Seeking Polymorphism with Duloxetine Hydrochloride

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1. Introduction

- Duloxetine HCl (Figure 1) is an antidepressant that acts mainly as a serotonin and noradrenaline re-uptake inhibitor. Despite the importance of this new pharmaceutical and claims of polymorphism in the patent literature, there is relatively little understanding of its structural diversity, information crucial for formulation, manufacturing processing and patent applications.

- This study compares Duloxetine HCl in its pure enantiomeric form, with its racemic form, its acetone solvate and its marketed form as 'Cymbalta', with the aim of developing methods to detect and quantify new and existing polymorphs.

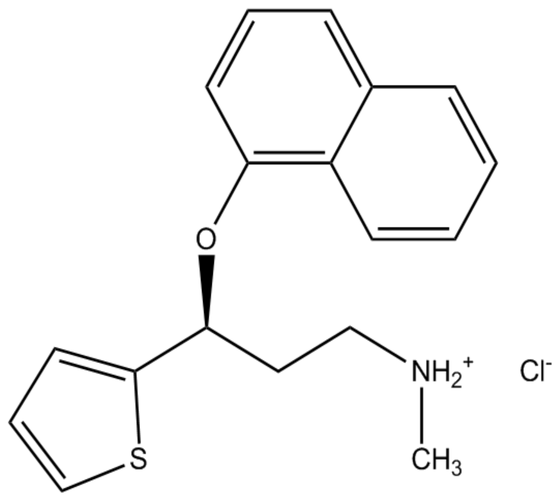

Figure 1: Structure of Duloxetine HCl

2. Structural Analysis by Solid State ^{13}C NMR Spectroscopy

- Solid state ^{13}C NMR at ambient temperature shows 16 of the 18 carbon atoms, Figure 2A. The 'missing' peaks were revealed in a variable temperature study (see Figure 3). Duloxetine HCl recrystallised from acetone to give the meta-stable acetone solvate (Figure 2C), which as a *sealed* sample seems indefinitely stable. The marketed drug, Cymbalta, shows only Form 1, in Fig. 2D, and no other forms such as the racemate, Fig. 2C.

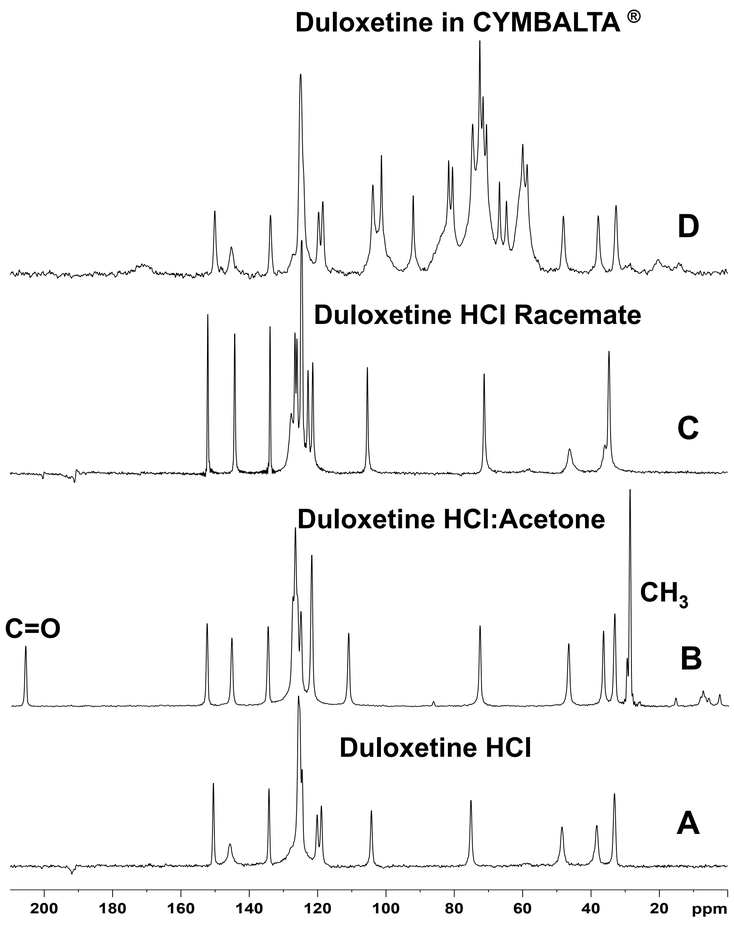

Figure 2: Solid State TOSS-CPMAS NMR Spectra of [A]Duloxetine HCl; [B] Duloxetine HCl:Acetone *solvate*; [C] Duloxetine HCl *racemate*; [D] Cymbalta, 60 mg Tablet. MAS, 8kHz.

- Variable temperature TOSS-CPMAS experiments from 335 to 235 K sharpened several peaks of the thiophene ring which is rotating slowly in the solid state and frozen out at ~235 K. This agrees with the single crystal structure measured at 153 K which shows two conformations for the thiophene ring.

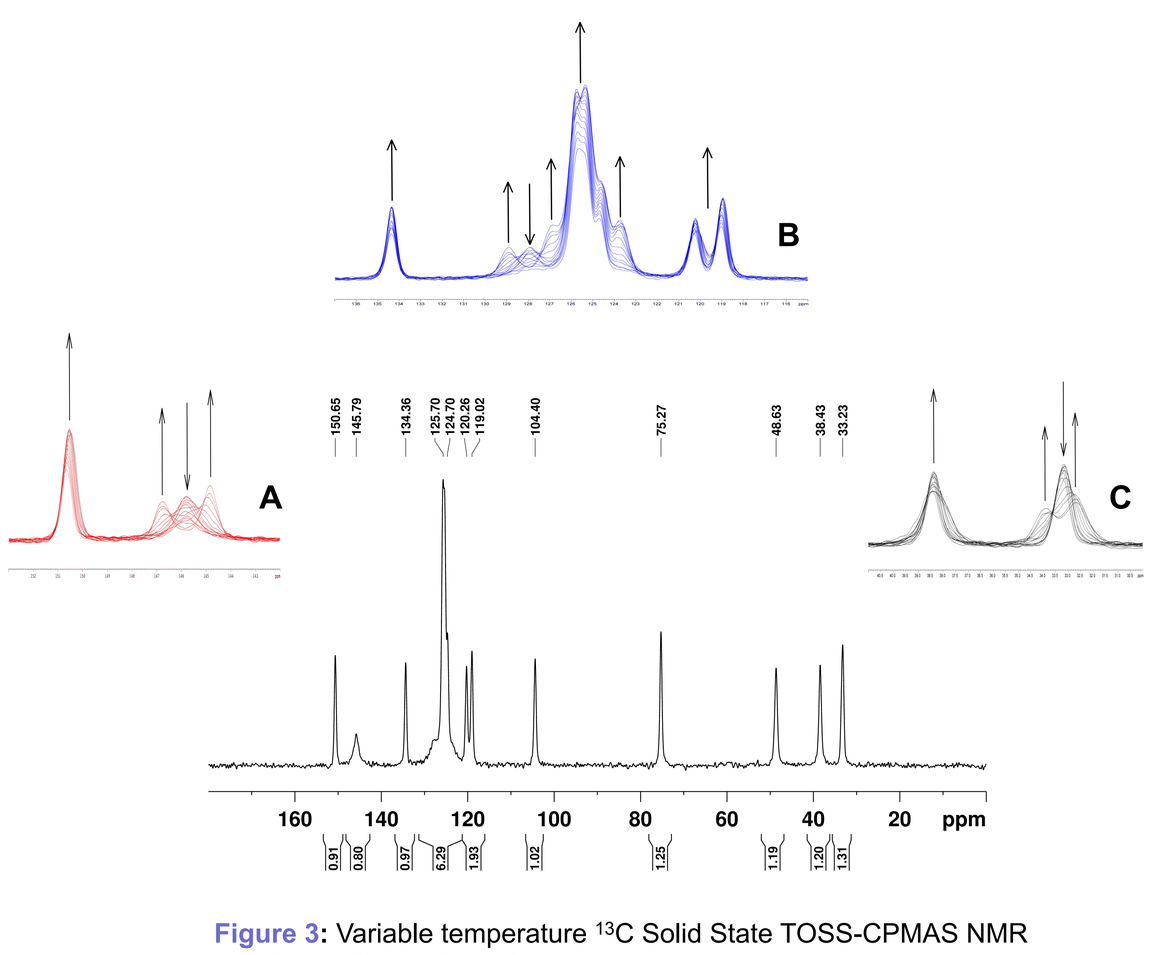

Figure 3: Variable temperature ^{13}C Solid State TOSS-CPMAS NMR Spectra of Duloxetine HCl, showing expansions of regions: [A]160-140 ppm; [B] 140-115 ppm; [C] 40-30 ppm, over the temperature range 235-335 K.

3. Structural Analysis by Single Crystal X-ray Diffraction

- The duloxetine naphthalene groups form channels in the solvate structure (Figure 4), where the acetone molecules lie in an ordered way within the channels.

- Desolvation is rapid at room temperature resulting in a "collapse" of the channels to form a stable close-packed structure identical with Form 1 (Figure 5).

- This major disruption to the packing is only accompanied by small changes in the conformation of the duloxetine host (Fig. 6). Molecular rearrangement does not appear to be a driving force for discharge of the solvent molecules.

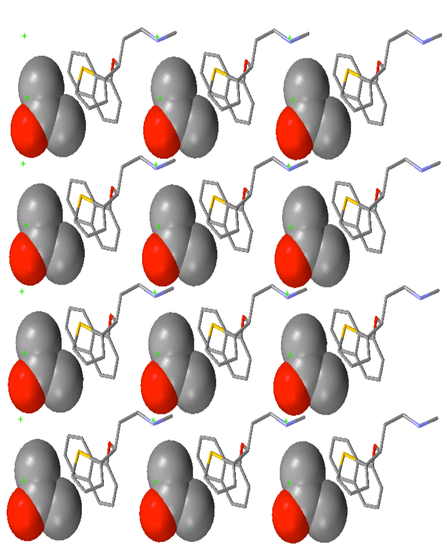

Figure 4: View down *c*-axis of the solvate showing vertical channels (along *a*-axis) filled with acetone.

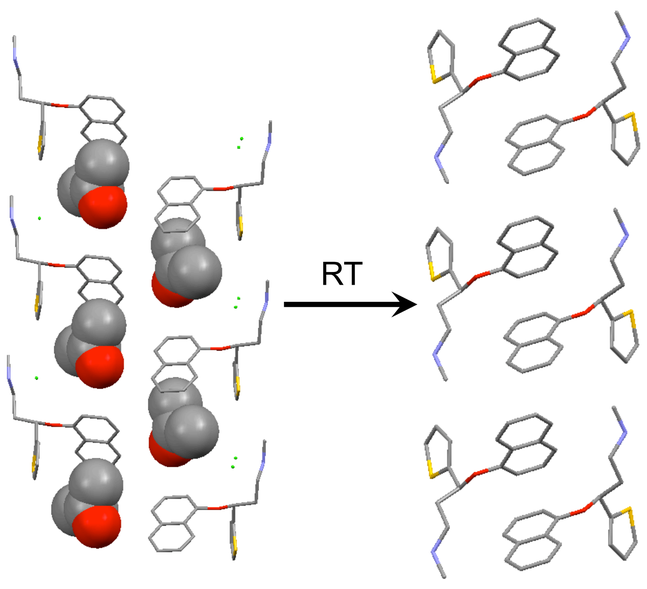

Figure 5: View *down* channels of the acetone solvate (left) and desolvated structure (right).

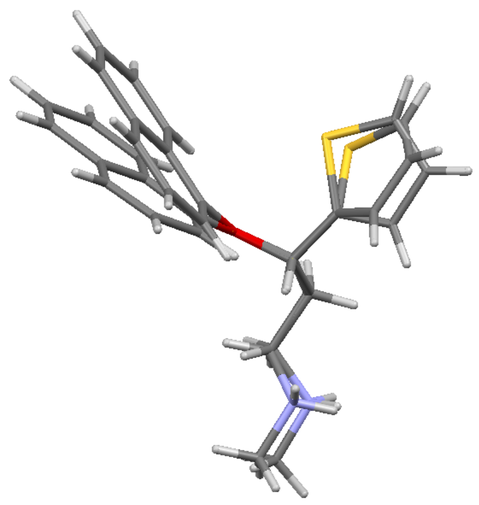

Figure 6: Overlay of structures: duloxetine.HCl.acetone solvate and duloxetine HCl Form I.

References: (1) M.Bhadbhade, J. Hook, C. Marjo, A. Rich and Q. Lin, ***Acta Cryst.*** **2009**, E65, o2294
(2) C. Marjo, M.Bhadbhade, J. Hook, and A. Rich. ***Molecular Pharmaceutics***, **2011**, on-line.