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MS32-P6 Dehydration of paroxetine hydrochloride forms I and II

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Paroxetine hydrochloride has two hydrate forms: a stoichiometric hemihydrate (form I) and a non-stoichiometric hydrate (form II). Both forms can be dehydrated to give two distinct anhydrous forms, which are isostructural with their respective parent hydrates.^{1,2}

The water content and unit cell volume of form II change rapidly, continuously and without any noticeable hysteresis in response to changes in relative humidity at 30°C. Form I, on the other hand, shows a clear first order phase transition on heating, producing the pure dehydrated form after ca. 1 h at 100°C. Dehydrated form I converts back to hemihydrate form I at room temperature at relative humidities as low as 1%.

The dehydration process was monitored in-situ using synchrotron powder diffraction experiments. There was no evidence of any intermediate phase and the data allowed structure determination of form I dehydrate. It was revealed that both form I and its dehydrate are isostructural with the corresponding paroxetine hydrobromide forms.³

Comparison of the structures gives an explanation of the different stabilities and transformation kinetics observed. Form II contains solvent pockets separated by easy-to-open gates, and consequently it behaves as a channel hydrate. Molecular dynamics simulations show the mechanism of opening the gates, which are formed by hydrophobic rings with only weak intermolecular interactions between them. In form I, however, water molecules are separated from each other by strongly hydrogen-bonded chloride ions, so their removal is much more difficult. The dehydrates show poor hydrogen bond coordination,⁴ which explains their low stability and easy conversion back to the isostructural hydrate form.

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