

# An Investigation into the Dehydration Behavior of Paroxetine HCl Form I Using a Combination of Thermal and Diffraction Methods: The Identification and Characterization of a New Anhydrous Form

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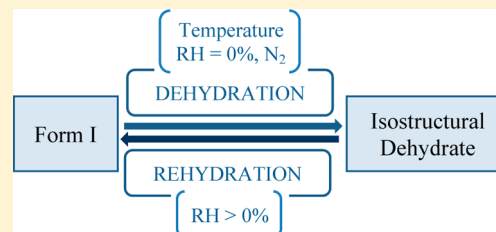
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## S Supporting Information

**ABSTRACT:** Paroxetine HCl can exist as a nonstoichiometric hydrate (Form II) or as a stoichiometric hemihydrate (Form I); the latter is considered to be the stable form and its structure is well-known. However, little work has been performed to investigate its dehydration behavior; hence, the generation of the anhydrous form via dehydration of Form I was investigated. A combination of thermal (differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)) and diffraction (variable-temperature X-ray powder diffraction (VT-XRPD)) techniques was used. Dehydrated Form I was prepared using ultradry conditions, and the resulting product was compared to dehydrated Form II. DSC indicated that the two dehydrated forms of Forms I and II had distinct melting points. TGA experiments allowed the calculation of the activation energy for the dehydration of Form I, which varies between 86 and 114 kJ/mol. Pawley refinement of the VT-XRPD data suggested that Form I dehydrates to an isostructural anhydrate, since the unit cell parameters of this new form were very similar to those of Form I with only a smaller volume as a consequence of dehydration. Comparison with dehydrated Form II indicated that these two forms represent different crystal entities; hence, a new anhydrous form of paroxetine HCl has been identified.



## INTRODUCTION

Hydrates are often the most physically stable form of an active pharmaceutical ingredient (API) under conditions of relative humidity (RH) typically found on storage; hence, their use remains extremely widespread. Nevertheless, their dehydration and rehydration behavior is often complex, with multiple forms possible, which render thorough investigation of such interchanges necessary for both practical and regulatory reasons. The dehydration process occurs when the water activity of the surrounding environment is lower than the water activity in the solid compound.<sup>1</sup> Once the water is removed from the crystal structure packing, a range of structural consequences may occur:<sup>2</sup>

- breakage of the crystal lattice, followed by a rearrangement into a new anhydrous form;<sup>3</sup>
- the crystal structure remains the same after dehydration, forming an isomorphic/isostructural dehydrate;<sup>4–8</sup>
- a partially or totally disordered state, followed by a collapse into an amorphous phase.<sup>9,10</sup>

Isostructural dehydrates (b) are associated with high free energy, which may be reduced by reincorporation of solvent molecules into the lattice, rendering these types of compounds

highly hygroscopic.<sup>11</sup> Dehydration is not always a straightforward process, and a mix of phases can be obtained with a combination of more than one of the aforementioned mechanisms taking place. An example is the case of eprosartan mesylate dihydrate whereby, after losing the first water molecule, the monohydrate dehydrates and collapses into an amorphous state, followed by recrystallization into an anhydrate form of eprosartan mesylate.<sup>12</sup> Another case is the dehydration of trehalose dihydrate whereby the product obtained is highly dependent on the dehydration conditions employed.<sup>13</sup> More specifically, fast dehydration produces an amorphous phase, whereas a slow dehydration produces a crystalline phase ( $\alpha$ -polymorph) of anhydrous trehalose.

Thermal analysis techniques such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) are widely used to evaluate the dehydration behavior and the solid state stability of pharmaceutical hydrates. Experiments can be set isothermally or nonisothermally, and kinetic analysis can be

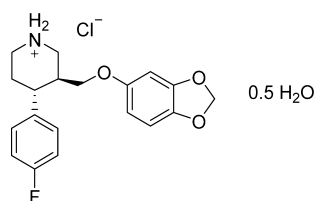
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performed by using either model-fitting or model-free methods. Model-fitting methods involve expressions to which the experimental data (isothermal or nonisothermal) are fitted. Model-fitting methods assume a single value of activation energy ( $E_a$ , the potential energy barrier that must be overcome for the desolvation process to proceed) for the overall reaction process, thereby implying a single reaction mechanism, and do not provide an adequate interpretation of complex kinetic reactions.<sup>14</sup> On the other hand, model-free methods, as the designation implies, are applied without any mechanistic assumptions and, therefore, irrespectively of the underlying reaction process. As a result, they are capable of quantifying  $E_a$  at each conversion fraction,  $\alpha$ , allowing both the detection of multistep processes and the extraction of mechanistic conclusions.<sup>15</sup>

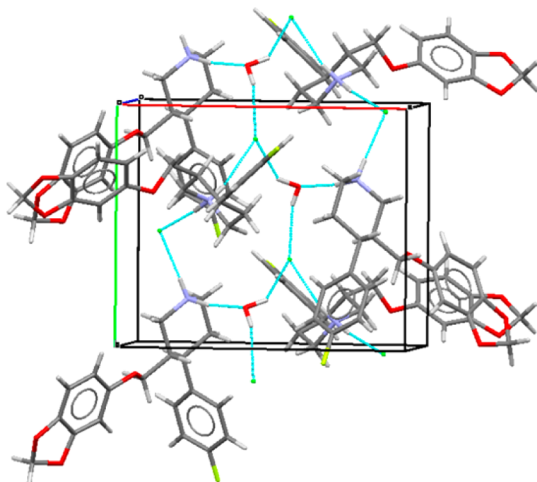
Paroxetine hydrochloride (HCl) Form I is a stoichiometric hydrate with half a mole of water per mole of drug, as shown by its chemical structure in Figure 1.



**Figure 1.** Chemical structure of paroxetine HCl Form I.

Barnes et al.<sup>16</sup> reported the preparation of Form I and described this form as being extremely stable, with the removal of the water from the crystalline structure being possible under extreme desiccant conditions, with a quick rehydration to the hemihydrate form.

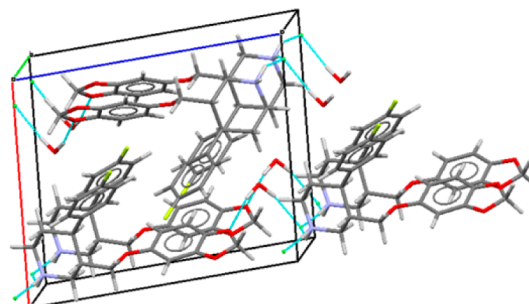
Though the crystal structure of paroxetine HCl Form I is now well-known,<sup>17</sup> an important gap in the understanding of this form is related to its dehydration behavior.<sup>18</sup> The water molecules in Form I are involved in three strong hydrogen bonds, formed with two chloride ions and with a protonated ammonium nitrogen, respectively, explaining the observed stability of Form I (Figure 2).<sup>7,17</sup> The overall hydrogen bond network comprises extended ribbons along the monoclinic  $b$  axis. Adjacent ribbons are separated by the hydrophobic rings



**Figure 2.** Crystal structure of paroxetine HCl Form I.

of the molecules, thereby forming hydrophilic “channels” across the structure. Note, however, that there are no continuous water channels in the structure, which would allow the escape of the water molecules without a structural rearrangement.

Paroxetine HCl can also exist in Form II, which we recently identified as being a nonstoichiometric hydrate (Figure 3).<sup>7,19</sup>



**Figure 3.** Crystal structure of paroxetine HCl Form II.

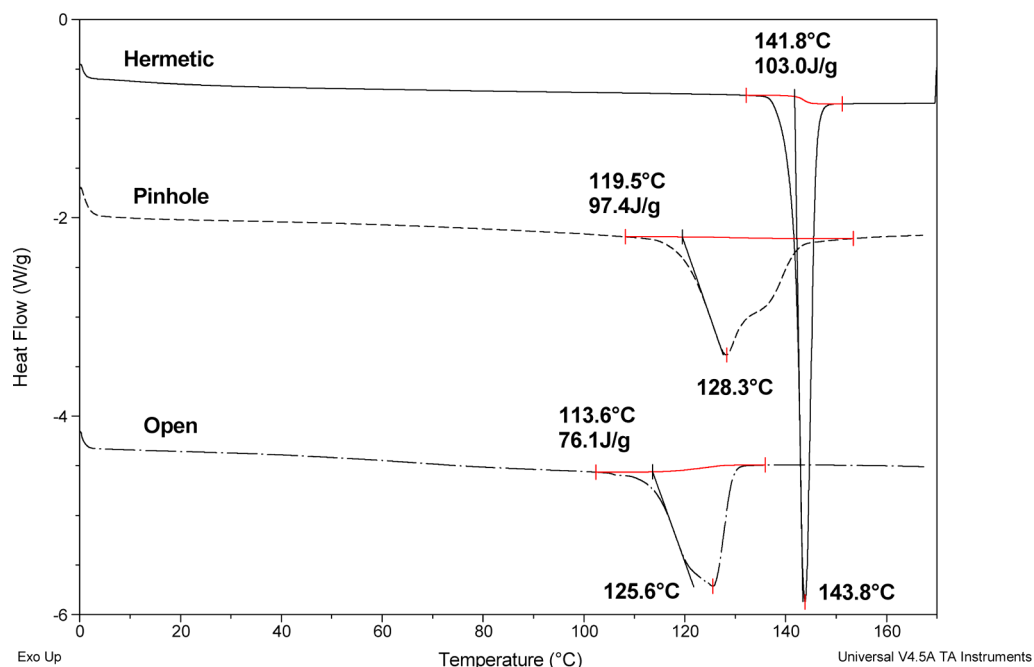
In this structure, the water molecules form only one strong hydrogen bond with a chloride ion and a weak bond with a dioxole oxygen atom. Although the water molecules do not form continuous channels, only weak van der Waals interactions need to be broken to create an opening between adjacent water sites. Accordingly, Form II retains the same crystal structure when dehydrated, undergoing gradual expansion and contraction on exposure to different water activity conditions.

In an effort to better understand the interplay between hydrated and anhydrous forms of paroxetine HCl, a thorough investigation into the dehydration behavior of Form I was carried out using a combination of thermoanalytical techniques (standard differential scanning calorimetry (DSC), modulated temperature DSC (MTDSC), and thermogravimetric analysis (TGA)) and high-resolution variable-temperature X-ray powder diffraction (VT-XRPD). The water content of Form I was determined by Karl Fischer titrimetry (KFT), and the purity of the sample obtained after the dehydration of Form I was determined using high-performance liquid chromatography (HPLC). Additionally, the  $E_a$  needed to dehydrate Form I was calculated using nonisothermal model-free (Ozawa–Flynn–Wall) approaches. Our intention is to examine whether dehydration from two significantly distinct hydrate forms leads to the same anhydrate for this material. This question is particularly pertinent given the unusual nature of the nonstoichiometric Form II and, as will be shown, the very unstable nature of the Form I anhydrate; hence, little precedent exists to determine whether the Form I (hemihydrate) will yield the same dehydrated form.

## EXPERIMENTAL SECTION

**Materials.** Paroxetine HCl Form I (purity of 99.5%) was purchased from Afine (China) and was used as received or after being kept over phosphorus pentoxide ( $P_2O_5$ ), Alfa Aesar (U.K.), or in a static oven, as stated.

**Methods.** *Thermal Analysis.* Standard differential scanning calorimetry (DSC, Q2000 TA Instruments, USA) analysis was performed at heating rates of 2, 5, 10, 20, and 50 °C/min. Modulated temperature DSC (MTDSC, Q2000 TA Instruments, USA) analysis was conducted using a heating rate of 2 °C/min, an amplitude of  $\pm 0.318$  °C, and a period of 60 s. The particle size of Form I was controlled, and a size fraction of 63–106  $\mu\text{m}$  was used. Scans were carried out within the temperature range 0–170 °C. Pinhole,



**Figure 4.** DSC traces of paroxetine HCl Form I at 10 °C/min in hermetic, pinhole, and open pans.

hermetically sealed, and open pans (pinhole 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 analysis (TGA, Q5000 TA Instruments, USA) was performed in aluminum open pans by weighing approximately 5 mg of Form I with a controlled particle size between 63 and 106  $\mu\text{m}$ . Nitrogen purge gas at a constant rate of 25 mL/min was maintained during each run. Nonisothermal experiments were performed at heating rates of 1, 2, 3, 4, and 5 °C/min from 30 °C until 300 °C. Isothermal studies were carried out at 75, 80, 85, 90, and 95 °C with Form I having been rapidly heated to the set temperature at 50 °C/min and kept isothermal until a constant weight change was achieved.

Isothermal and nonisothermal data were used to calculate the conversion fraction ( $\alpha$ ) as a function of time ( $\alpha_t$ ) or temperature ( $\alpha_T$ ), as shown by eqs 1 and 2, respectively

$$\alpha_t = \frac{m_0 - m_t}{m_0 - m_\infty} \quad (1)$$

where  $m_0$  is the initial sample weight,  $m_t$  is the sample weight at the time,  $t$ , and  $m_\infty$  is the final sample weight

$$\alpha_T = \frac{m_0 - m_T}{m_0 - m_\infty} \quad (2)$$

where  $m_T$  is the sample weight at temperature,  $T$ .

**Karl Fischer Titrimetry (KFT).** KFT (DL38, Mettler Toledo, U.K.) for water determination of Form I was carried out by weighing approximately 40–50 mg of the untreated bulk sample.

**High-Performance Liquid Chromatography (HPLC).** HPLC (Agilent HP 1100 Series System, Germany) was carried out using a Supelco Ascentis Express C18 (Sigma, U.K.). The mobile phase consisted of 0.1% TFA in water and 0.085% TFA in acetonitrile, and a flow rate of 2.0 mL/min was used. The samples were analyzed at 255.9 nm.

**Variable-Temperature X-ray Power Diffraction (VT-XRPD).** VT-XRPD experiments (Bruker D8 Advance, Bruker, U.K.) data sets were collected from 5.0° to 30.0° at  $2\theta$  under nitrogen purge with a flow rate of approximately 50 mL/min and 99.9% purity. The sample was placed in an Anton-Paar TTK450 (Anton-Paar, Austria) chamber at 25 °C. The temperature was controlled by a Temperature Control Unit TCU 100 (Anton-Paar, Austria), and the applied heating rate was set

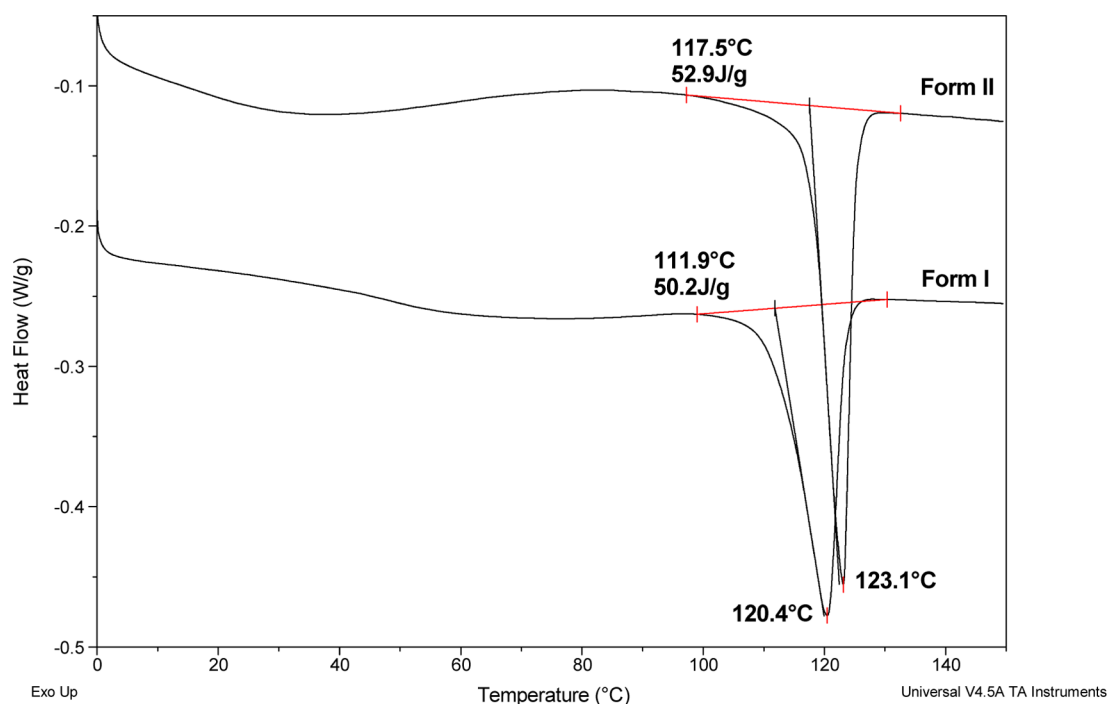
by default to 0.167 K·s<sup>-1</sup>. Diffractograms were recorded during heating at 25, 50, 75, 100, and 110 °C, and cooling at the same temperatures as during heating. The sample was maintained under isothermal conditions for different periods of time at each temperature, according to the knowledge provided by preliminary studies.

Unit cell parameters were determined by Pawley refinement of the collected patterns using the software TOPAS-Academic.<sup>20</sup> The initial values of the cell parameters for the refinement at 25 °C were taken from the single crystal structure of Form I. Refinements of powder patterns at higher temperatures were initiated from cell parameters refined in the previous heating or cooling step. The pattern recorded at 100 °C during cooling was indexed by fitting 20 peaks between  $2\theta = 6.5\text{--}20.5^\circ$  in DASH<sup>21</sup> and indexing them using DICVOL.<sup>22</sup> All peaks were successfully indexed with  $M(20) = 39.2$ .

## RESULTS

**Thermoanalytical Investigation of the Dehydration Process.** The thermal behavior of paroxetine HCl Form I was investigated by DSC using three types of pans: pinhole, hermetic, and open. As presented in Figure 4, the type of pan used has a profound effect on the thermal response observed. As expected, it was found that the accurate melting point of Form I has to be measured in hermetic pans (in order to avoid dehydration) and has an onset temperature of  $142.0 \pm 0.2$  °C, which is in agreement with the reported value in the literature.<sup>16</sup> However, when pinhole and open pans were used, the onset melting temperature of Form I was shifted to lower temperatures and appeared as a broad and poorly resolved profile.

The effect of the heating rate (HR) (2, 5, 10, 20, and 50 °C/min) was tested using the three types of pans (data not shown). In pinhole pans, as the heating rate increased, the peaks became broader and, at 50 °C/min, the melting event was shifted closer to the melting of the hydrate Form I. The results obtained at different HRs with hermetic pans were the same at all the heating programs used. With open pans, a significant dependence on heating rate was observed, with slower rates indicating a distinct endotherm that we associate with a



**Figure 5.** DSC traces of paroxetine HCl Forms I and II when heated in open pans at 2 °C/min.

**Table 1.** Dehydration Studies of Paroxetine HCl Form I and Form II Performed at Different Drying Conditions

sample	experimental drying procedure	$T_m$ onset (°C)	$\Delta H_{\text{melting}}$ (J/g)	$T_m$ peak (°C)
Form I	DSC open pans	111.9 ± 0.4	50.4 ± 1.4	120.4 ± 0.1
	<sup>a</sup> oven 100 °C/24 h	136.7 ± 0.8	85.2 ± 0.2	140.9 ± 0.1
	<sup>a</sup> P <sub>2</sub> O <sub>5</sub> /48 h	138.9 ± 0.9	91.5 ± 2.4	141.1 ± 1.5
Form II	DSC open pans	117.5 ± 0.4	53.1 ± 1.0	123.1 ± 0.1
	<sup>a</sup> oven 100 °C/1 h	116.6 ± 0.2	56.2 ± 2.0	120.1 ± 0.3
	<sup>a</sup> P <sub>2</sub> O <sub>5</sub> /48 h	117.2 ± 0.9	53.2 ± 0.2	120.5 ± 1.7

<sup>a</sup>Measurements were made in hermetic pans. All the experiments were performed at 2 °C/min.

dehydration process (supported by TGA studies as discussed later).

The thermal response of paroxetine HCl Form II under similar experimental conditions (pan type and heating rate) was fully investigated in our previous work.<sup>7</sup> We found that Form II dehydrated in open pans (Figure 5), whereas, in hermetic conditions, Form II transformed on heating to the stable Form I (Supporting Information, Figure SI 1).

Figure 5 shows the DSC responses of paroxetine HCl Forms I and II in open pans (2 °C/min) so as to highlight the differences in behavior between the two forms studied under identical conditions. First of all, the water loss was detected at different temperature ranges for the two forms. In the case of Form II, the water loss started from the beginning of the run, whereas, for Form I, the loss occurred roughly between 50 and 100 °C. The onset melting temperature was detected at 111.9 ± 0.4 °C for Form I and at 117.5 ± 0.4 °C for Form II, resulting in a difference of almost 6 °C between the onset melting points of these two forms, while the peak melting temperatures differed by almost 3 °C. At this early stage of the investigation, these results, while not conclusive, indicated that there may be differences in the anhydrate forms generated from the dehydration of the two hydrate forms.

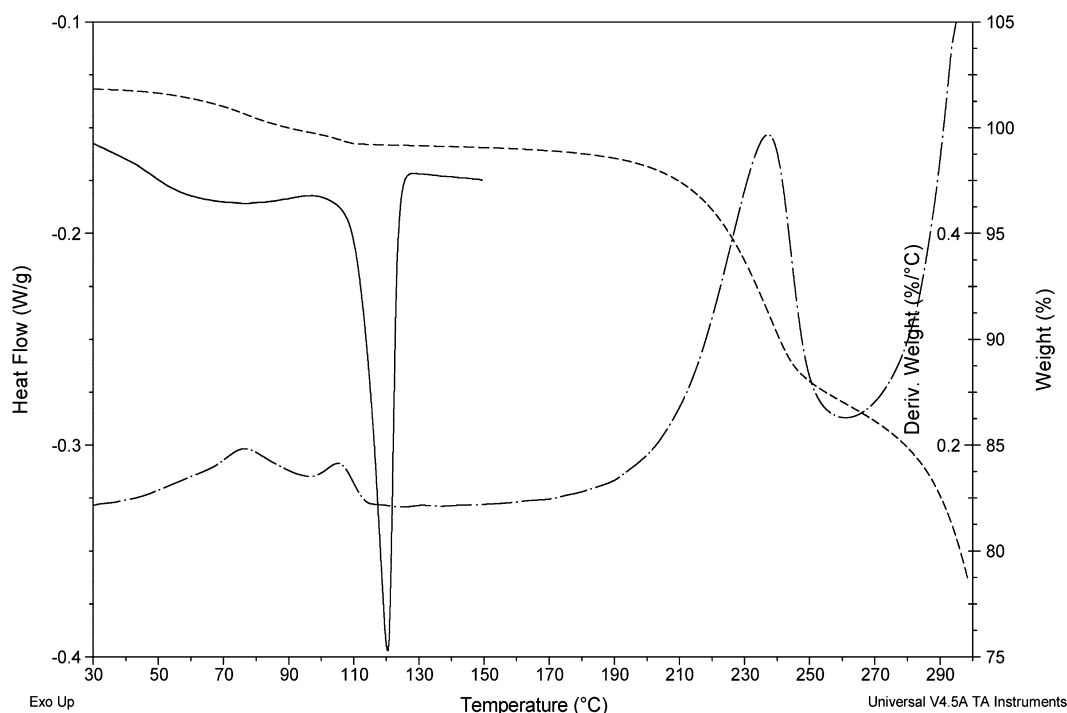
We then investigated the conditions required to dehydrate Form I, working on the assumption that the anhydrate (I) could be identified by a melting point onset of ca. 112 °C.

Surprisingly, the only means of producing this form was within the DSC, with storage over P<sub>2</sub>O<sub>5</sub> or oven drying both resulting in only partial dehydration (Table 1). Preliminary studies indicated that a functioning water filter on the nitrogen supply was also essential (data not shown), further reinforcing the hypothesis that the environment must be extremely dry to allow dehydration of Form I to occur. This also led to the consideration that physical isolation of the anhydrate was extremely difficult, as any exposure to humidity resulted in reconversion. Consequently, all our subsequent studies involve the assessment of the structure within the instrument used to generate the anhydrate.

In contrast, Form II was completely dehydrated inside the DSC, when held isothermally in the oven or stored over P<sub>2</sub>O<sub>5</sub>. Complete dehydration of Form II was confirmed by the detection of a single endotherm event corresponding to the melting of the dehydrated Form II (≈117 °C). Overall, this set of comparative experiments suggested that the dehydration of Form II is a much simpler process than the dehydration of Form I, able to happen over a wider range of conditions with a more stable product being generated.

Another important aspect in this study was to ensure that the complete dehydration of paroxetine HCl Form I was not associated with any amorphization of the sample. Therefore, a heat-cool-heat procedure was set up at 2 °C/min using open pans. We noticed during the second heating cycle a broad





**Figure 6.** DSC (—) and TGA (---) thermographs for paroxetine HCl Form I in open pans at 2 °C/min. The derivative weight curve (— · —) is presented for clarity.

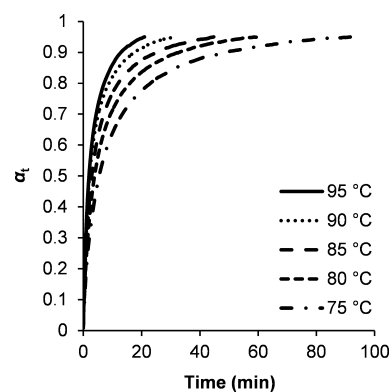
endothermic transition between 40 and 60 °C (Supporting Information, Figure SI 2). The first assumption made was that this transition could be a glass transition event as a consequence of amorphization after dehydration. However, the transition was not observed on the reversing heat flow signal, which then excluded this hypothesis. The possibility of this transition being an artifact was eliminated, with the same results being obtained either using pans from different batches or the same procedure carried out using different DSC instruments. At this point, the most likely explanation for the transition was water evaporation. However, as the DSC cell is a closed system, the only possible source of moisture would be the nitrogen purge gas. We, therefore, suggest that, even with a water filter, the system is sufficiently hygroscopic to pick up water, probably via surface sorption as there was no evidence of regeneration of the hydrate form. This further demonstrates the experimental difficulties associated with handling such a hygroscopic sample.

Given the above results, it was considered important to evaluate the strength of the interactions between the water and the drug within the hydrate, which may be achieved using TGA. In Figure 6, the DSC and TGA thermograms of paroxetine HCl Form I have been overlaid. For a particular slow HR of 2 °C/min, the water loss commenced at around 50 °C and occurred continuously until approximately 115 °C; the loss can be divided in two main temperature regions. The first one between 50 and 95 °C covered the majority of the water loss and the second one near the endothermic melting event, as we can observe from the DSC curve.

The water content of the raw Form I was determined by KFT to be  $2.71 \pm 0.25\%$  w/w. This value was in a good agreement with the designation of this form as the hemihydrate,  $0.56 \pm 0.05$  mol of water per mole of drug and matched the total weight lost measured by TGA ( $2.59 \pm 0.04\%$  w/w). In addition, HPLC was used to confirm that dehydration and the

subsequent melting process did not yield to any degradation of the sample. Analyses were performed on the untreated paroxetine HCl Form I and on the sample heated in the TGA until 130 °C. No sign of degradation was found on the heated sample (purity of 99.6%) when compared to the raw Form I (purity of 99.5%).

A closer inspection of the derivative curve shows that, at a HR of 2 °C/min, part of the water (0.61% of the 2.59%) can only be released at high temperatures, i.e., near the melting point of the dehydrated Form I. However, this idea was not supported by the isothermal experiments, as shown in Figure 7.



**Figure 7.** Representation of the conversion fraction ( $\alpha_t$ ) versus time obtained from TGA isothermal data at the different temperatures.

For example, when the sample was kept at 90 °C, the dehydration was completed after 30 min. The TGA isothermal experiments were also important to access the dehydration conditions when performing VT-XRPD, though a direct correlation could not be made due to the environmental differences between the two techniques.

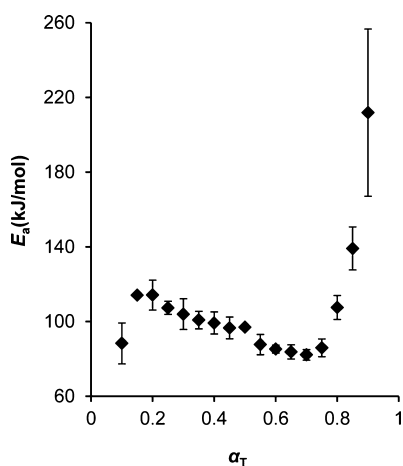
**Dehydration Kinetics.** Model-free analysis was performed using nonisothermal data, allowing the calculation of the activation energy,  $E_a$ , as a function of the conversion fraction,  $\alpha_T$ . On the basis of the graphical shape of the isothermal curves, as shown (Figure 7), the dehydration rate decreases as the reaction proceeds, and thereby, the kinetic model for this reaction is known as decelerating. There are three other major groups of kinetic models described in the literature as accelerating, linear, and sigmoidal.<sup>14</sup> Both isothermal and nonisothermal methods have advantages and disadvantages. The main issue encountered with isothermal methods is the unavoidable nonisothermal heat-up to the set up isothermal temperature. On the other hand, the biggest disadvantage of nonisothermal experiments is the difficulty in differentiating between acceleratory and sigmoidal models.<sup>14,23</sup>

The  $E_a$  for the dehydration of paroxetine HCl Form I was calculated using a nonisothermal isoconversional method developed by Ozawa, Flynn, and Wall<sup>24,25</sup> and, therefore, commonly referred to as the OFW method, which can be expressed by eq 3

$$\log \beta = \log \frac{AE_a}{g(\alpha_T)R} - 0.457 \frac{E_a}{RT} - 2.315 \quad (3)$$

where  $\beta$  is the heating rate,  $g(\alpha_T)$  is the integral reaction model, and  $R$  is the gas constant.

Plotting  $\log \beta$  versus  $1000/T$  at each  $\alpha_T$  yields  $E_a$  from the slope. Figure 8 shows the variation of the  $E_a$  as a function of the conversion fraction ( $\alpha_T$ ).



**Figure 8.** Activation energy,  $E_a$ , plotted as a function of the extent of conversion,  $\alpha_T$ , for the dehydration of paroxetine HCl Form I under nonisothermal conditions.

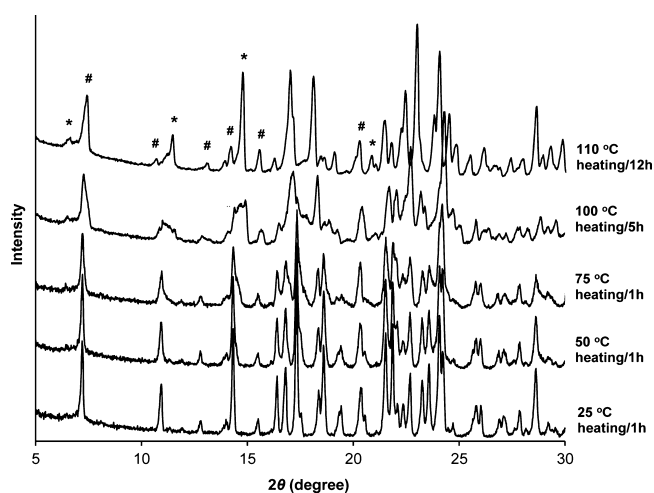
By analyzing in more detail the dependence of  $E_a$  with  $\alpha_T$  through the kinetic reaction, as shown in Figure 8, a decrease in the  $E_a$  from 114.1 to 99.2 kJ/mol within  $0.15 \leq \alpha_T \leq 0.40$ , followed by an approximately constant value of 85.9–96.2 kJ/mol in the range of  $0.45 \leq \alpha_T \leq 0.75$ , can be observed. The initial decrease of the  $E_a$  vs  $\alpha_T$  is characteristic of reversible reactions and could indicate a departure from the initial equilibrium.<sup>14</sup> After this nearly constant period, the  $E_a$  started to increase gradually until an abrupt high value (211.8 kJ/mol) when  $\alpha_T = 0.9$ . This increase in the  $E_a$  for the final conversion fractions can be linked to the observations in TGA, showing that the removal of the final fractions of water took place at higher temperatures, therefore, requiring more energy.

However, one should also bear in mind that a loss of linearity and a higher error are expected at the final points of  $\alpha_T$ , weakening the correlation with the TGA results. Nevertheless, this variation of  $E_a$  with  $\alpha_T$  indicates that the process is kinetically complex and a single-step rate equation cannot describe the whole reaction.

Attempts to analyze isothermal data using model-free methods were unsuccessful since good correlations could only be obtained for high values of conversion ( $\alpha_t \geq 0.40$ ) as the rate of the reaction is faster in the beginning (decelerating model). As a result, there is a significant extent of conversion during the heat-up time even using an HR of 50 °C/min to quickly reach the desired isothermal temperature.

The acquired knowledge up to this stage allowed us to understand the thermal behavior of Form I when exposed to different dehydration conditions and carefully set up the XRPD experiments, as follows, which are essential to provide information on the structure of the dehydrated form.

**Structural Studies Using VT-XRPD.** VT-XRPD experiments of Form I were performed in a closed system constantly purged with dry nitrogen gas in order to mimic the conditions inside the DSC and TGA furnaces. A change in the XRPD pattern started to be apparent after 1 h at 75 °C, with some of the diffraction peaks becoming broader. The changes were clearly observed as the temperature increased (Figure 9). After

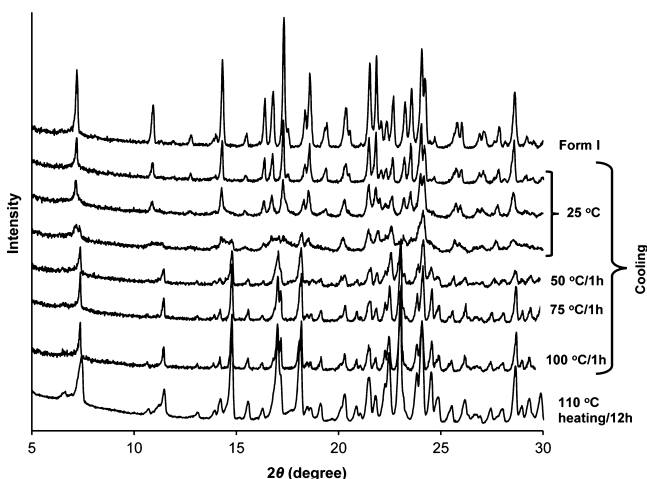


**Figure 9.** VT-XRPD diffractograms collected on paroxetine HCl Form I at 25, 50, 75, 100, and 110 °C (upward). Peaks identified with (\*) correspond to the new anhydrous form, and those identified with (#) are related to the initial Form I.

5 h isothermal treatment at 100 °C, the existing peaks became less sharp and new peaks appeared, which may be associated with the departure of the water molecules and the concomitant appearance of a new phase. This phenomenon was more evident when the temperature increased to 110 °C, and the sample was kept isothermal for 12 h. After that time, and analyzing the spectrum at lower angles, it is possible to distinguish the new peaks that appeared (\*) and the peaks from the hydrated Form I that started to disappear (#). However, at higher angles, the discrimination between the two phases is more difficult due to the overlap between some of the peaks. Pawley refinement<sup>20</sup> using the unit cell parameters of Form I gave a good fit to the experimental patterns at temperatures below 75 °C, but at 100 and 110 °C, the fit was very poor due

to the presence of more than one form (Supporting Information, Figure SI 3 and Table SI 1).

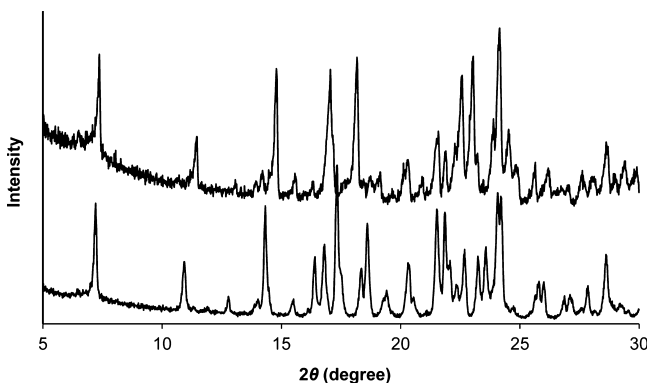
On cooling, it was possible to index the pattern collected after 1 h at 100 °C as a single phase. Pawley refinement with the new unit cell parameters from indexing gave a good fit to the diffraction pattern. The refined cell parameters ( $a = 14.400(2)$  Å,  $b = 10.5362(15)$  Å, and  $c = 12.7706(13)$  Å) were found to be very similar to those of the hemihydrate Form I at 75 °C ( $a = 14.655(5)$  Å,  $b = 10.191(3)$  Å, and  $c = 13.039(5)$  Å), but with a smaller unit cell volume. The space group of the new anhydrous form (I) was found to be  $P2_1$ , the same as Form I. A similar pattern to the one collected at 100 °C was maintained on further cooling down to 50 °C (Figure 10).



**Figure 10.** VT-XRPD patterns of paroxetine HCl Form I collected during cooling from 110 to 25 °C (upward). At 25 °C, the diffractograms were collected after 1, 2, and 6 h isothermal at that temperature.

When the temperature dropped to 25 °C, the pattern changed significantly, which might be ascribed to the re-entry of water molecules into the crystal structure. At this stage, the fitting using the anhydrous (I) unit cell parameters became very poor, as the pattern started gradually to revert to the initial Form I.

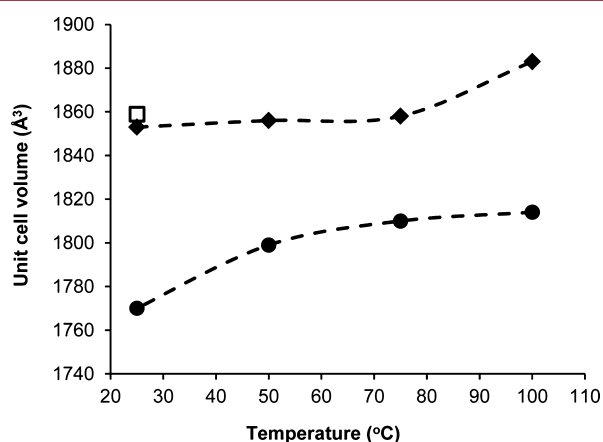
Figure 11 presents, for comparison, the patterns collected at 50 °C on heating and at the same temperature on cooling. As we can see, the two XRPD patterns at this temperature were different, confirming that the observed changes were not owing to thermal expansion but to the presence of two different



**Figure 11.** VT-XRPD data collected on heating (hydrated Form I) and on cooling (dehydrated Form I) at 50 °C, upward.

crystalline forms (hydrated Form I on heating and dehydrated Form I on cooling).

Figure 12 depicts the changes in the unit cell volume as a function of temperature. It is clear that, during heating, the unit

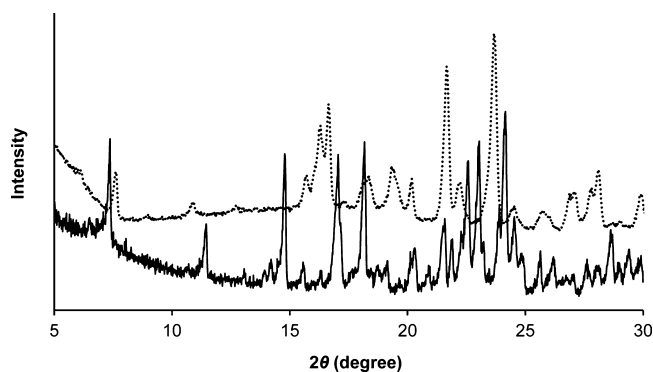


**Figure 12.** Changes in the unit cell volume of paroxetine HCl Form I during heating at 25, 50, 75, and 100 °C (◆); during cooling of the anhydrous form (●) at the same temperatures as during heating; and after cooling at 25 °C for 6 h (□). Note that Form I was heated to 110 °C; however, indexing was not possible at this temperature. The refinement at 100 °C on heating and after 1 h at 25 °C on cooling gave a poor fitting; thus, these results are less reliable.

cell volume increased slightly, as expected for thermal expansion. The unit cell volume of the new form at 50 °C was found to be 56 Å<sup>3</sup> smaller than that of Form I at the same temperature, which is consistent with dehydration (Table SI 1). After 6 h at 25 °C, the unit cell volume was found to be the same as that of the hydrate Form I, indicating that full rehydration took place.

From these observations, we can suggest that Form I dehydrated to an isostructural anhydrous form. Although we were unable to determine the structure of the dehydrated form (I), the similarity of its unit cell parameters to the hydrated structure allows a tentative explanation for its instability. Removal of the water molecules from the hemihydrate (Figure 2) requires a significant rearrangement of strong hydrogen bonds, which explains why high temperature and low RH are required for dehydration. Since the powder patterns are similar, the resulting structure is expected to show limited changes and is most probably restricted to small shifts of the molecules relative to each other. The hydrogen bonds involving water molecules in the hydrate need to be replaced by ammonium–chloride hydrogen bonds in the anhydrate (I). It is apparent from Figure 2 that it is impossible to fully satisfy the acceptor capacity of chloride ions within the constraints of limited molecular rearrangement, and even those bonds that can form may well induce steric strain. Consequently, the anhydrate (I) structure is expected to be highly unstable and react with water easily.

Finally, by comparing the pattern obtained for the dehydrated Form II at 30 °C/1% RH obtained from our previous work<sup>7</sup> and the pattern collected in this study at 50 °C for the dehydrated Form I, we can see that these two crystalline patterns are different (Figure 13). As Form II forms an isostructural anhydrate when dehydrated, only shifts on the diffraction peaks were observed without any changes in terms of appearance/disappearance of peaks. Attempts to fit the



**Figure 13.** VT-XRPD pattern of the dehydrated Form I at 50 °C on cooling (bottom) and VH-XRPD pattern of the dehydrated Form II (top) collected at 30 °C/1% RH (data collected from ref 7).

pattern of dehydrated Form I using the unit cell parameters of the dehydrated Form II were unsuccessful, reinforcing the hypothesis that these two dehydrated forms are structurally different.

## DISCUSSION

The combination of thermal and diffraction techniques allowed investigation of the dehydration behavior of paroxetine HCl Form I and, consequently, suggested the existence of a new anhydrous form as a result of this process. Dehydration was first observed when Form I was heated in pinhole or open pans in the DSC. However, the melting peak temperature observed for the dehydrated Form I (120 °C) was fairly close to the melting of the isostructural dehydrate Form II (123 °C), which made the differentiation between these two dehydrated forms difficult using thermal techniques.

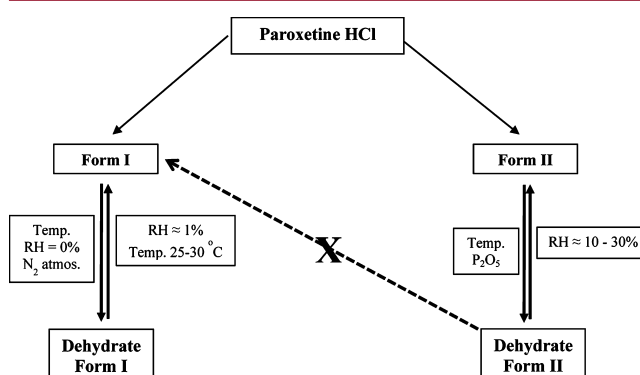
Therefore, VT-XRPD experiments were performed in a closed system blanket with dry nitrogen gas (99.9% purity) in similar conditions as those observed in the DSC and TGA furnaces. The changes in the XRPD pattern started to be observed as the temperature increased, with the appearance of new diffraction peaks after the sample was kept isothermal for 5 h at 100 °C. The Pawley refinement showed that the unit cell parameters of the new anhydrous form (I) were very similar to those of the hydrate Form I, the main difference being a smaller unit cell volume, as a result of dehydration. Therefore, we can conclude that Form I dehydrates to an isostructural dehydrate form.

During cooling, as a result of the temperature drop, residual moisture in the N<sub>2</sub> source (in theory around 1%), and probably not completely hermetically sealed VT chamber, the pattern started gradually to revert to the initial Form I after 1 h at 25 °C. Pawley refinement using the pattern collected after 6 h at 25 °C showed that the unit cell had the same volume as the hydrate Form I, confirming that the new anhydrous form fully rehydrated to Form I. The structural rehydration observed during cooling in the VT-XRPD experiments was supported by the results obtained when the sample was cycled inside the DSC in open pans, with the dehydrate Form I picking up moisture from the nitrogen gas.

The dehydration kinetic studies of Form I were conducted using nonisothermal TGA data with a view to estimate the  $E_a$  required to dehydrate Form I. Model-free analysis was used to calculate the  $E_a$  for dehydration of Form I, which varies between 86 and 114 kJ/mol. This value of  $E_a$  is much higher than the reported value (60 kJ/mol) for stable hydrates under

ambient conditions,<sup>26</sup> supporting again the great stability observed for the hydrate Form I.

Figure 14 is a schematic representation of the relationships between hydrated and dehydrated forms of paroxetine HCl.



**Figure 14.** Representative scheme of the relationship between the two forms of paroxetine HCl.

Form II dehydrated to an isostructural anhydrous form that rehydrated back at 10–30% RH (data presented in our previous work<sup>7</sup>). The dehydration of Form I was a more complex process, implying a completely dry environment and high temperatures. The dehydrated Form I was found to be very unstable with quick reconversion to the hydrate Form I when RH ≈ 1%. The two dehydrated forms of Forms I and II were structurally different, and therefore, a new form of paroxetine HCl has been found.

The significance of these findings lies not only in the identification of a new structure for an important drug molecule but also in highlighting the complexity of dehydration and rehydration behavior of low molecular weight molecules. The Form I anhydrate was extremely difficult to produce and isolate due to the high resistance to dehydration and extreme affinity for water. The anhydrate (I) is extremely unstable and hence is not a viable candidate for commercial use. However, taken in the context of the unusual hydration behavior of Form II highlighted in our previous study,<sup>7</sup> this drug also serves as a potentially highly important model for understanding the relationship between chemical structure and hydration behavior. In particular, the current study has highlighted the extreme affinity of the dehydrated Form I for water, which is in itself of interest in understanding hydrate formation and stability.

## CONCLUSIONS

In this study, we have shown that the dehydration of paroxetine HCl Form I is a complex and uncommon process for a stoichiometric hydrate. The prepared anhydrous form (I) is structurally different from the dehydrated Form II; thereby, a new anhydrous form of paroxetine HCl has been identified. Moreover, the structure of the new anhydrous form (I) was found to be very similar to that of the hydrate Form I, which supported its high instability and tendency to quickly rehydrate. These findings are of considerable relevance on the understanding of the solid-state relationships of paroxetine HCl. Furthermore, the study presents new insights into the behavior of hydrates with high resistance to dehydration, with the possibility of new forms being identified and enhanced understanding of the driving factors determining hydrate formation and stability.



## ■ ASSOCIATED CONTENT

### Supporting Information

DSC traces of both Forms I and II and Pawley fitting results performed at the different temperatures. 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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