a hydrated form. The new analysis of the original data confirmed this hypothesis, as water molecules were found in the structure in a very disordered way. So, a new crystal form was solved corresponding to a sesquihydrate of NF. Surprisingly, this structure corresponded to a new polymorph (Figure 6, Form II) different from the one formerly described (Figure 2, Form I).

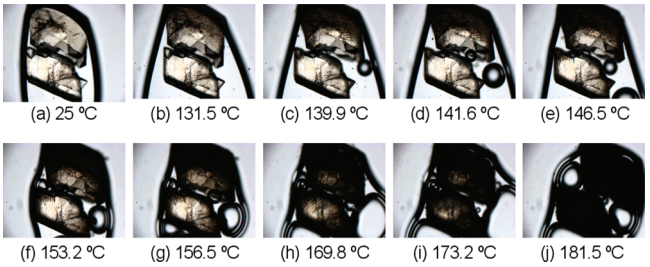

Figure 5. Photomicrographs of norfloxacin sesquihydrate in polarized light showing the loss of bound water upon heating.

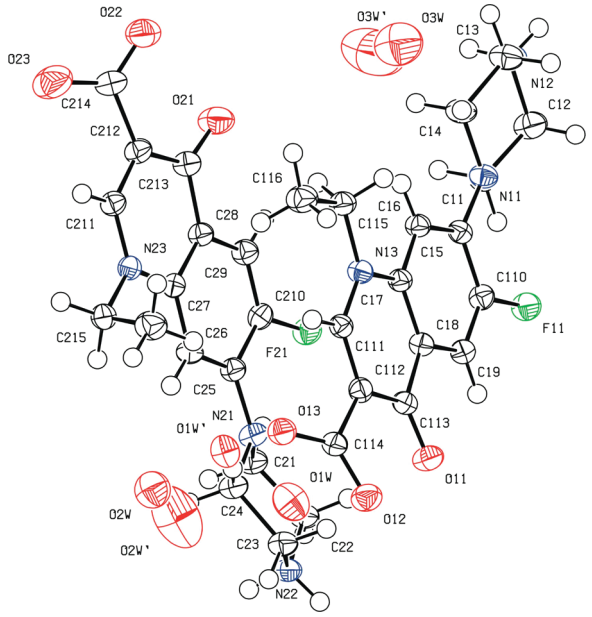

Figure 6. ORTEP representation of Form II of NF sesquihydrate, showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level, and the H atoms are drawn as arbitrary radii. Water molecules show different site occupancies in the asymmetric unit.

These two new polymorphs of NF sesquihydrate show similar conformations and crystallize in the monoclinic system with the same space group $P2_1/c$. The a and b cell parameters are similar whereas the c parameter is twice as large in Form II as compared with the case in Form I, with the β angle being slightly different between both forms. Crystallographic data are summarized in Table 1. Form I has one NF molecule, one water molecule (O1W), and a second water molecule (O2W) of 0.5 site occupancy in the asymmetric unit whereas Form II has two different NF molecules and six water molecules of different site occupancies (O1W 75%, O1W′ 25%, O2W 80%, O2W′ 20%, O3W 80%, and O3W′ 20%) in the asymmetric unit. Both structures are zwitterionic, as the piperazinyl N atom is protonated, revealing a proton transfer from the carboxylic group. This can be deduced from the similarity between the two C−O distances of the carboxylic group (Form I: 1.238(3) and 1.251(3) Å; Form II molecule 1: 1.233(3) and 1.273(3) Å; Form II molecule 2: 1.261(2) and 1.258(2) Å). This zwitterionic state is in agreement with all previous NF hydrates reported in the literature.

The piperazinyl ring in Form I and molecule 1 of Form II is in the chair conformation (θ = 2.9(2)° and 4.7(2)°, respectively), while molecule 2 of Form II exhibits a distorted chair conformation (θ = 22.6(4)°). The most significant difference between both molecules of Form II is the torsion angle of the ethyl group. The ethyl group of molecule 1 of Form II is perpendicular to the quinolone plane with a torsion angle of 90.1(2)°, while in molecule 2 it is coplanar with a torsion angle of 1.0(3)°. On the other hand, the ethyl group of Form I is almost perpendicular to the quinolone plane (85.9(3)°), revealing a great similarity with molecule 1 of Form II. In all three cases, there are short distances between F and H1 atoms forming a pseudo six-member ring. The molecular packing of the two forms is very similar (Figure 7), forming parallel layers stabilized by π-stacking

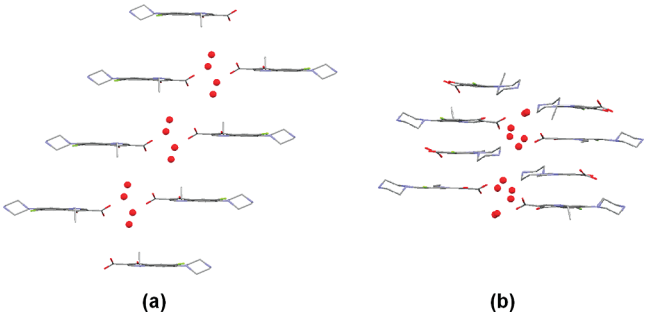

Figure 7. Water molecules forming channels in the crystal structures of Form I (a) and Form II (b).

Table 1. X-ray Crystallographic Parameters of the Two Polymorphs of NF Sesquihydrate Compared to Those of the Known Hydrates

	sesquihydrate form I[12]	sesquihydrate form II	dihydrate[7]	1.25 hydrate[5]	1.125 hydrate[5]
empirical formula	$C_{16}H_{18}FN_3O_3 \cdot 1.5(H_2O)$	$2(C_{16}H_{18}FN_3O_3) \cdot 3(H_2O)$	$C_{16}H_{18}FN_3O_3 \cdot 2(H_2O)$	$C_{16}H_{18}FN_3O_3 \cdot 1.25(H_2O)$	$C_{16}H_{18}FN_3O_3 \cdot 1.125(H_2O)$
T (K)	293(2)	150(2)	123(2)	100(2)	100(2)
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$
a (Å)	8.870(7)	8.5532(4)	8.265(3)	17.5341(11)	17.4911(16)
b (Å)	22.282(9)	22.2552(10)	21.698(4)	8.9942(6)	8.9542(8)
c (Å)	8.754(2)	17.1680(8)	9.5250(17)	19.9186(13)	19.7990(18)
α (deg)	90	90	90	90	90
β (deg)	109.39(3)	102.100(2)	110.794(19)	90.411(1)	90.252(2)
γ (deg)	90	90	90	90	90
V (Å^3)	1632.0(15)	3195.4(3)	1596.9(6)	3141.2(4)	3100.9(5)
Z	4	4	4	8	8
R factor	0.0571	0.0436	0.053	0.0484	0.1122

(Form I: 3.663(3) Å; molecule 1 Form II: 3.6378(13) Å; molecule 2 Form II: 3.5687(12) Å).

Molecules in every layer are structured in chains running along the *b* axis and including water molecules connected via hydrogen bonds (see Table 1 in the Supporting Information).

One important fact to be noted is that although both crystal structures have been solved at different temperatures (Form I at 298 K and Form II at 150 K), Form I of NF sesquihydrate has been obtained trying to reproduce the experimental conditions which led to Form II. Taking into account that there could be a possibility for a phase transition while cooling, we decided to perform a DSC experiment cooling from room temperature to −150 °C and heating from −150 °C to room temperature. As can be seen in Figure 8, a reversible solid−solid transition was observed at −57 °C while cooling and at −41 °C while heating. Therefore, this suggests that we have now obtained the same polymorph of NF sesquihydrate as before. However, the first time we solved a different polymorph because the measurement was performed at 150 K and a solid−solid transition had taken place. Besides, this experiment allows us to establish the relative thermodynamic stability between both forms, which is a matter of great relevance. According to the heat of transition rule,[13] Forms I and II are enantiotropically related, with Form I being the most stable at room temperature and Form II the most stable under approximately −40 °C.

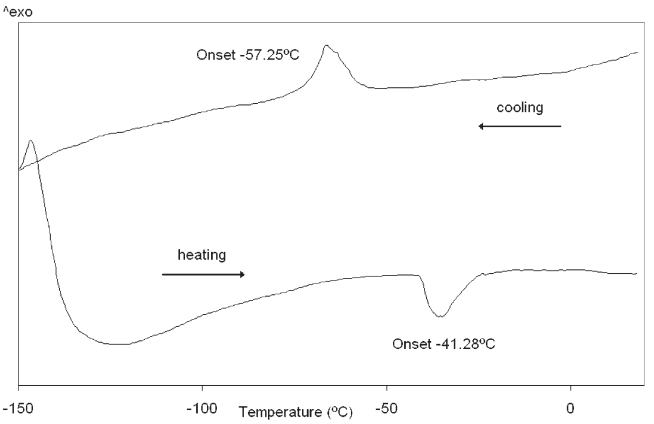

Figure 8. Cooling−heating DSC experiment, where the reversibility of the solid−solid transition of Norfloxacin sesquihydrate can be observed.

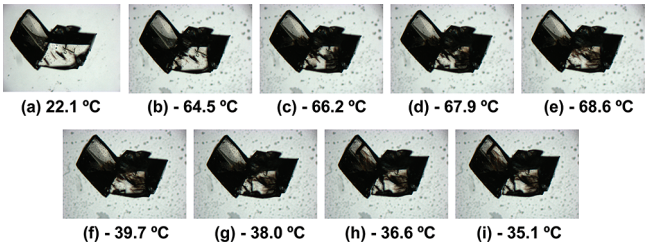

Figure 9. Photomicrographs of norfloxacin sesquihydrate in polarized light. Solid phase transition from Form I to Form II upon cooling (a−e) and upon heating (f−i) at a rate of 20 °C/min under nitrogen atmosphere.

It was also possible to study the reversible phase transition of Form I to Form II by means of thermomicroscopy as shown in Figure 9. While cooling Form I from room temperature at a rate of 20 °C/min, the beginning of the transformation to Form II was detected at −64.5 °C (Figure 10b) and complete conversion to the new form was finally observed at −68.6 °C (Figure 10e). Once this sample was heated to reach again room temperature, the reversible solid transition was completed at −35.1 °C (Figure 10i).

Moreover, the variable temperature PXRD experiment demonstrates that Form I of NF sesquihydrate undergoes a phase transformation into Form II while cooling down. Figure 10 depicts the experimental X-ray powder diffraction pattern at the different analyzed temperatures. At 292 and 273 and back again at 292 K, the patterns are essentially the same and correspond to Form I of NF sesquihydrate. At 223 K the pattern appears as a mixture of Form I (major phase) and Form II (minor phase) of NF sesquihydrate. At 173 and 123 K, the patterns correspond to Form II of NF sesquihydrate.

Rietveld analysis[14] of the patterns at the different analyzed temperatures, using the fixed crystal structures of Form I and Form II of NF sesquihydrate but refining the cell parameters, has been performed. Figures 11 and 12 depict the Rietveld plots of the initial pattern at 292 K and of the pattern at 173 K using respectively the crystal structures of Form I and Form II of NF sesquihydrate. The reasonably good concordance between the observed and calculated patterns and the obtained cell parameters (included in the figures), matching well that obtained from the crystal structure determinations (Table 1), ensures that at 292 K the pattern corresponds to Form I and that at 173 K the pattern corresponds to Form II, confirming the phase transformation.

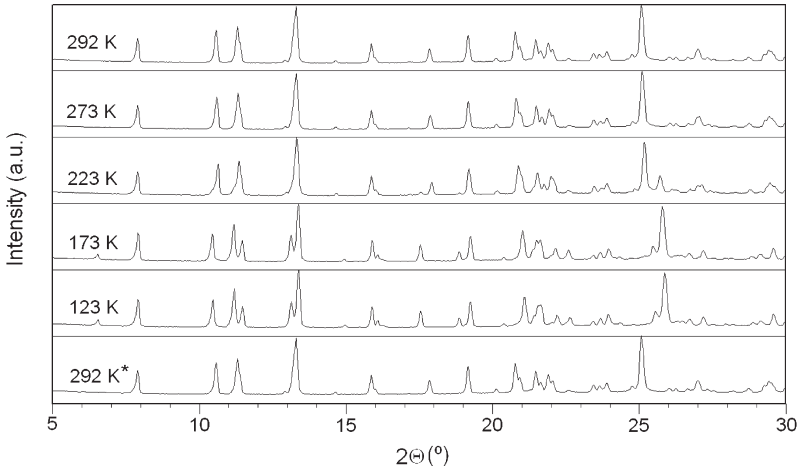

Figure 10. X-ray powder diffraction diagrams of NF sesquihydrate showing the phase transition from Form I to Form II. After cooling to 123 K, the sample was heated back to 292 K (*).

This result highlights the risk of solving crystal structures at low temperature when no information about the thermal stability of crystal forms is available.

Comparison of Norfloxacin Hydrates' Structures. All NF hydrates described to date in the literature are monoclinical with the same $P2_1/c$ space group but with differences in their unit cell parameters (Table 1). The piperazine ring is protonated in all the hydrates. NF sesquihydrate Form I has one NF molecule and the corresponding water molecules in the asymmetric unit as the dihydrate, while Form II of NF sesquihydrate has two NF molecules in the asymmetric unit as the 1.25 and 1.125 hydrates (together with the corresponding water molecules in each case). In all cases, norfloxacin molecules adopt a similar conformation except for the ethyl group of molecule 2 of Form II of NF sesquihydrate, which is coplanar with the quinolone plane. In Figure 13, slight differences among all forms can be seen regarding the COO and the ethyl groups orientation and the torsion angle of the piperazinyl ring, with this variation being more significant in the case of molecule 2 of Form II of NF sesquihydrate.

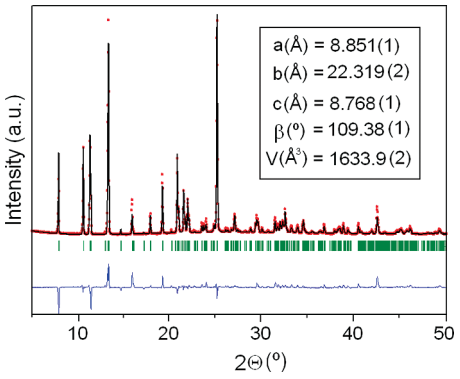

Figure 11. Rietveld plot of the X-ray powder diffraction pattern of NF sesquihydrate Form I at 292 K and resulting cell parameters.

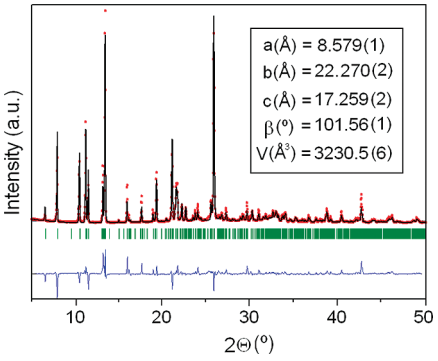

Figure 12. Rietveld plot of the X-ray powder diffraction pattern of NF sesquihydrate Form II at 173 K and resulting cell parameters.

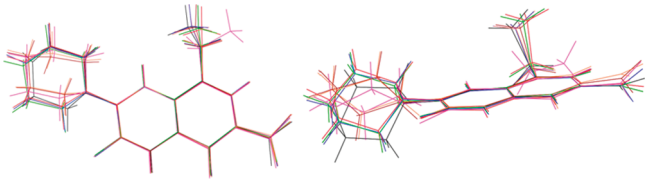

Figure 13. Overlay of norfloxacin molecules of Form I of sesquihydrate (red), molecule 1 of Form II of sesquihydrate (green), molecule 2 of Form II of sesquihydrate (pink), dihydrate (blue), molecule A of 1.25 hydrate (orange), molecule B of 1.25 hydrate (brown), and anhydrous Form A (black).

Two main differences arise from the observation of these structures: NF anhydrate is neutral and crystallizes in the triclinic system while hydrates are zwitterionic and prefer the monoclinic system to crystallize. Form A has one NF molecule in the asymmetric unit like the dihydrate and the sesquihydrate Form I of NF. The carboxylic acid group in the anhydrous form is coplanar with the quinolone moiety and participates in an intramolecular hydrogen bonding with the adjacent carbonyl oxygen atom of the quinolone moiety. On the other hand, the carboxylate group of NF hydrates is not coplanar with the quinolone moiety, due to the repulsion of the carboxylate and quinolone oxygen atoms. The influence of water molecules over the crystal structure of the hydrates with respect to the anhydrous form is obvious: the water mediated proton transfer causes the disappearance of the intermolecular $H_{aromatic}$–carbonyl synthon and the intramolecular carboxylic acid–carbonyl interaction together with the creation of polar channels for ionic interactions. The presence of charged functional groups prevents the formation of weak supramolecular synthons, as the strong

In the literature, a crystal structure of the methanolate hydrate of NF has also been reported.[9] Again, a solvent mediated proton transfer can be inferred to explain the same carboxylate-ammonium intermolecular interaction as observed in the other hydrates. Although the carboxylic group appears protonated in the original cif file, the deprotonation can be deduced from the similar C–O distances (aproximately 1.23 and 1.26 Å).

Comparison of Hydrate and Anhydrous Forms of Norfloxacin. Anhydrous NF exists as three polymorphic modifications. Form A is reported in the triclinic crystal system.[10] A polymorph screen of NF under anhydrous conditions was conducted in order to obtain single crystals of the other anhydrates; however, crystals of Forms B and C suitable for crystal structure determination could not be grown. Therefore, here we compare NF hydrates with Form A, the only crystal structure reported so far of an anhydrous NF, by discussing their main structural differences.

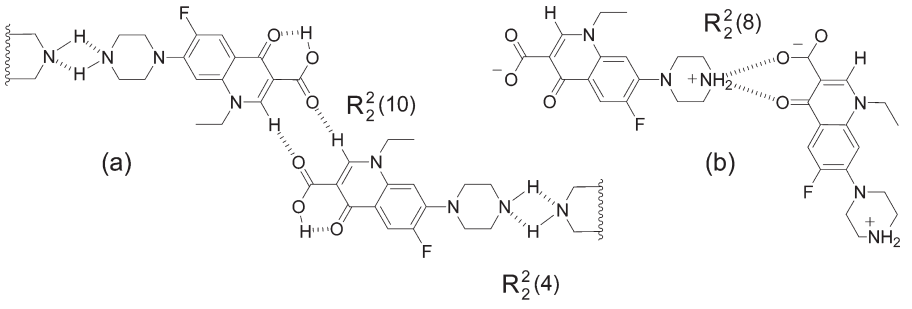

Figure 14. Differences in intermolecular interactions between anhydrous Form A (a) and hydrates (b) of NF.

ammonium−carboxylate interaction dominates, irrespective of hydrate stoichiometry. The observed intra- and intermolecular interactions in the solid state can be summarized for anhydrous and hydrated forms of NF in Figure 14.

It is also important to mention the example of zwitterionic NF in its cocrystal with isonicotinamide and chloroform.[10] In this case, even in the absence of water, the zwitterion is formed.

Conclusions

We have reinvestigated the monoclinic NF previously reported by us, demonstrating a mistaken identification of such a structure with the true Form A, which is triclinic. We can then confirm the former hypothesis of the zwitterionic behavior for hydrated forms and a neutral state for anhydrous forms of NF. Moreover, in this study we have reported two polymorphs of NF sesquihydrate differing in the number of NF molecules in the asymmetric unit and determined their relative stability through the observation of a solid−solid transition by thermal analysis, variable temperature powder X-ray diffraction, and thermomicroscopy, with Form I being the most stable at room temperature and Form II the most stable under −40 °C. Therefore, this study updates the crystallographic knowledge of NF hydrates, with a total of five structures reported to date.

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Supporting Information Available: Table listing hydrogen bond donor−acceptor distances of NF sesquihydrates, experimental PXRD pattern of NF sesquihydrate after dehydration, and CIF files of the two NF sesquihydrates. This material is available free of charge via the Internet at http://pubs.acs.org.

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