Supporting Information

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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Thermal Analysis of Form II

Figure SI 1 shows the thermal response of paroxetine HCl Form II when heated in hermetic pans at 2 ^{o}C/min. The melting point of Form II was detected at 118.8 ± 0.6 ^{o}C, followed by a recrystallization step and finally an endotherm at 139.8 ± 0.5 ^{o}C, which corresponds to the melting of the stable Form I. These results indicated that Form II is forming the hydrate Form I on heating. Full characterization of Form II can be found in the reference [1].

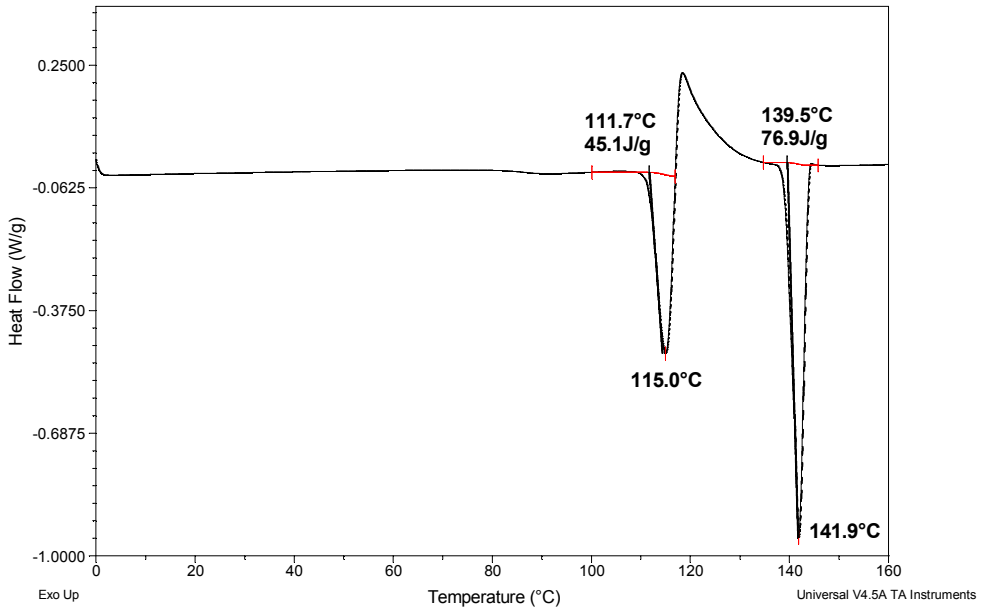


Figure SI 1. DSC analysis of paroxetine HCl Form II at 2 ^{o}C/min in hermetic pans.

Heat-Cool-Heat Cycle of Form I

Figure SI 2 presents the thermal behavior of paroxetine HCl Form I during a heat-cool-heat procedure at 2 ^{o}C/min in open pans. As shown below, it is possible to observe a typical water loss signal for Form I in the 1st heating cycle. On cooling, no thermal events were detected either in total or reversing heat flow. The endothermic transition between 40 and 60 ^{o}C was associated with water evaporation from the surface. This was confirmed by repeating the same cycling procedure using pinhole pans. Under these conditions, the endothermic transition was not observed in the 2nd heating cycle (data not shown) since the exposure of the sample to the nitrogen gas was partially restricted.

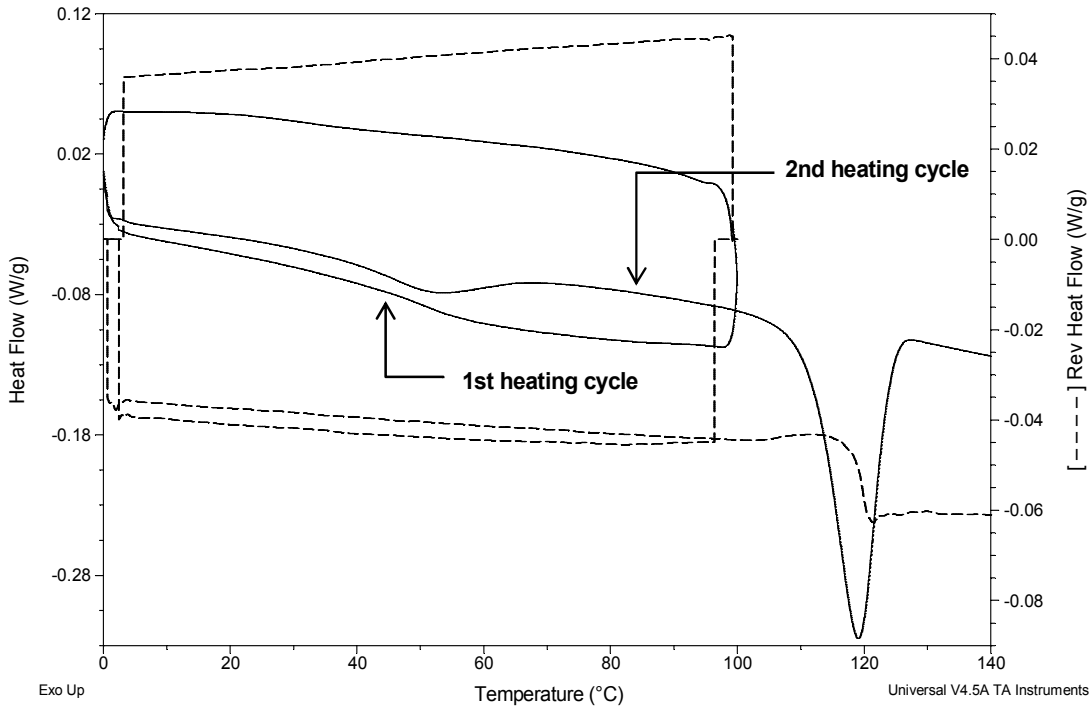
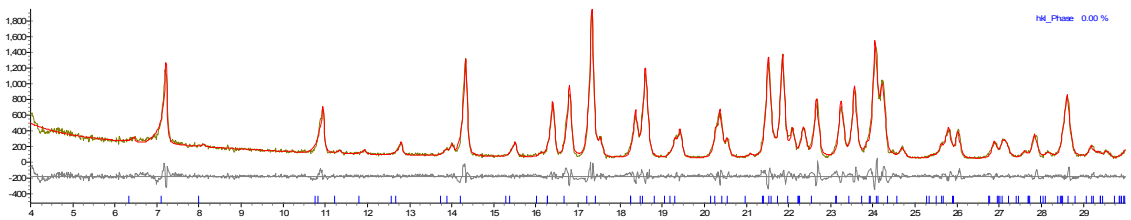


Figure SI 2. Dehydration of paroxetine HCl Form I inside DSC through heat-cool-heat cycling procedure in open pans. MTDSC was used with a heating rate of 2 ^{o}C/min, modulation amplitude of ± 0.318 ^{o}C and a period of 60 sec.

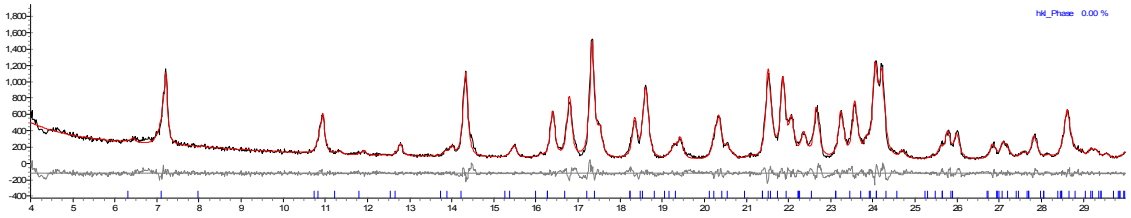
Analysis of Diffraction Patterns

Pawley refinement[2] was performed at each temperature either using the unit cell parameters of the hemihydrate Form I or the new parameters obtained by indexing the anhydrous form. The results of the fitting are presented in Figure SI 3. The unit cell parameters obtained are shown in Table SI 1.

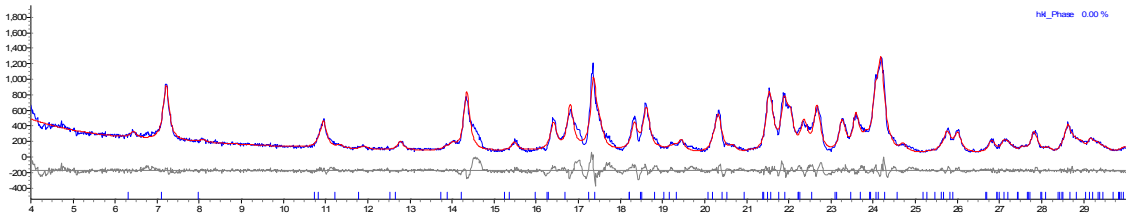
a) Heating 25 ^{o}C/1h – Unit cell parameters of the hydrate Form I



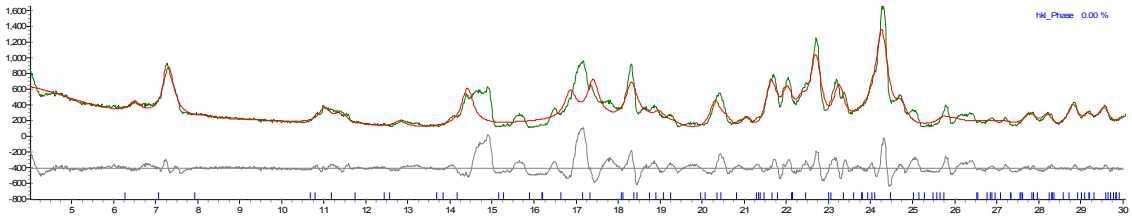
b) Heating 50 °C/1h – Unit cell parameters of the hydrate Form I



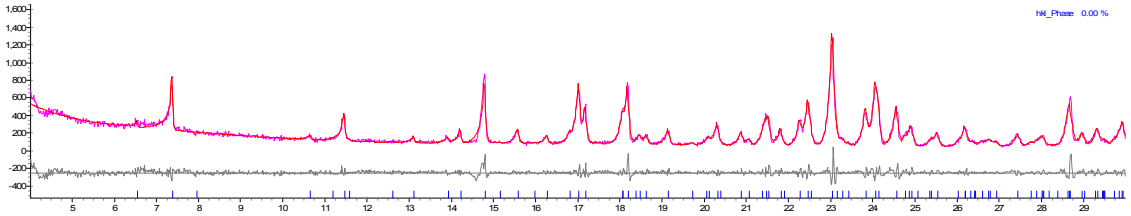
c) Heating 75 °C/1h – Unit cell parameters of the hydrate Form I



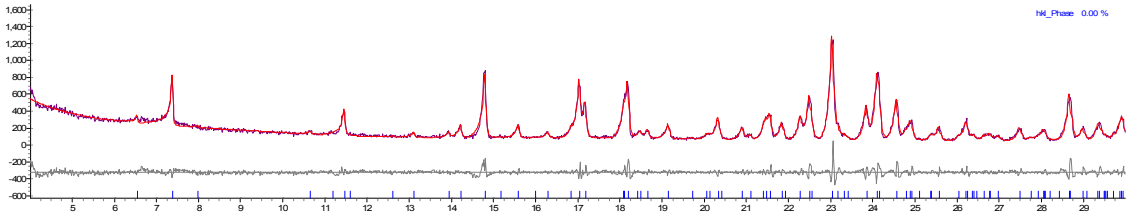
d) Heating 100 °C/5h – Unit cell parameters of the hydrate Form I



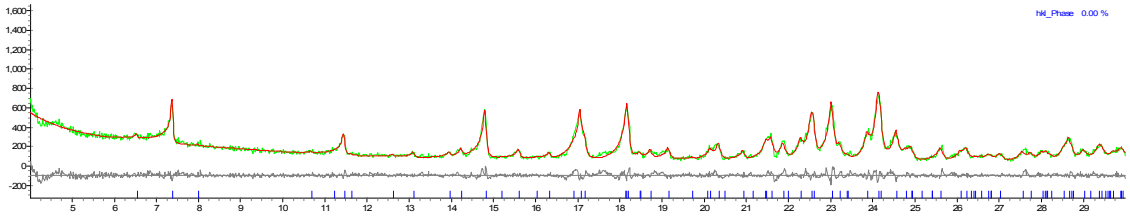
e) Cooling 100 °C/1h – Unit cell parameters of the new anhydrous form



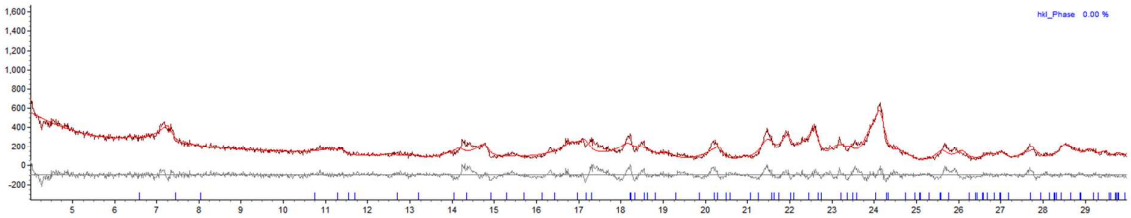
f) Cooling 75 °C/1h – Unit cell parameters of the new anhydrous form



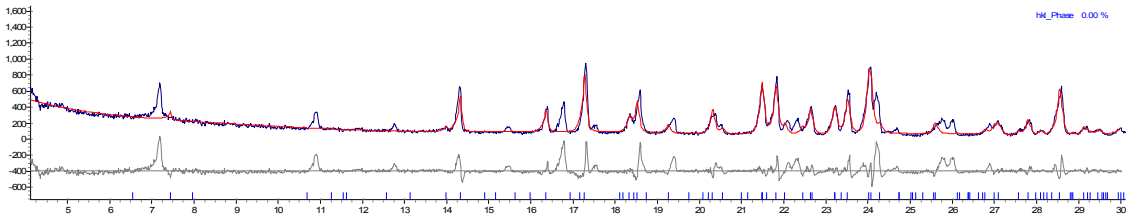
g) Cooling 50 °C/1h – Unit cell parameters of the new anhydrous form



h) Cooling 25 °C/1h – Unit cell parameters of the new anhydrous form



i) Cooling 25 °C/6h – Unit cell parameters of the new anhydrous form



j) Cooling 25 °C/6h – Unit cell parameters of the hydrate Form I

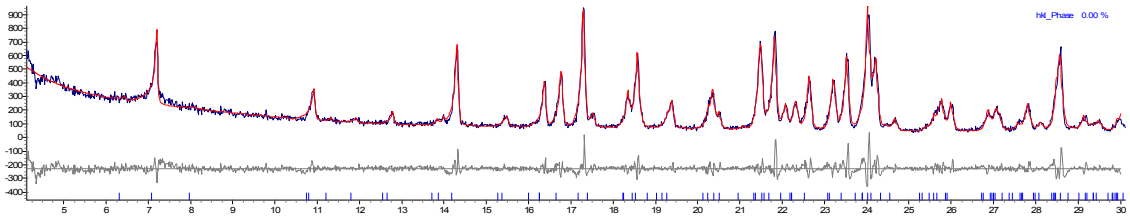


Figure SI 3. Experimental XRPD pattern, fitted curve (red) and difference (grey) obtained in the Pawley fit.

Table SI 1. Unit cell parameters obtained at each temperature. The rows in red are less reliable due to the poor fit. During heating the unit cell parameters of the hydrate Form I (hyd) were used and during cooling the unit cell parameters of the new anhydrous form (anh), except for the last measurement at 25 °C/6h, where the parameters of the hydrate cell were used.

	Temperature (°C)	***a*/Å**	***b*/Å**	***c*/Å**	***β*/°**	***V*/Å^3**	***Rwp***
Heat	25 °C/1h (hyd)	14.615(2)	10.1819(11)	13.0419(17)	107.194(5)	1854.0(4)	0.108
	50 °C/1h (hyd)	14.632(2)	10.1864(14)	13.044(2)	107.273(7)	1856.5(5)	0.099
	75 °C/1h (hyd)	14.655(5)	10.191(3)	13.039(5)	107.411(13)	1858.2(12)	0.125
	100 °C/5h (hyd)	14.75(3)	10.227(18)	13.09(3)	107.44(9)	1884(7)	0.195
Cool	100 °C/1h (anh)	14.400(2)	10.5362(15)	12.7706(13)	110.490(5)	1814.9(4)	0.112
	75 °C/1h (anh)	14.392(2)	10.5184(14)	12.7572(13)	110.396(5)	1810.1(4)	0.114
	50 °C/1h (anh)	14.385(2)	10.473(2)	12.738(2)	110.297(7)	1799.8(6)	0.101
	25 °C/1h (anh)	14.291(16)	10.439(12)	12.662(13)	110.37(7)	1771(4)	0.137
	25 °C/6h (anh)	14.427(5)	10.464(3)	12.711(5)	110.866(14)	1793.1(11)	0.244
	25 °C/6h (hyd)	14.6253(16)	10.1862(13)	13.0620(16)	107.150(5)	1859.4(4)	0.120

Dual phase refinement

An attempt was made to confirm that the X-ray pattern collected at 100 °C during heating was a mixture of the known hydrate, Form I, and its dehydrated form. A dual phase Pawley refinement was performed, with the unit cell parameters of the dehydrated form being kept fixed and the unit cell parameters of the hydrated form refined freely. The fixed parameters for the dehydrated form were taken from the refinement at 100 °C during the cooling cycle (Table SI 1). A reasonable fit for the experimental pattern was obtained (Figure SI 4, R_{wp} = 0.072), but the refined cell (a = 14.77(2), b = 10.189(7), c = 12.926(8), α = 90°, β = 109.3(11)°, γ = 90°) showed an intermediate volume (1836(4) Å^3) between the volumes expected for a hydrated and a dehydrated form. While this may indicate the presence of an intermediate phase, it can also be a consequence of 'averaging' between poorly resolved hydrate and anhydrate peaks. The latter explanation is supported by attempts of refining the parameters of both unit cells simultaneously. These results depend significantly on the initial parameter estimates and refinement steps applied.

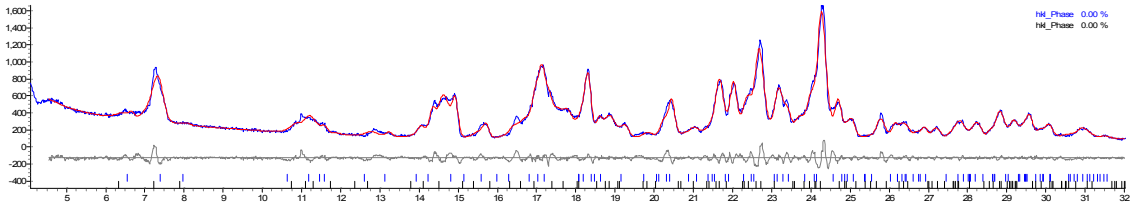


Figure SI 4. Experimental XRPD pattern, fitted curve (red) and difference (grey) obtained in a mixed-phase Pawley fit of the powder pattern collected at 100°C during the heating cycle.

References

(1) Pina, M. F.; Pinto, J. F.; Sousa, J. J.; Fábián, L.; Zhao, M.; Craig, D. Q. M., Identification and characterization of stoichiometric and nonstoichiometric hydrate forms of paroxetine HCl: Reversible changes in crystal dimensions as a function of water absorption. *Molecular Pharmaceutics* **2012,** 9, 3515-3525.

(2) Coelho, A., *TOPAS Academic User Manual. Version 4.1*. ed.; Australia, 2007.