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Identification and Characterization of Stoichiometric and Nonstoichiometric Hydrate Forms of Paroxetine HCl: Reversible Changes in Crystal Dimensions as a Function of Water Absorption

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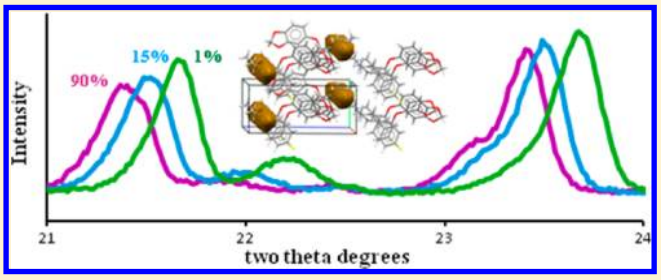
Supporting Information

ABSTRACT: Paroxetine hydrochloride (HCl) is an antidepressant drug, reported to exist in the anhydrous form (form II) and as a stable hemihydrate (form I). In this study, we investigate the hydration behavior of paroxetine HCl form II with a view to understanding both the nature of the interaction with water and the interchange between forms II and I as a function of both temperature and water content. In particular, we present new evidence for both the structure and the interconversion process to be more complex than previously recognized. A combination of characterization techniques was used, including thermal (differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)), spectroscopic (attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR)), dynamic vapor sorption (DVS) and X-ray powder diffraction (XRPD) with variable humidity, along with computational molecular modeling of the crystal structures. The total amount of water present in form II was surprisingly high (3.8% w/w, 0.8 mol of water/mol of drug), with conversion to the hemihydrate noted on heating in hermetically sealed DSC pans. XRPD, supported by ATR-FTIR and DVS, indicated changes in the unit cell dimensions as a function of water content, with clear evidence for reversible expansion and contraction as a function of relative humidity (RH). Based on these data, we suggest that paroxetine HCl form II is not an anhydrate but rather a nonstoichiometric hydrate. However, no continuous channels are present and, according to molecular modeling simulation, the water is moderately strongly bonded to the crystal, which is in itself an uncommon feature when referring to nonstoichiometric hydrates. Overall, therefore, we suggest that the anhydrous form of paroxetine HCl is not only a nonstoichiometric hydrate but also one that shows highly unusual characteristics in terms of gradual unit cell expansion and contraction despite the absence of continuous channels. These structural features in turn influence the tendency of this drug to convert to the more stable hemihydrate. The study has implications for the recognition and understanding of the behavior of pharmaceutical nonstoichiometric hydrates.



KEYWORDS: *paroxetine HCl, solid state, hydrate, stoichiometric, nonstoichiometric*

INTRODUCTION

Polymorphism and solvatomorphism are well studied phenomena within the pharmaceutical arena, with the most widely studied manifestation of the latter being hydrate formation. Indeed, the possible interaction with water during certain processing steps (freeze-drying, spray-drying or wet granulation) as well as contact with atmospheric humidity upon storage renders hydrate formation extremely common.[1,2] Typically, such materials are considered to be stoichiometric, with a precise and defined molecular ratio between the water and host in the crystal lattice, although undefined incorporation is also possible, these being known as nonstoichiometric or variable hydrates.[3,4]

For stoichiometric hydrates, the water may play a crucial role in the stabilization of the molecular network and therefore dehydration may result in a disordered or amorphous state.[5−7] In contrast, nonstoichiometric hydrates may reversibly gain or lose water while retaining the same crystalline structure (isomorphic dehydrates), with the water molecules entering and leaving the crystal lattice in a manner determined by the environmental RH.[8] This therefore presents issues for the formulator in that differentiation from simple surface adsorption may be challenging, with the well-known indicators of hydrate formation (e.g. powder X-ray diffraction and thermogravimetric analysis) not yielding the same unequivocal identification of lattice alteration as is usual for stoichiometric hydrates. On this basis the possible existence of nonstoichiometric hydrates is not fully appreciated within the pharmaceutical field, with an accompanying lack of the development of characterization tools for their identification and structural elucidation.

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Hydrates can also be classified based on their crystal structures.[9] In class I, or isolated site hydrates, water has a well-defined isolated location, and therefore hydrates of this class are often stoichiometric. In class II, channel or planar hydrates, water is packed inside the crystalline structure so as to form continuous channels or planes. Class III refers to ion coordinated hydrates, in which water molecules are coordinated to metal ions. Class II hydrates are, in general, nonstoichiometric, while Class III hydrates can be either stoichiometric or nonstoichiometric.

Differentiation between hydrate formation and nonspecific hygroscopicity may be challenging. Water can interact with crystalline materials in several ways (adsorption, absorption, deliquescence and hydrate formation), all of which may have a large impact on the solid state properties, processing and handling of drugs.[10] This difficulty is exemplified by the study of Reutzel and Russell[11] on the muscarinic agonist, LY297802 tartrate. The considerable hygroscopicity for this material was found to be, in fact, due to nonstoichiometric hydrate formation whereby, rather than simple surface sorption, water migrates between hydrogen-bonding sites located in crystal lattice channels.

In this work, we investigated the hydration behavior of paroxetine HCl. Paroxetine HCl is a potent and selective inhibitor of the neuronal reuptake of serotonin (5-hydroxytryptamine, 5-HT) and is currently clinically approved for the treatment of depression, social phobia, obsessive-compulsive disorder, post-traumatic stress and general anxiety.[12] The structure of the hydrochloride salt of paroxetine ($C_{19}H_{21}ClFNO_3$) is given in Figure 1. This molecule is of particular interest due to the confusion

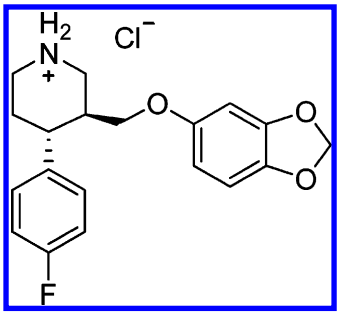

Figure 1. Chemical structure of paroxetine HCl.

associated with its physical forms, with three nomenclature systems being used to describe them. Initially, Barnes et al.[13] described in their patent the preparation of paroxetine HCl hemihydrate and, in Example 8 of the same document, the preparation of paroxetine HCl anhydrate. Less than one year later, in 1987, Buxton et al.[14] further investigated the above forms and named the hemihydrate as form I and the anhydrate as form II. Form I is described as a nonhygroscopic hemihydrate with a melting point (mp) of 143 °C, which represents the most stable form and is currently included in commercially available pharmaceutical formulations, while form II is described as a hygroscopic anhydrate with a mp of 118 °C with a moisture content controlled by environmental humidity. More recently, Ward et al.[15] described the preparation of three new anhydrate forms of paroxetine HCl, named as A, B and C. They suggest that paroxetine HCl form A (mp 123–125 °C) can be distinguished from the anhydrate form II reported by Buxton et al.[14] by the crystal shape. However, the data available (infrared and thermal analyses) suggest that in terms of internal structure these two forms (A and II) are probably, but not definitely, equivalent. The reported characteristics of the other two forms, B (mp at 137 °C) and C (mp at 161 °C), do not comply with those of the form investigated here, and no such transitions were seen in the present study, hence we conclude that these forms do not impinge on our own study.

This therefore leads to an immediate issue of nomenclature, as three classifications are currently in use (anhydrate/hemihydrate, I and II, A, B and C). In this work, we will follow the nomenclature form I (hemihydrate) and II (anhydrate) for the sake of simplicity. However, as will be demonstrated, we go on to challenge the notion of form II being a true anhydrate, hence we avoid the use of this term other than to point out its nominal description so as to avoid confusion.

In this investigation we use a combination of thermal analysis, variable humidity powder XRD with associated modeling, attenuated reflection FTIR and dynamic water sorption studies to examine the interplay between the form II and hydrated forms, with a view to clarifying the physical structures and transformation processes associated with exposure of form II to water.

EXPERIMENTAL SECTION

Materials. Paroxetine HCl form II was purchased from Huahai Pharmaceuticals (China) and was used as received as well as predried over phosphorus pentoxide (P_2O_5), Alfa Aesar (U.K.), as stated. The correspondence to the nominally anhydrous form was confirmed using thermal and spectroscopic analysis, as outlined below.

Methods. *Thermal Analysis.* Standard differential scanning calorimetry (DSC, Q-1000 TA Instruments) was performed at heating rates of 5, 10, 20 and 50 °C/min. Modulated temperature DSC (MTDSC, Q-1000 DSC TA Instruments) analyses were performed using a heating rate of 2 °C/min, amplitude ±0.212 °C and a period of 40 s. Scans were carried out within the temperature range 0 °C to170 °C. Pinholed, hermetically sealed and open pans (pinholed pans without lid) were used as stated. Nitrogen purge was used for all the DSC experiments with a flow rate of 50 mL/min. Calibration was performed using *n*-octadecane, benzoic acid, indium and tin. Thermogravimetric (TGA, Hi-Res TGA 2950 TA Instruments) analysis was performed in open aluminum pans with a heating rate of 10 °C/min, from 30 to 300 °C.

Karl Fischer Titration (KFT). Karl Fischer Titrations (KFT, Mettler Toledo DL38) were carried out by accurately weighing between 40 and 41 mg of bulk and predried samples. The bulk sample was kept under ambient conditions, and the dried sample was stored at P_2O_5 for seven days prior to testing. The reagents used were Titrant 5 and Hydranal solvent.

Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) Spectroscopy. The infrared spectra of the samples were collected using a Brüker Optics IFS60/6 spectrometer, with 64 scans being acquired for each sample from 4000 cm^{-1} to 550 cm^{-1} with a resolution of 2 cm^{-1}. Variable temperature ATR-FTIR experiments were carried out by connecting a temperature controller to the diamond ATR top plate. A constant heating rate of 2 °C/min was employed.

Dynamic Vapor Sorption (DVS). Dynamic vapor sorption (DVS, TGA Q5000 TA Instruments) experiments were performed at a constant temperature set at 30 °C. The sample previously stored over P_2O_5 for seven days was equilibrated at 0% RH for two hours inside the DVS chamber before starting the sorption/desorption experiments. The starting relative humidity was 10% RH, which was first increased to 30% RH, and then at 10% RH/step to 90% RH. Desorption was studied by reducing the relative humidity from 90% to 25% RH, then to 15%, 5% and 1% RH. At each target RH, the isothermal sorption procedure

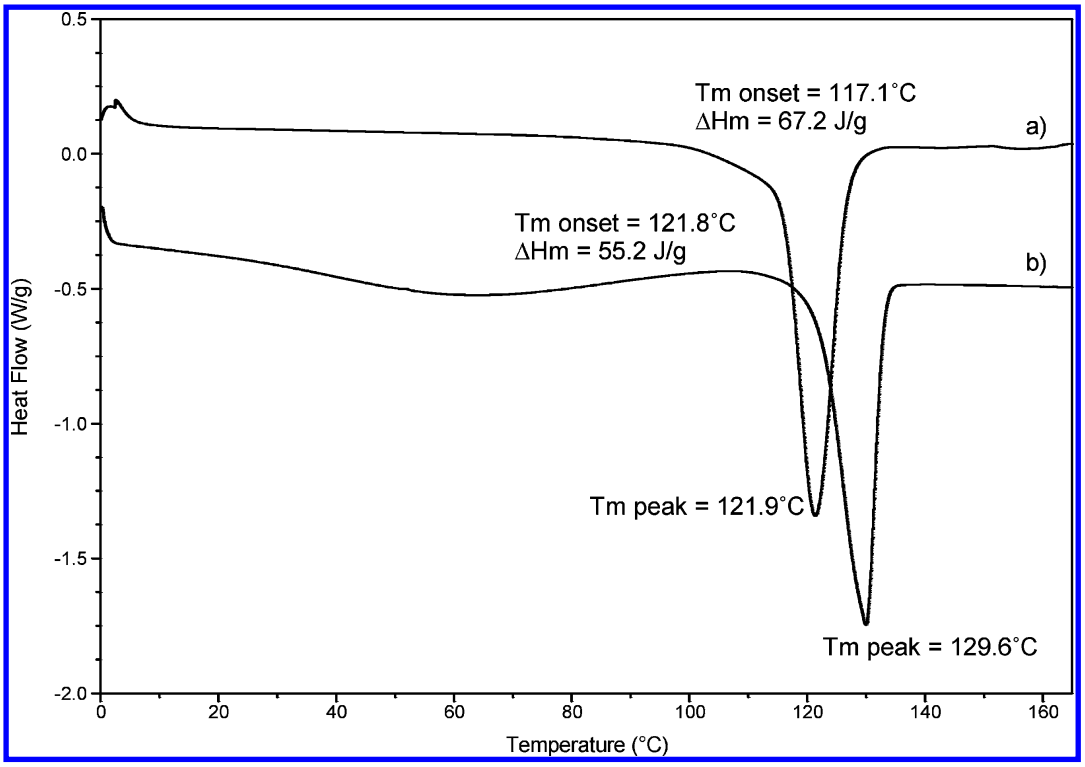

Figure 2. Standard DSC analyses (10 °C/min) of paroxetine HCl form II in pinhole pans (a) and open pans (b).

was performed for 40 min. Note that, for relative humidities higher than 10%, no mass change was detected after 40 min in any of the steps.

Variable Humidity X-ray Power Diffraction (VH-XRPD). X-ray powder diffraction (XRPD, Philips XPERT Pro) patterns were collected from scans in the range of 2θ from 5.0° to 50.0° with a step size of 0.0010°, at different RH using a relative humidity generator (RH200). The temperature was controlled by using a temperature control unit (TUC 50, Anton Paar). The RH steps and equilibration time were the same as in the DVS experiment. Unit cell parameters were determined by Pawley refinement of the collected patterns using the program TOPAS-Academic.[16] A specimen displacement parameter was included in the refinement to account for the macroscopic expansion or displacement of the sample in response to environmental changes. The value of the displacement parameter varied between 0.63 and 0.67 mm, which would, in itself, cause very little change in the powder pattern (~0.02° shift of peak positions around $2\theta = 20°$).

Computational Modeling of Crystal Structures. Lattice energy minimizations were performed using the rational function optimization method implemented in the GULP package.[17] The force field used comprised the Dreiding parameter set[18] and AM1-BCC charges.[19] The initial ($P2_1$) symmetry of the crystal structure was maintained during the minimizations. The starting configurations were generated from the experimental structure by assuming either full or zero occupancy for the water molecule.

RESULTS

Differential Scanning Calorimetry. We initially explored the thermal behavior of paroxetine HCl form II using standard and modulated DSC. Three types of pans, pinholed, hermetic and open, were used to examine the influence of water on the thermal behavior while modulated measurements were used in order to aid identification of any nonobvious thermal events that may arise such as glass transitions. Figure 2 presents data for paroxetine HCl form II at 10 °C/min in pinholed and open pans. A single endotherm melting point was detected in both cases with an onset temperature of 117.1 ± 0.7 °C in pinholed and 121.8 ± 0.3 °C in open pans. This is in good agreement with reported values from Buxton et al.[14] (118.3 °C) for form II and also from Ward et al.[15] (123−125 °C) for form A. The "bowing" endotherm seen for the open pan systems is associated with water loss which will be expected to occur over a relatively narrow temperature range, and hence be thermally visible, due to the unrestricted nature of the water evaporation on heating for an anhydrous form; we will revisit this notion later in the paper.

It is apparent that the melting event of paroxetine HCl form II is influenced by the experimental conditions, with a difference of almost 5 °C in the onset melting temperature seen using different pan types. This indicates the inherent difficulties in establishing the "correct" value for the melting point of this form; again we will suggest an explanation for this difference later in the paper.

When using hermetically sealed pans, a distinct thermal profile was obtained (Figure 3). The melting response was detected at 111.8 ± 0.6 °C, followed by an exotherm (which we suggest is associated with recrystallization, T_{rec}) at 118.1 ± 0.6 °C and finally an endotherm at 139.8 ± 0.5 °C corresponding to the reported melting of the form I, as per previous studies.[13] It is therefore reasonable to conclude that form II is forming the hydrate form on heating, using the associated water to form the stoichiometric hydrate. We believe this to be a highly unusual behavior pattern, and we are not aware of previous reports to this effect.

Furthermore, when using higher heating rates the recrystallization signal disappeared and, at 50 °C/min, no melting of the form I was detected (Figure 4). The melting peak of form II showed a broader appearance, as is usual when increasing heating rate due to thermal lag effects. However we also suggest that the

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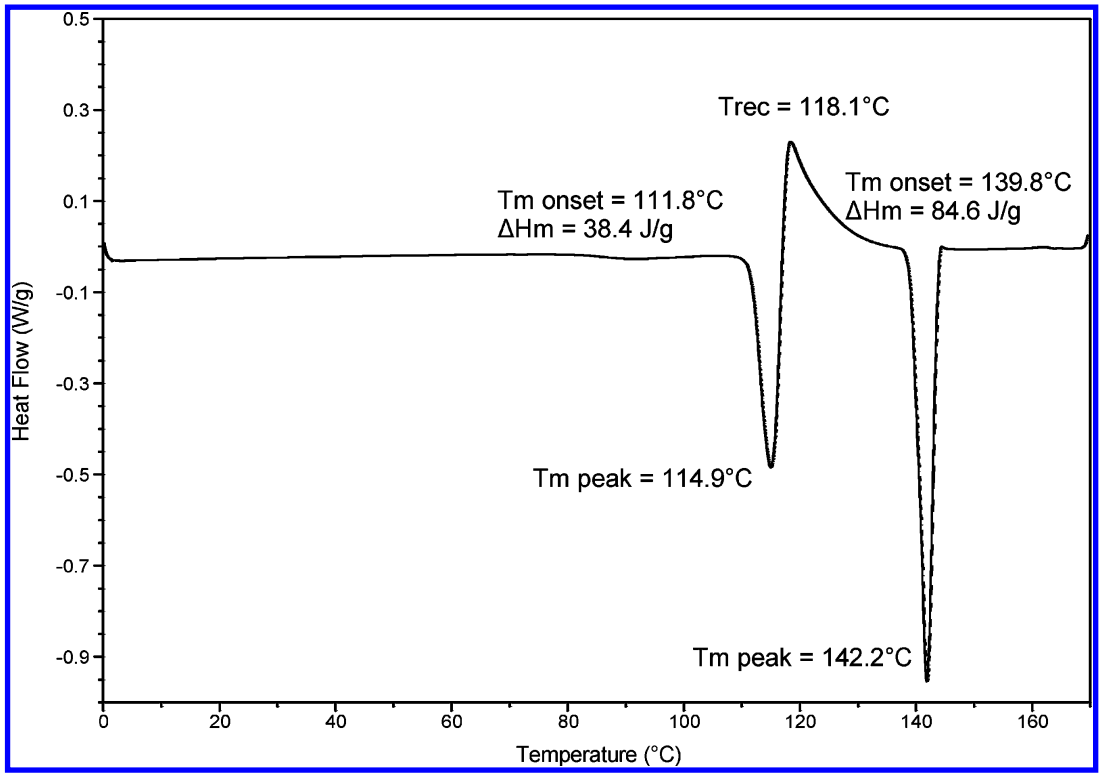

Figure 3. MTDSC analysis (total heat flow, 2 °C/min) of paroxetine HCl form II in hermetically sealed pans.

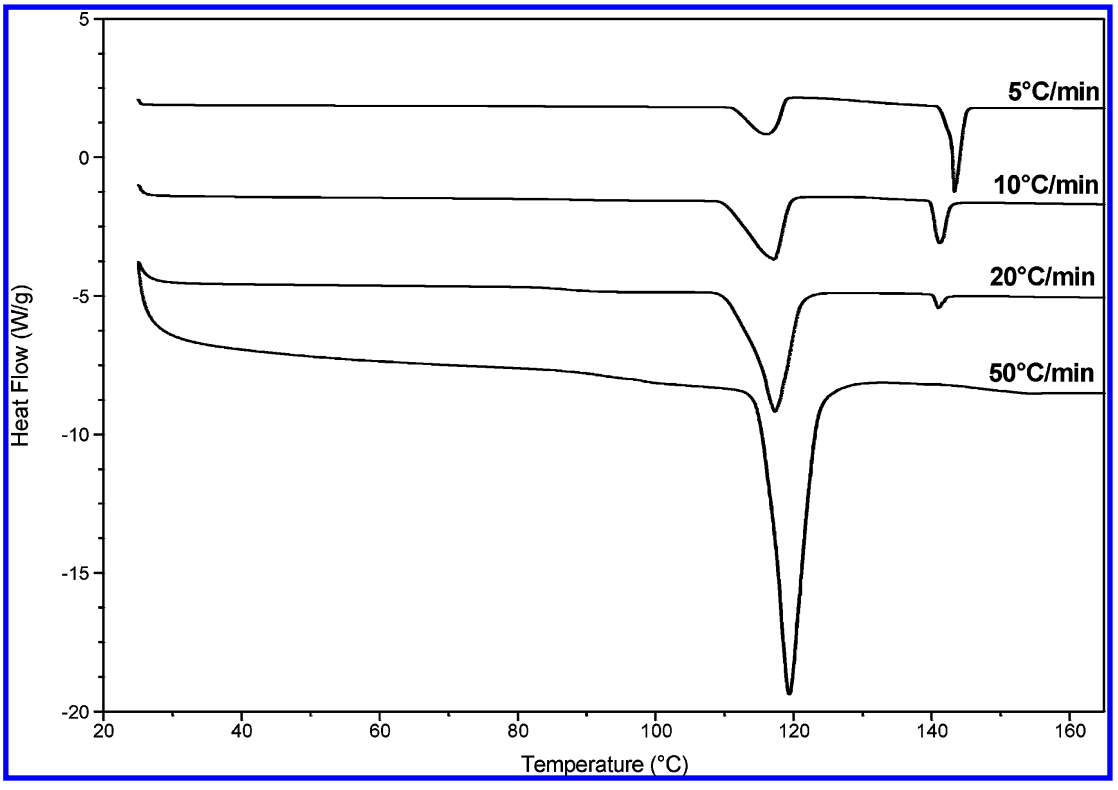

Figure 4. Influence of the heating rate on the transformation between forms II and I of paroxetine HCl. Standard DSC runs at 5, 10, 20 and 50 °C/min (top to bottom) were performed in hermetically sealed pans.

recrystallization to form I is kinetically hindered and hence does not take place at higher heating rates. Furthermore, samples run in hermetically sealed pans at 2 °C/min but predried over P_2O_5 also showed no evidence of transformation to form I, further supporting the hypothesis that the conversion involved sorbed water becoming stoichiometrically bound on heating.

Thermogravimetric Analysis. Given the role of sorbed water (using the term loosely) that has been identified above,

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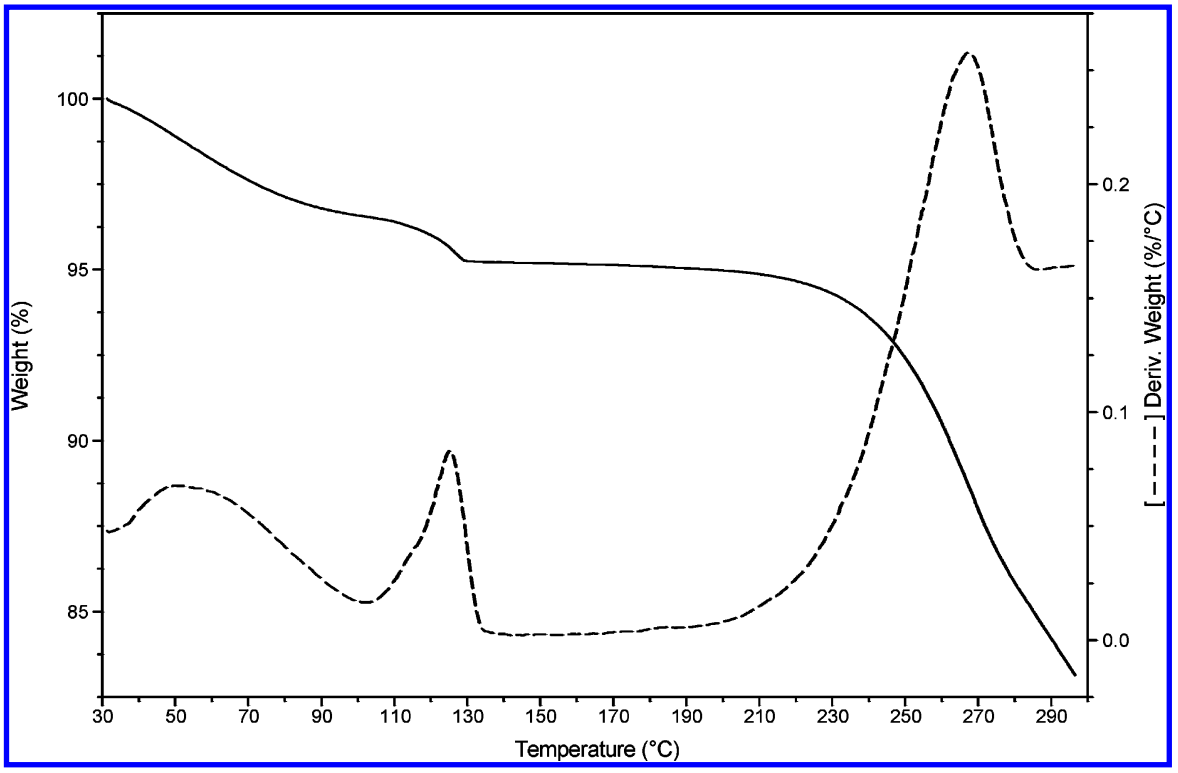

Figure 5. TGA curve of paroxetine HCl form II, showing the weight loss (—) and associated derivative loss (- - -) curves.

it was clearly essential to have some measurements of both the quantity and binding characteristics of the water present. The TGA signal (Figure 5) showed a water weight loss process completed by approximately 140 °C. A continuous weight loss was observed from the starting temperature until approximately 90 °C, and after that an evident sharper drop in the weight was noticed, between 100 and 130 °C, which corresponds, in total, to a weight loss of 4.45 ± 0.26%. The last and higher drop in the weight around 260 °C is due to the decomposition of the sample. These processes are shown in the derivative signal for clarity.

In general, when a stoichiometric hydrate is present, the water molecules are incorporated in the crystal lattice and the water loss signal shows a sharp discontinuity, typically between 80 and 140 °C. Alternatively, when the water molecules are simply present on the crystal surfaces (adsorbed water), the water loss signal tends to be broader and appears over a wider and lower temperature range, frequently between 60 and 90 °C.[20] The behavior shown here appears to demonstrate a steady water loss, typically associated with sorbed water, followed by a sharper loss corresponding to the melting of form II, indicating release of any remaining water on breakdown of the crystal structure.

On the other hand, the TGA trace of form I (data not shown) did not show a continuous weight loss, but rather showed a sharp drop in weight in a narrow temperature range between 100 and 125 °C. This is in good agreement with the typical dehydration behavior of stoichiometric hydrates. The weight loss at this temperature corresponds to 2.60 ± 0.15% (0.55 ± 0.02 mol of water per mole of drug), which matches well the designation of form I as a hemihydrate.

Karl Fischer Titration. The water content of untreated and dried samples was determined by Karl Fischer titrimetry under ambient humidity (53% RH) and temperature (25.5 °C). The untreated sample was found to have a water content of 3.83 ± 0.05% w/w, which corresponds to 0.80 ± 0.01 mol of water per mol of paroxetine HCl. The water content of the sample previously dried over P_2O_5 for seven days was calculated as 1.65 ± 0.17% w/w, 0.33 ± 0.03 mol of water per mol of paroxetine HCl. Each determination was repeated five times.

These results are surprising in that they are high for such a relatively nonpolar low molecular weight material; indeed, the amount of water in the dry sample is quite high for a material stored for seven days at 0% RH. However, as the measurements were performed under atmospheric conditions, the time between weighing and measurement may have been sufficient for some moisture sorption. Even so, this implies quite considerable hygroscopicity. This may be a result of high surface adsorption or, alternatively, molecular internalization of water, i.e., nonstoichiometric hydrate formation. On this basis a series of spectroscopic and water sorption studies were performed in order to investigate the possibility of such hydrate formation.

Attenuated Total Reflection Fourier Transformer Infrared Spectroscopy. Infrared spectroscopy is a potentially useful tool to distinguish between the two forms of paroxetine HCl (form II and form I) by analyzing the spectra between 3700 and 3200 cm^{-1} corresponding to the OH stretching region. This area is also useful to monitor temperature-dependent transitions between those forms. The spectrum of form II, as shown in Figure 6, has two main bands at 3630 cm^{-1} and 3403 cm^{-1}, which can be assigned to stretching vibrations involving weakly and strongly H-bonded water H atoms, respectively. If paroxetine HCl form II was a true anhydrate, it should not show any OH vibration at high wavenumbers, as no water would be present in the crystal lattice. In contrast, form I shows a doublet band at 3399 and 3334 cm^{-1}, which correspond to two strong H-bonds in different chemical environments.

Some misinterpretations can be easily made in this region due to the presence of a secondary amine, as we can see from Figure 1. The NH stretching in secondary amines usually appears as a

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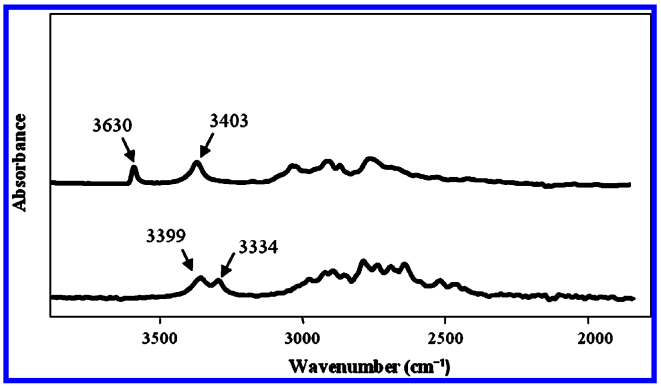

Figure 6. FTIR-ATR spectrum of paroxetine HCl form II (top) and form I form (bottom).

single band in the range between 3380 and 3205 cm^{-1}. However the HCl salt formation can cause a considerable attenuation of the normal NH stretching band and displace it toward lower frequencies (2760 and 2690 cm^{-1}).[21,22] Owing to the complexity of the spectra in this region, especially due to the overlapping of the aromatic ring vibrations, a clear and precise assignment of the NH band is hard to make.

The assignment of the OH stretching bands presented in this section for paroxetine HCl forms I and II is consistent with their respective structural models and H-bonding. Since these will be described in more detail in the molecular modeling section, only a brief discussion, relevant to differences in the ATR-FTIR spectra, will be presented here. The water molecules in form II can establish two different types of hydrogen bonding: a very weak one to an oxygen from the dioxole ring, which appears as a free OH band with a sharp appearance at a high wavenumber (3630 cm^{-1}); and a strong one to a chloride ion, which appears as a broad band at a lower wavenumber (3403 cm^{-1}), an indication of stronger hydrogen bond formation.[23] In form I the water molecules can establish three strong hydrogen bonds. In two of them the water molecules donate their hydrogen atoms to chloride ions, giving the doublet band observed at 3399 and 3334 cm^{-1}. The third hydrogen bond is formed with the protonated ammonium nitrogen as the donor and water as the acceptor.

By using variable temperature ATR-FTIR spectroscopy with a constant heating rate of 2 °C/min, it was possible to observe the solvatomorphic transformation between form II and form I (Figure 7). It should be noted that the sample holder is such that, while the sample is not sealed hermetically, water movement is nevertheless partially restricted, rendering these results only partially comparable to the DSC data. Nevertheless, the data set provides a useful corroborative perspective by which the transformation may be further studied.

Initially, the spectra show the response associated with form II (from top to bottom). However, when the temperature reached 50 °C, a small shoulder started to appear in the region of the hydrogen-bonded OH (3334 cm^{-1}) and the intensity of the free OH stretching band started to decrease. These observations, together with the initial description of those bands, suggest that a new intermolecular hydrogen bond between the OH group from the water molecules and the chloride ion starts to become established, which results in a split of this band characteristic of form I. Changes in the spectrum can also be observed in the region at 2500−3000 cm^{-1}.

Overall, Figure 7 not only clearly shows transformation between form II and form I but also indicates that, at temperatures as low as 50 °C, the interaction between the drug and water is specific and intrinsic to the crystalline lattice structure, rather than being a simple surface adsorption process. While the highest temperatures clearly indicate form I formation, the intermediate temperatures indicate a mixture between form II and form I, which again is supportive of the suggestion of nonstoichiometric hydrate formation.

Dynamic Vapor Sorption. The hydration behavior of paroxetine HCl form II under defined humidity and temperature conditions was investigated. Pretreatment of the sample included drying over P_2O_5 for seven days, plus an additional drying step of two hours at 30 °C and 0% RH inside the DVS chamber to ensure that any residual water was dried off prior to starting, as confirmed by the achievement of a constant weight.

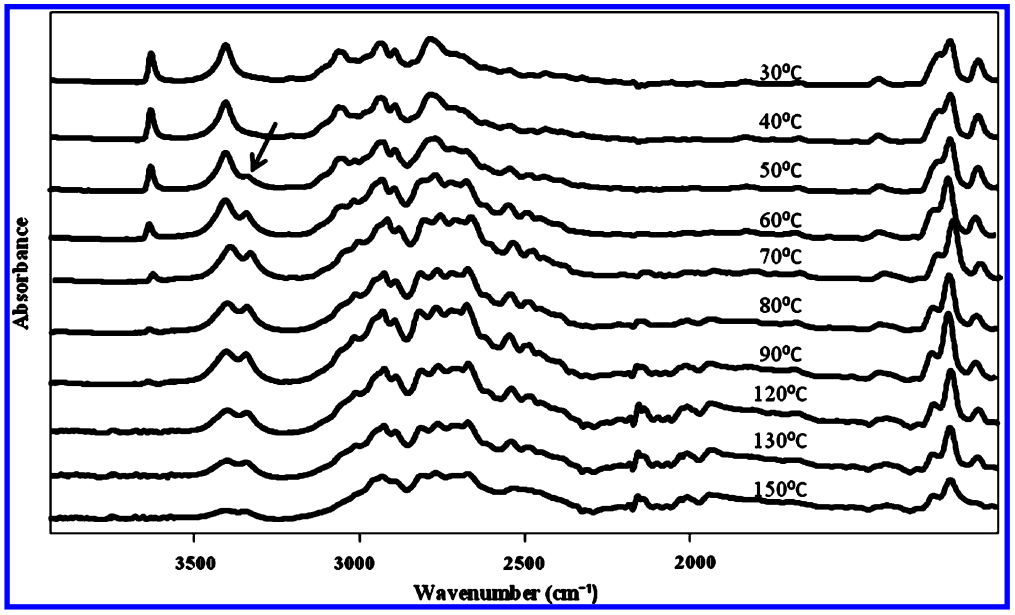

Figure 7. Variable temperature ATR-FTIR spectra of paroxetine HCl form II, measured using a constant heating rate of 2 °C/min.

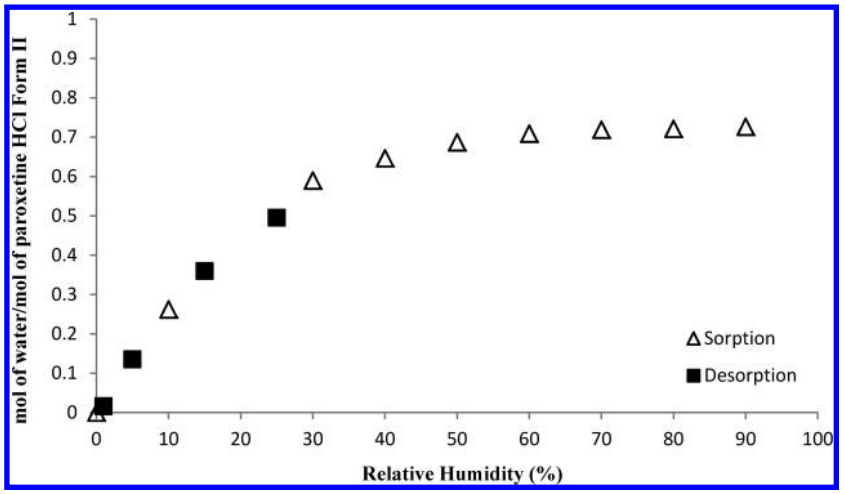

Figure 8. Dynamic vapor sorption data for paroxetine HCl form II. Sorption and desorption cycles are superimposable.

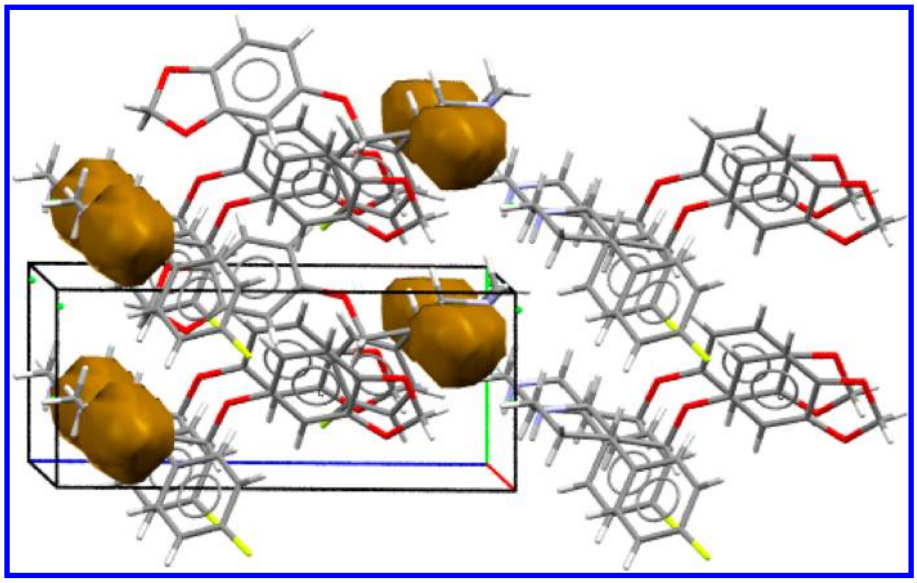

Figure 9. Crystal structure of form II with the water-containing voids highlighted in brown. Generated from data presented in ref 28.

Figure 8 shows the DVS data for paroxetine HCl form II. During the sorption cycle a weight gain of 3.53% was observed from 10 to 90% RH, which corresponds to 0.73 mol of water per mol of drug, with 81% of the total water uptake taking place between 10 and 30% RH. From 40 to 90% RH the change in weight is significantly smaller.

The high absolute amounts of water gained, together with the reversibility of the uptake and desorption, again support the existence of a nonstoichiometric hydrate. More specifically, the reversibility of the sorption process and the relatively rapid time scales over which the process takes place are, in general, properties of channel hydrates. Several nonstoichiometric hydrates have been identified to have such water channels at a molecular level,[24−26] which enables the water molecules to move easily both within the structure and between the solid and its environment without causing any structural disruption. On this basis it was considered essential to examine the X-ray powder diffraction profile as a function of both temperature and humidity in order to elucidate whether paroxetine HCl form II shows similar structural characteristics.

Variable Humidity X-ray Powder Diffraction (VH-XRPD). The crystal structures of two paroxetine HCl hydrate forms have been determined previously: form I[27] and a form with the composition paroxetine HCl·0.8H_2O.[28] The latter structure has been submitted to the Cambridge Structural Database[29] as a private communication (reference code EHOXEE), so no detailed information about the origin or preparation of the sample is available. However, the powder diffraction pattern calculated for paroxetine HCl·0.8H_2O matched the experimental diffraction pattern measured for form II, confirming that they represent the same crystal structure. While the drug:water ratio of 1:0.8 suggests a nonstoichiometric hydrate, the water molecules of this form II are located in isolated voids (Figure 9), an observation which is usually associated with stable stoichiometric hydrates. We also note that this ratio of water to drug is very similar to the saturation value found from our own DVS studies, hence we conclude that the structure given in ref 28 represents the equivalent of a hydrated form of paroxetine HCl but, if our hypothesis is correct, that form is in fact a nonstoichiometric hydrate.

To establish the nature of form II, variable humidity powder X-ray experiments were performed. If form II is a variable hydrate, then the crystal structure should change continuously with changing RH. If form II is not a variable hydrate and the gradual change of mass seen in the DVS experiments is caused by

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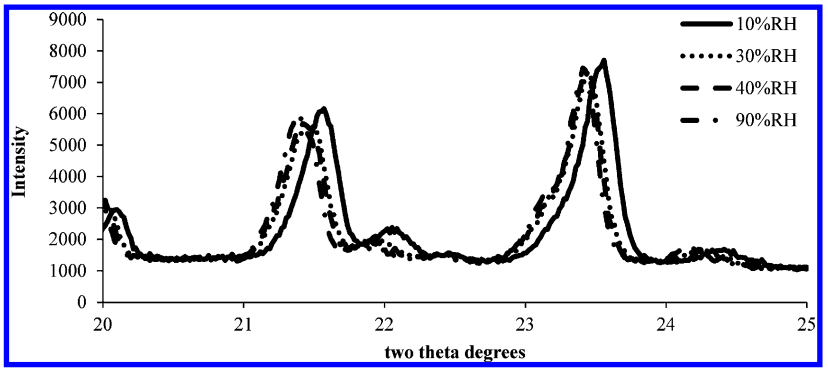

Figure 10. Shifts in the diffractogram peaks upon increasing RH. Only a part of the full XRPD diffractogram (5.0 to 50.0°) is shown to make the peak shifts visible.

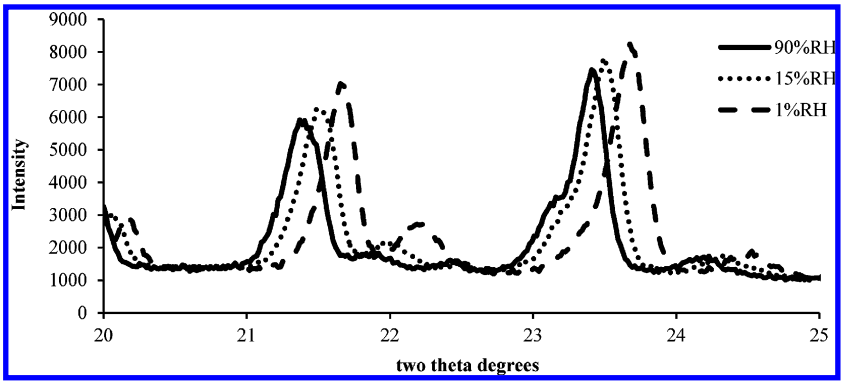

Figure 11. XRPD patterns of paroxetine HCl form II during desorption of water.

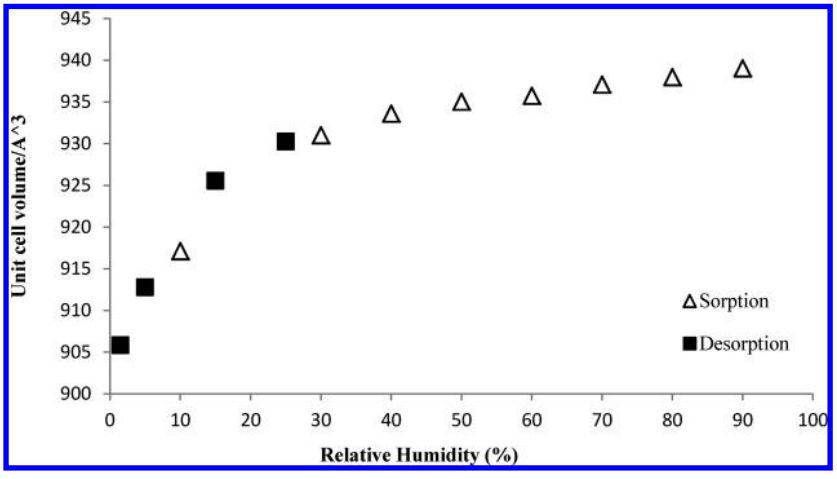

Figure 12. Changes in the unit cell volume of paroxetine HCl form II according to variation in RH.

the adsorption of water on the surface, the powder diffraction pattern should remain the same.

The results showed that the peak positions shifted in response to changes in RH (Figures 10 and 11). In accordance with the DVS results, most of the change occurs at low RH (below 30%), after which the peak shifts are very small. No appearance/disappearance of peaks was observed in the 1−90% RH range, suggesting that humidity alone is insufficient to induce transformation between form II and form I; however changes in humidity are capable of causing changes in the lattice spacings, indicating that the lattice is expanding to allow entry of the water.

The peak shifts indicate changes in the dimensions of the unit cell, namely, expansion upon sorption and contraction during desorption (Figure 12). The cell volumes determined during sorption and desorption fall on the same trend line, demonstrating that the transformation is reversible with no apparent hysteresis. The remarkable similarity between the unit cell volume vs % RH (Figure 12) and the mass vs % RH (Figure 8) curves confirms that vapor sorption occurs predominantly by incorporating water molecules into the crystal structure, i.e., that the "anhydrate" form II is in fact a variable hydrate.

The gradual peak shifts in the XRPD pattern are again characteristic of nonstoichiometric channel hydrates (e.g., risedronate,[30] cefazolin and cromolyn sodium[24]), where water molecules can move in (sorption) and out (desorption) of the crystal while its basic structure remains the same. As a typical example, the crystal structure of cromolyn sodium[31,32] contains wide channels, which

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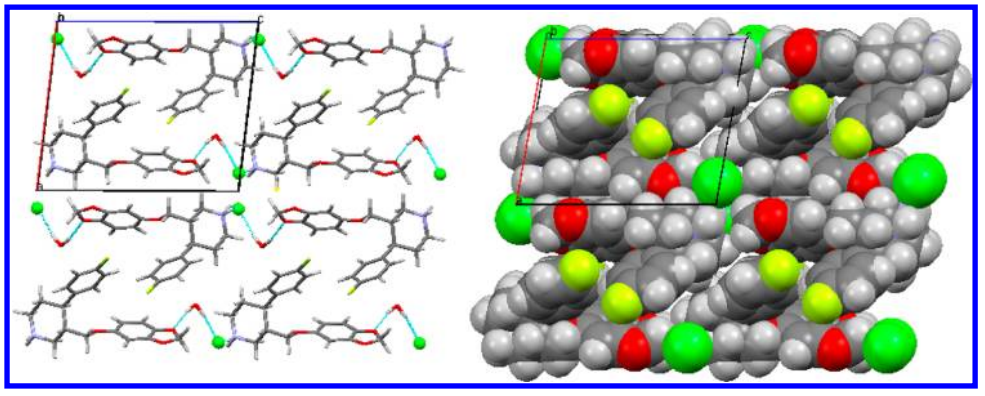

Figure 13. Comparison of the hydrate (left) and anhydrate (right) models of form II. The anhydrate is presented as a space-filling model to show the lack of unoccupied space in the structure.

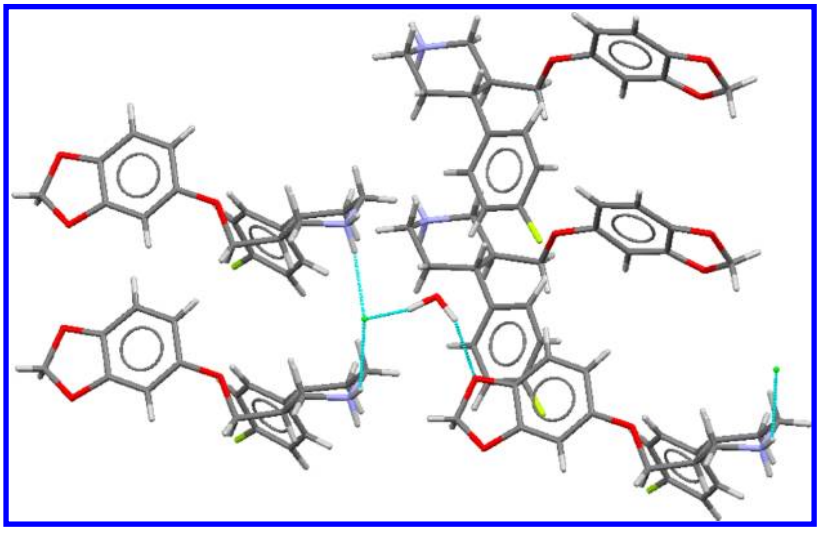

Figure 14. Hydrogen-bonding environment of the water molecule in paroxetine HCl form II.

readily explains why water can move within the lattice without disrupting it.

However, in paroxetine HCl form II the water molecules are located in small voids/pockets instead of channels, so dehydration without disruption is unexpected. The only other example of a variable hydrate with no continuous solvent channels and with an isomorphic desolvate known to us is the "monohydrate" form of vitamin B_1.[33] It has been suggested that dehydration/hydration of this material occurs through a cooperative deformation mechanism, which allows retention of structural information.[34,35]

A unique feature of paroxetine HCl form II is that it reaches equilibrium at each RH within minutes. Such a fast equilibration is more characteristic of surface water than of hydrates, which explains why this material is currently believed to be a hygroscopic anhydrate form.

Crystal Structure Models. The experimental crystal structure of form II is incomplete, because the H atom positions of the water molecule have not been determined. The water O atom appears to be involved in an extremely short CH···O contact ($d_{H\cdots O}$ = 2.26 Å), which is probably an experimental error arising from the high uncertainty with which the water O coordinates could be determined from powder diffraction data. To obtain a more detailed description of the structure, models of both a monohydrate and an isostructural dehydrate were generated computationally from the experimental structure. In the initial configuration of the monohydrate model, one of the missing H atoms was placed to point toward a nearby chloride ion, which is well within H-bonding distance of the water molecule ($d_{O\cdots Cl}$ = 3.14 Å in the experimental structure). The other water H atom was pointing in an arbitrary direction enclosing a bond angle of 109.5° with the first one. The initial configuration for the anhydrate was generated by simply removing the water O atom from the experimental structure. The final computational models were then obtained by geometry optimization starting from these initial configurations. The unit cell volumes for the fully hydrated and the anhydrate models are 948 $Å^3$ and 915 $Å^3$, which are in good agreement with the highest and lowest unit cell volumes found in the VH-XRPD experiments, 939 $Å^3$ and 905 $Å^3$, respectively.

As expected, the two structures remain highly similar both to each other and to the experimental structure (Figure 13). In contrast to most channel hydrates, the dehydrate form does not contain residual voids, i.e. it is nonporous. The fact that such a simple computational protocol gave a nonporous model highlights the possibility of a smooth and continuous transition between the hydrated and dehydrated states of form II, and it is consistent with the experimentally observed retention of the same overall structure even when the RH is reduced to 1%.

In general, the water molecules of nonstoichiometric hydrates are weakly bound and can be removed without significant changes in the rest of the structure. The model of paroxetine HCl

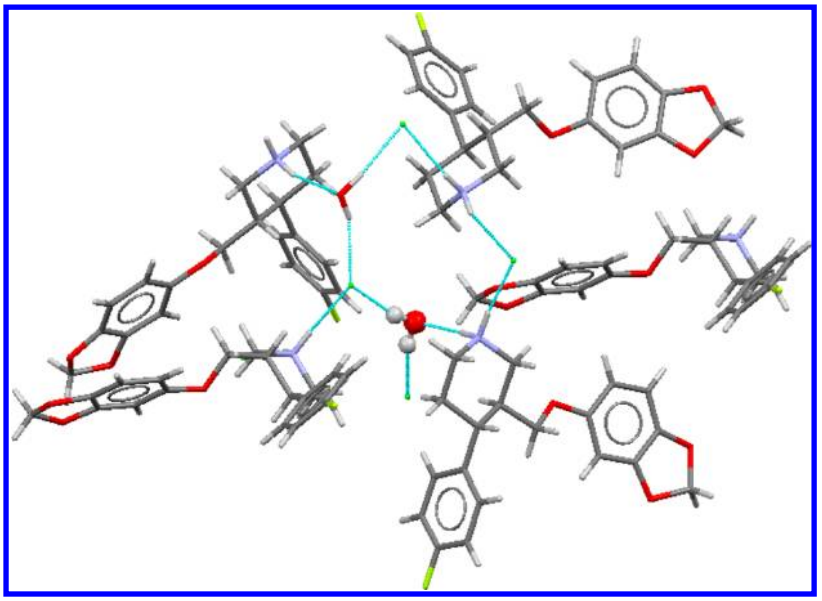

Figure 15. Hydrogen-bonding environment of the water molecule in form I.

form II shows (Figure 14) that each water molecule hydrogen bonds to a chloride ion (strong acceptor) and to an oxygen atom in the dioxole ring of the drug molecule (weak acceptor).

Consequently, removal of a water molecule from form II requires breaking of at least one strong hydrogen bond in addition to some structural rearrangement to allow movement of the water molecule between adjacent cavities. These requirements make the quick hydration/dehydration of form II rather surprising. Note, however, that the water molecules of form I are involved in three strong hydrogen bonds, formed with two chloride ions and with a protonated ammonium nitrogen, respectively, so the higher stability of form I is readily explained (Figure 15).

DISCUSSION

The distinction between strong hygroscopic behavior and hydrate formation is sometimes very opaque and can lead to misinterpretations. In this study, we suggest that the hygroscopic nature of paroxetine HCl has led to incorrect classification of this material as an anhydrate. The evidence for this is as follows. First, the large amount of water content determined by using TGA, KF titration and DVS raises doubts regarding the anhydrate classification of this drug. In general, the water adsorbed on the surface of an API is around 1%, but paroxetine HCl form II has a water uptake more than three times higher than this. The rapid and extensive water uptake into the structure at low RH (≈30%) in itself indicates that paroxetine HCl form II is likely to be a nonstoichiometric hydrate. This is also supported by the thermal analysis (DSC) data that indicated that the sorbed water associated with this form, on heating slowly under hermetic conditions, becomes incorporated into the structure of the drug to generate form I. This is in itself very unusual behavior, but is consistent with the notion of the water being incorporated into the structure rather than simply sorbed onto the surface.

Second, to support the nonstoichiometric hydrate hypothesis, variable humidity XRPD studies were performed. It was observed that, on increasing the RH, shifts in the peak positions of the XRPD diffractogram were evident until 30% RH, which is in accordance with the observations in DVS. During desorption, the shifts in the peaks followed the decrease in the RH. In both cases there were no changes to the crystalline pattern, showing that the water sorption process led to changes in lattice spacing but no fundamental change to the lattice arrangement.

In most recorded cases, this water sorption behavior is characteristic of a specific subgroup of nonstoichiometric hydrates, the channel hydrates, where the existence of connecting pathways allows the smooth departure of the water without any structural deformation. However our analysis of the structure of form II indicates that the water is located not in channels but in small voids and also is not weakly bonded to the crystalline structure, as expected, which makes the hydration/dehydration of this material an uncommon feature. The location of the water within the structure together with the energy supply explains the solvatomorphic transformation observed both in the MTDSC, when hermetic sealed pans were used, and in variable temperature ATR-FTIR experiments.

CONCLUSION

As a conclusion, we suggest that the classification of paroxetine HCl form II should be reviewed, since the designation as an anhydrate form is no longer reliable. We also suggest nonstandard behavior for this nonstoichiometric hydrate in that the water is present not in channels but in pores, rendering the absence of hysteresis on sorption and desorption, along with the change in lattice dimensions, extremely unusual. However, the broader implications of the study lie with the notion that differentiation between a hygroscopic anhydrate and a nonstoichiometric hydrate may be extremely difficult and hence the question naturally arises as to whether such nonstoichiometric systems are more common than is generally appreciated. Such knowledge is of considerable relevance to pharmaceutical performance, in terms of quality control of a system which changes its crystal structure reversibly in different humidity environments but also in terms of physical and possibly chemical stability.

ASSOCIATED CONTENT

Supporting Information

XRPD data for paroxetine HCl forms I and II. TGA profile of paroxetine HCl form I. Unit cell dimensions of paroxetine HCl

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form II. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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