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Polymorphism and a Metastable Solvate of Duloxetine Hydrochloride

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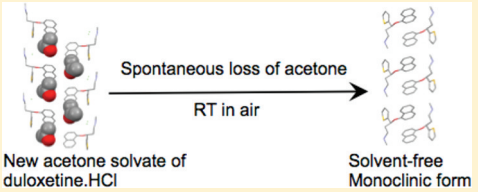
Supporting Information

ABSTRACT: Duloxetine hydrochloride (**1**) is an important antidepressant that acts as a serotonin and noradrenaline reuptake inhibitor that has only recently been characterized by single-crystal X-ray diffraction. This study describes an investigation into polymorphism of duloxetine hydrochloride, discusses the challenges of characterizing new structures, and reports a new metastable solvate ($\mathbf{1}_{acetone}$) where acetone is trapped in a duloxetine hydrochloride host lattice. In view of the importance of formulation processing and bioavailability characteristics of the crystalline forms of **1**, a comprehensive structural study of $\mathbf{1}_{acetone}$ was carried out using single-crystal and powder X-ray diffraction, infrared and Raman spectroscopies, and solid-state NMR spectroscopy. The rapid desolvation from $\mathbf{1}_{acetone}$ to the stable unsolvated form was investigated, and the structures of free and solvated forms are discussed in terms of the noncovalent intermolecular interactions.

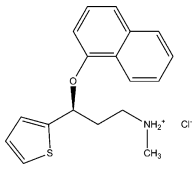


KEYWORDS: *duloxetine hydrochloride, polymorphism, solvate, solid-state NMR, X-ray diffraction, Raman spectroscopy, FTIR, desolvation kinetics*

INTRODUCTION

Understanding structural diversity, in particular the formation and behavior of polymorphs and solvates, is critical for establishing uniqueness in a pharmaceutical patent, as well as optimizing conditions for tablet compression and powder flow required for pharmaceutical compounding.[1] In addition to processing considerations, the rate of dissolution of an active ingredient can be significantly affected by the polymorph used[2] potentially changing the effective dose for the patient. Duloxetine hydrochloride **1** (Scheme 1), (+)-(*S*)-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine, is an important new pharmaceutical[3] with significant market value that has attracted some interest in its polymorphism, mainly in the patent literature.[4] Formulations containing duloxetine hydrochloride (**1**) are manufactured by Eli Lilly and Boehringer Ingelheim and branded as Ariclaim, Cymbalta, Xeristar, and Yentreve. The molecule acts as a serotonin and noradrenaline reuptake inhibitor for treatment of depression and anxiety, stress urinary incontinence in women and chronic pain disorders. Previous reports have noted three polymorphic forms as well as solvates based on characterization by powder X-ray diffraction (XRD), vibrational spectroscopy and differential scanning calorimetry (DSC). However, no single-crystal X-ray structure of any form of **1** had been reported until a recent study by the authors.[5] The resulting crystallographic structure determination revealed a monoclinic form of **1** that could be the stable form used for pharmaceutical formulations (hereafter referred to as $\mathbf{1}_{monoclinic}$). Further work on **1** has led to the discovery of a metastable acetone solvate, designated as $\mathbf{1}_{acetone}$. Solvation has been proposed as a subclassification of polymorphism,[6] however the presence of acetone in **1** means this is a chemically distinct structural form and does not represent true polymorphism as normally accepted in the literature.

Scheme 1. Structure of Duloxetine Hydrochloride (1)



This new structural form of **1** has been comprehensively characterized by a number of independent techniques that are established methods for characterization of polymorphs and comprise the basis of this report. The prevalence of powder X-ray diffraction, calorimetry measurements, mid-infrared spectroscopy,[7] and microscopy for analysis of polymorphs in the literature has recently been highlighted,[1] and these important techniques were included in this study. Solid-state NMR is less commonly used than these techniques in the literature, although it is a well-established and complementary technique to XRD for studying polymorphism,[8] and was indispensible for this study. Additional techniques available to the authors included Raman[9] and single-crystal XRD, the latter being critical for unambiguous assignment of structure to the data

Received: September 6, 2011
Revised: October 30, 2011
Accepted: November 3, 2011
Published: November 3, 2011

from each of the other techniques. The collected characterization data may be directly relevant to polymorph assessment and formulation processing of this important pharmaceutical in the future.

EXPERIMENTAL SECTION

Four variants of duloxetine hydrochloride were measured that represented a diversity of structure and chirality in the molecule: the pure enantiomer, $\mathbf{1}_{monoclinic}$; the solvate of the enantiomer, $\mathbf{1}_{acetone}$; the racemic form $\mathbf{1}_{racemate}$; and an example of a pharmaceutical formulation, 60 mg Cymbalta capsules from Eli Lilly designated as $\mathbf{1}_{pharma}$.

Differential Scanning Calorimetry (DSC). A 2 mg sample of $\mathbf{1}_{monoclinic}$ was placed in a hermetically sealed aluminum crucible. The lid of the crucible was pierced prior to starting the experiment. An empty hermetically sealed crucible with a pierced lid was used as a reference. The double furnace DSC 8000 from PerkinElmer was used to run the sample from 30 to 200 °C at 10 °C/min under a nitrogen gas atmosphere.

Single-crystal XRD was performed by selecting a suitable single crystal under a polarizing microscope (Leica M165Z) and mounting it on a cryo loop with paraffin oil, which fixed onto it upon freezing at the temperature of data collection (150 K). The intensities were measured on a Bruker kappa APEX-II CCD diffractometer equipped with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) and operating at a low temperature of 150(2) K maintained using an Oxford Cryostream 700 system. Upon obtaining an initial refinement of unit cell parameters, the data collection strategy achieved a redundancy of at least 4 throughout the resolution range (∞−0.80 Å) at 10 s exposure time per frame making use of the kappa offsets on the four-circle goniometer geometry. The data integration and reduction with the multiscan absorption correction method[10] were carried out using the APEX2 suite of software.[11] The structure was solved by direct methods using SHELXS-97[12] and was refined by the full-matrix least-squares refinement program SHELXL to the final R value. All non-hydrogen atoms were refined anisotropically. The H-atoms were located in the difference Fourier map, but all were constrained using the riding model option in SHELXL.[13] Molecular graphics were generated using ORTEP-3v2. Key crystallographic data and refinement details are shown in Table S1 in the Supporting Information.

Polymorphism and Inclusion Screening Studies. **1** was crystallized from a range of solvents by dissolving 5−10 mg in a 10 mm sample tube using gentle heating. Heating above 80 °C in acetone was avoided to minimize any chemical changes, notable by a yellowing of the normally colorless solution, and failure to precipitate any crystals over several weeks, presumably due to the presence of free HCl catalyzing other reactions in solution. Screening of the resulting crystals was performed by selecting a homogeneous crystal from the mass at 90× magnification and then using single-crystal XRD to measure the unit cell parameters and compare with those known for $\mathbf{1}_{monoclinic}$. As a solid, duloxetine hydrochloride appears to be relatively stable to heating up to its melting point.

$\mathbf{1}_{acetone}$: The 1:1 acetone solvate was prepared by combining 200 mg of $\mathbf{1}_{monoclinic}$ in 40 mL of AR grade acetone and heating the mixture to boiling in an open flask. Complete removal of $\mathbf{1}_{monoclinic}$ was required to ensure the acetone solvate was the sole product of crystallization, so the solution was decanted from any undissolved material and allowed to cool in a water bath at room temperature. The solution was stirred during cooling until a mass of long thin needles of the solvate crystallized over several minutes. The resulting slurry was gravity filtered through a fluted paper, and the solvate crystals were measured immediately using the required technique.

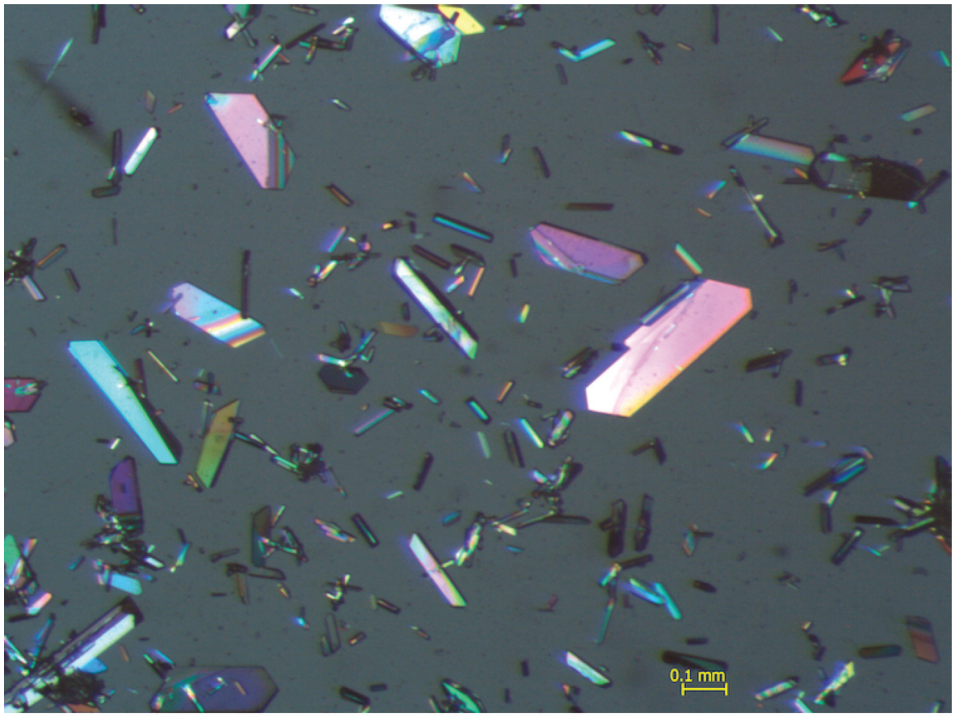
Powder X-ray diffraction (XRD) was performed on a PANalytical multipurpose diffractometer (MPD) using a Cu Kα source and fitted with a Pixel array detector. The samples of $\mathbf{1}_{monoclinic}$, $\mathbf{1}_{acetone}$, $\mathbf{1}_{racemate}$ and $\mathbf{1}_{pharma}$ were each packed into a 20 mm stainless steel sample holder fitted with a plastic disk to minimize the sample volume required. XRD was performed in a continuous scanning mode to collect diffraction peaks from 5° to 50° 2θ. Dynamic studies were performed by leaving the detector in static mode to enable simultaneous collection of diffraction peaks over a 2θ range of 3.4° every 10 s.

Raman microspectroscopy was performed using a PerkinElmer RamanStation 400F spectrometer, equipped with a high-resolution echelle spectrograph and a 785 nm excitation source (∼100 mW at the sample). Solid-state transition studies were performed by placing a small quantity of freshly filtered solvate on to a glass microscope slide, focusing the laser on to a crystalline mass, and measuring a Raman spectrum every minute for 2 h.

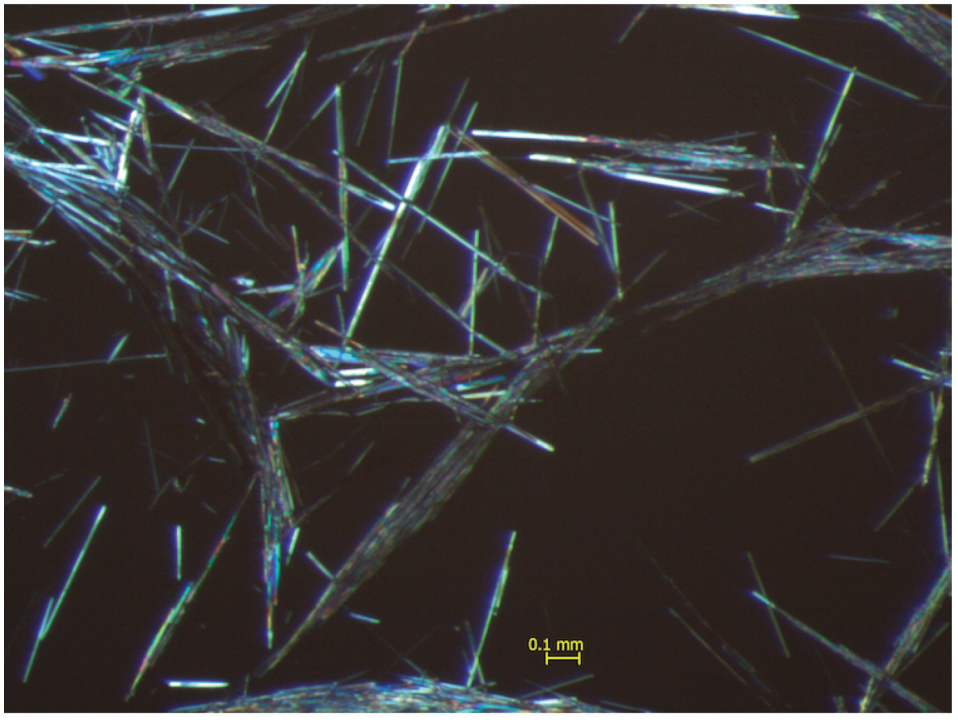
Infrared spectra were measured on a PerkinElmer Spotlight 400 FTIR spectrometer fitted with a liquid-nitrogen-cooled MCT detector and recorded in transmission mode by focusing the incident beam through a single-crystal of $\mathbf{1}_{acetone}$. The sample was placed between two CaF_2 plates fitted with a polymer O-ring to avoid compression and the assembly sealed to minimize evaporation of acetone. The conversion was monitored by recording a spectrum every minute for one hour and a final spectrum recorded after leaving the sample overnight.

Solid-state nuclear magnetic resonance (NMR) spectroscopy was performed using a Bruker Avance III NMR spectrometer using a 300 MHz operating frequency. Samples of $\mathbf{1}_{monoclinic}$, $\mathbf{1}_{acetone}$, $\mathbf{1}_{racemate}$ and $\mathbf{1}_{pharma}$ (∼80 mg) were packed into 4 mm o.d. zirconia rotors, capped with airtight Kel-F Bruker rotor caps and spun at the magic angle between 6 and 15 kHz, under control of a Bruker MAS II unit to ±2 Hz. Spectra were acquired at the respective ^{13}C frequencies of 75.47, 125.3, and 175.5 MHz, using cross-polarization (CP) and magic angle spinning (MAS), with 1−2 ms contact times, and 5−20 s recycle times. All high-power ^{1}H decoupling was performed with the Spinal64 sequence, with decoupling fields of 100 kHz (2.5 μs ^{1}H 90° pulse) on the 300 instrument. Where needed, the TOSS pulse sequence (total suppression of spinning side bands) was used to eliminate interference from spinning side bands, with an 8 μs ^{13}C 180° pulse. Variable temperature MAS experiments were conducted using a Bruker BCU-X for cooling and a Bruker BVT300 variable temperature unit for controlling the temperature. The instrument was set up for CPMAS experiments using KBr to calibrate the magic angle, and glycine to calibrate the Hartmann−Hahn match and decoupler fields. ^{13}C NMR chemical shifts were referenced to the glycine C=O at 176 ppm. The solution state nuclear magnetic resonance (NMR) spectroscopy given in the Supporting Information was performed using a Bruker Avance III NMR spectrometer at a 600 MHz operating frequency.

Gravimetric analysis of the evaporation rate of bulk acetone desolvation of $\mathbf{1}_{acetone}$ was performed at room temperature (23 °C) using freshly crystallized solvate on a 3-figure balance and monitoring the mass change over a 2 h time period.



(a)



(b)

Figure 1. Polarized light micrographs of (a) prisms of $\mathbf{1}_{monoclinic}$ crystallized from dioxane (b) and needles of $\mathbf{1}_{acetone}$ crystallized from acetone.

RESULTS AND DISCUSSION

Polymorphism Studies. Prior studies of the solid-state behavior of **1** have noted up to three different polymorphs of duloxetine hydrochloride characterized by DSC, vibrational spectroscopy and powder XRD.[4] Although these are common and useful techniques for characterization of new structures, there exists some possibility that polymorphs identified in this way are in fact new crystal structures arising from chemical changes to the sample.

This possibility encouraged us to undertake a structural investigation of **1** crystallized from a range of common organic solvents, and examining the resulting solids using X-ray crystallography and solid-state NMR, along with the other techniques used in previous studies. The selection of solvents was not comprehensive[13] but based on previous reports of

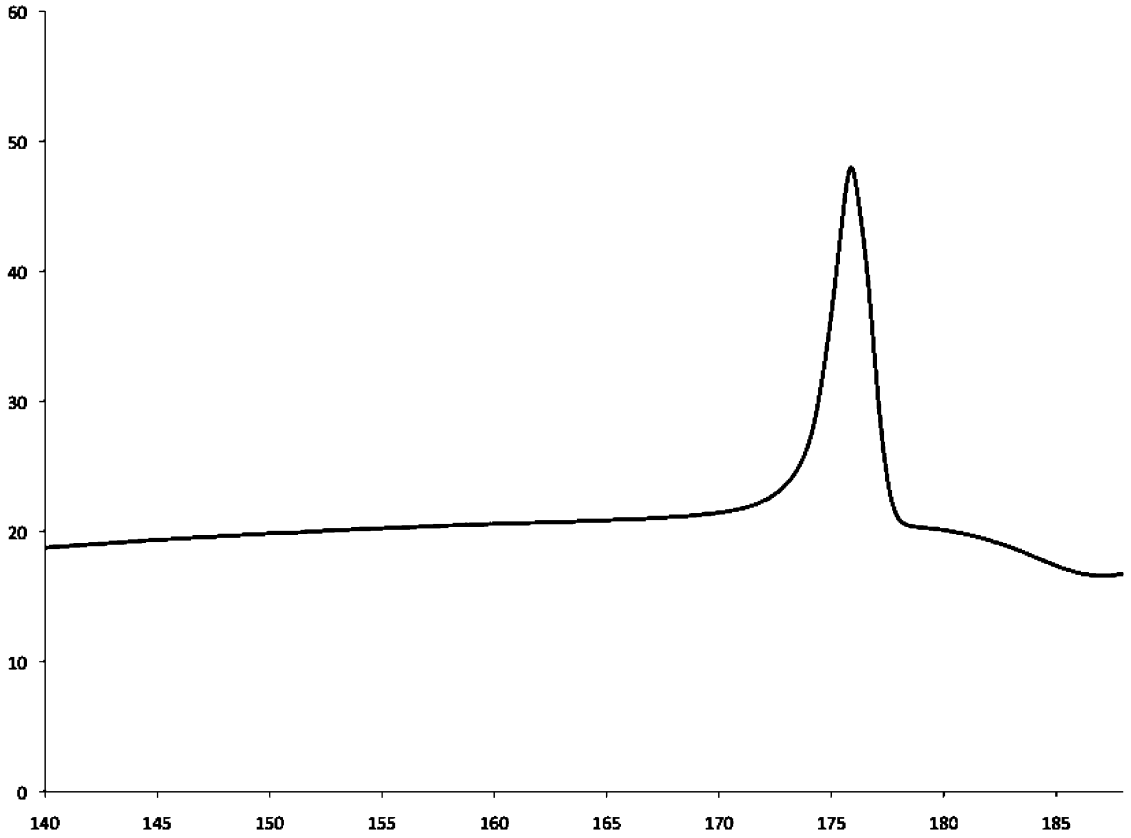


Figure 2. DSC trace showing heat flow (mW) versus temperature (°C) of $\mathbf{1}_{monoclinic}$. The only endotherm (positive peak) identified under the measurement conditions was that at 173 °C due to melting of the compound.

solvents likely to generate polymorphs.[4] The study also collected solid-state NMR and powder XRD data on the racemic **1**, to confirm that it was not present as a "false positive" due to epimerization at its stereocenter.

A previous study by the authors revealed that crystals from 1,4-dioxane were suitable for single-crystal X-ray structure determination resulting in $\mathbf{1}_{monoclinic}$ (Figure 1a). The unit cell parameters from the structure $\mathbf{1}_{monoclinic}$ enabled screening from various solvents using X-ray crystallography. Although relatively time-consuming, a structural technique like X-ray crystallography provides absolute certainty of the structure and chemistry arising from solvent inclusion or polymorphism and, in addition, can provide information about the short-term stability of these new structures at ambient temperature. In this study, single-crystal XRD confirmed that thin plates with identical unit cell dimensions to $\mathbf{1}_{monoclinic}$ were obtained when crystallizing from acetonitrile and 2-propanol. Crystals from chlorobenzene were very thin silky fibers unsuitable for single-crystal analysis. Crystals from the first three solvents yielded the same monoclinic P2(1) form having unit-cell parameters as given in Table S1 in the Supporting Information. No crystal resulted from solutions of dimethyl sulfoxide. Only acetone produced needles with a new unit cell, and they had to be taken out from the solution immediately and mounted along with its mother liquor with a coating of paraffin oil to prevent solvent loss to enable the inclusion compound to be measured (Figure 1b).

The $\mathbf{1}_{monoclinic}$ from 1,4-dioxane was examined using differential scanning calorimetry (DSC) to see if heating could induce any new structural transitions. The DSC trace (Figure 2) shows a single endotherm with an onset at 173 °C associated with melting of the compound. The absence of other endotherms suggests that no other structural changes from $\mathbf{1}_{monoclinic}$ have occurred under the conditions of the measurement, although this does not discount the possibility that $\mathbf{1}_{monoclinic}$ is a metastable polymorph. No attempt was made to examine the DSC of $\mathbf{1}_{acetone}$ owing to its spontaneous desolvation to $\mathbf{1}_{monoclinic}$ at ambient temperature and open atmosphere.

Structural Forms of 1. The X-ray crystal structure of the duloxetine acetone solvate reveals that $\mathbf{1}_{acetone}$ is a channel structure where naphthalene groups form channel walls (Figure 3) and acetone guest molecules lie in an ordered chain within the channel. Desolvation is rapid at room temperature resulting

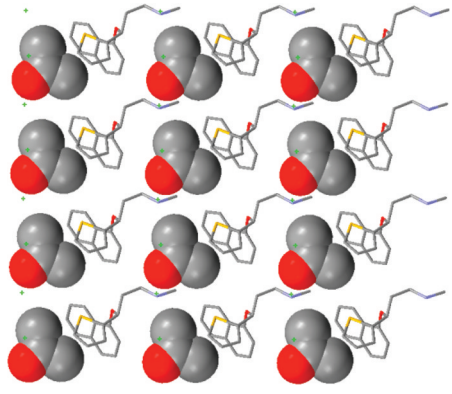


Figure 3. View down *c*-axis of the solvate showing three vertical channels (along *a*-axis) filled with acetone. Hydrogen atoms removed for clarity.

in an orderly "collapse" of the channels to form a microcrystalline solid with a more stable close-packed structure $\mathbf{1}_{monoclinic}$ (Figure 4).

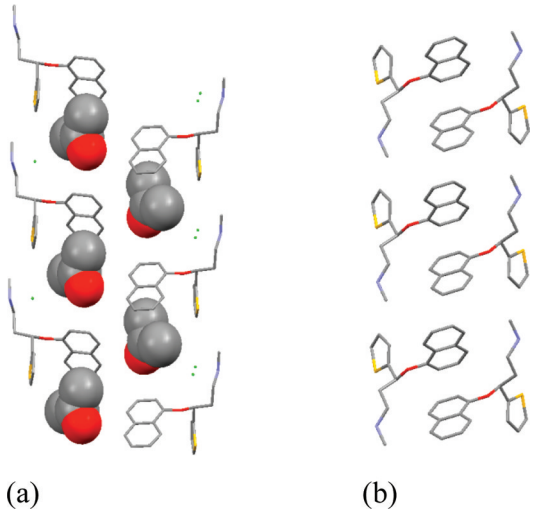


Figure 4. View down 5 channels of the acetone solvate $\mathbf{1}_{acetone}$ (a) and desolvated structure, $\mathbf{1}_{monoclinic}$, (b). Hydrogen atoms removed for clarity and chlorine ions shown in green.

Inclusion of a solvent within an open organic framework is a well-known phenomenon. Unlike open frameworks comprising strong metal−donor ligands (zeolite structures or covalently constrained organic cages), organic molecules that exhibit inclusion behavior typically pack poorly in the absence of a guest molecule. As a result it is often difficult to obtain unsolvated crystals suitable for single-crystal X-ray analysis from organic molecules prone to forming solvates. Duloxetine hydrochloride is relatively unusual in this regard since it provides high-quality crystals from acetone to form the solvate $\mathbf{1}_{acetone}$, but also crystallizes well from a range of similarly sized solvents to form its guest-free structure, $\mathbf{1}_{monoclinic}$. This provides start and end points for the solid-state transformation of $\mathbf{1}_{acetone}$ to $\mathbf{1}_{monoclinic}$ and enables speculation as to the molecular motions required to facilitate the transition.

Both $\mathbf{1}_{acetone}$ and $\mathbf{1}_{monoclinic}$ appear to lack strong noncovalent interactions, despite the presence of strong hydrogen bond donors and acceptors. The structures are dominated by close packing that maximizes van der Waals forces between nonpolar residues, a number of weak hydrogen bonds, and long-range electrostatic forces from the ammonium and chloride ions. Figure 5 shows acetone is only constrained by relatively weak noncovalent interactions.

The solvate $\mathbf{1}_{acetone}$ was found to be metastable when sealed with a slight excess of acetone. On exposing the solvate to atmospheric pressure, the acetone guest leaves the channels of **1**, resulting in clean conversion to the guest-free $\mathbf{1}_{monoclinic}$. The stackplot in Figure 6 shows the powder XRD patterns for the solvate (a) $\mathbf{1}_{acetone}$ and (b) $\mathbf{1}_{monoclinic}$. A complete conversion from the acetone solvate to $\mathbf{1}_{monoclinic}$ was observed by X-ray powder diffraction; there was no evidence of X-ray peaks from the solvate structure in the desolvated powder pattern. The X-ray powder pattern of the racemic form, $\mathbf{1}_{racemate}$ (Figure 6c), is also shown, and was not found to be present in any of the crystals of **1** produced by this study. This confirms that epimerization at the stereocenter had not occurred in our experiments, however it should provide a useful reference for

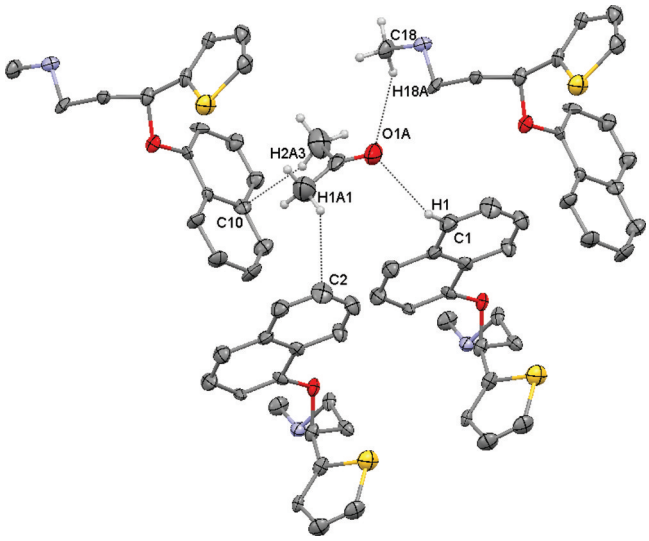


Figure 5. Weak CH−π and CH−O contacts between acetone and the naphthalene groups in $\mathbf{1}_{acetone}$ making up the channel wall of the solvate.

future studies of polymorphism of **1** or confirmation of structural purity of $\mathbf{1}_{monoclinic}$ that rely on powder diffraction data. The racemate has a distinct X-ray powder pattern compared to $\mathbf{1}_{monoclinic}$ that confirms that the racemate is not resolving itself into two sets of enantiopure crystals, but rather crystallizes as a single structure comprising both enantiomers.

The X-ray powder pattern of $\mathbf{1}_{pharma}$ in Figure 6d is a pharmaceutical formulation of 60 mg capsules of Cymbalta from Eli Lilly. A comparison with Figure 1a confirms that the stable form of duloxetine hydrochloride, $\mathbf{1}_{monoclinic}$, is present, however the presence of strong overlapping peaks from excipients used in the capsule formulation means that most of the peaks expected from $\mathbf{1}_{monoclinic}$ can be difficult to distinguish.

^{13}C solid-state NMR spectroscopy of each of the three different materials, $\mathbf{1}_{monoclinic}$, $\mathbf{1}_{acetone}$, and $\mathbf{1}_{racemate}$, revealed that there are quite distinct chemical environments for many of the carbon atoms in the duloxetine molecules, making them readily distinguishable by this technique (Figure 7). For ease of comparison, the ^{13}C NMR data is tabulated in Table 1. The assignment of the ^{13}C peaks was determined by extrapolation from the solution NMR assignments from high resolution ^{1}H and ^{13}C NMR 1-D and 2-D spectra acquired in chloroform-*d*, which have been included in the Supporting Information. Spectrum b in Figure 7 shows an obvious peak for the carbonyl group, and the methyl groups of the acetone guest at 205 ppm, and 29 ppm respectively. With a slight excess of acetone in the NMR rotor, no change was observed for over a period of more than 18 months when checked using ^{13}C solid-state NMR spectroscopy, confirming the stability of $\mathbf{1}_{acetone}$ in a closed system.

Although suitable crystals for single-crystal XRD of $\mathbf{1}_{racemate}$ have not as yet been obtained, the ^{13}C solid-state NMR of $\mathbf{1}_{racemate}$ (c) in Figure 7 supports the powder XRD data that the two enantiomers of **1** combine to form racemic crystals. A spontaneous resolution of the racemic material would give rise to powder XRD and ^{13}C solid-state NMR identical to the data for $\mathbf{1}_{monoclinic}$, and this is not observed.

The solid-state ^{13}C NMR spectra of $\mathbf{1}_{monoclinic}$, $\mathbf{1}_{acetone}$, and $\mathbf{1}_{racemate}$ demonstrate that the ^{13}C chemical shifts of **1** are highly

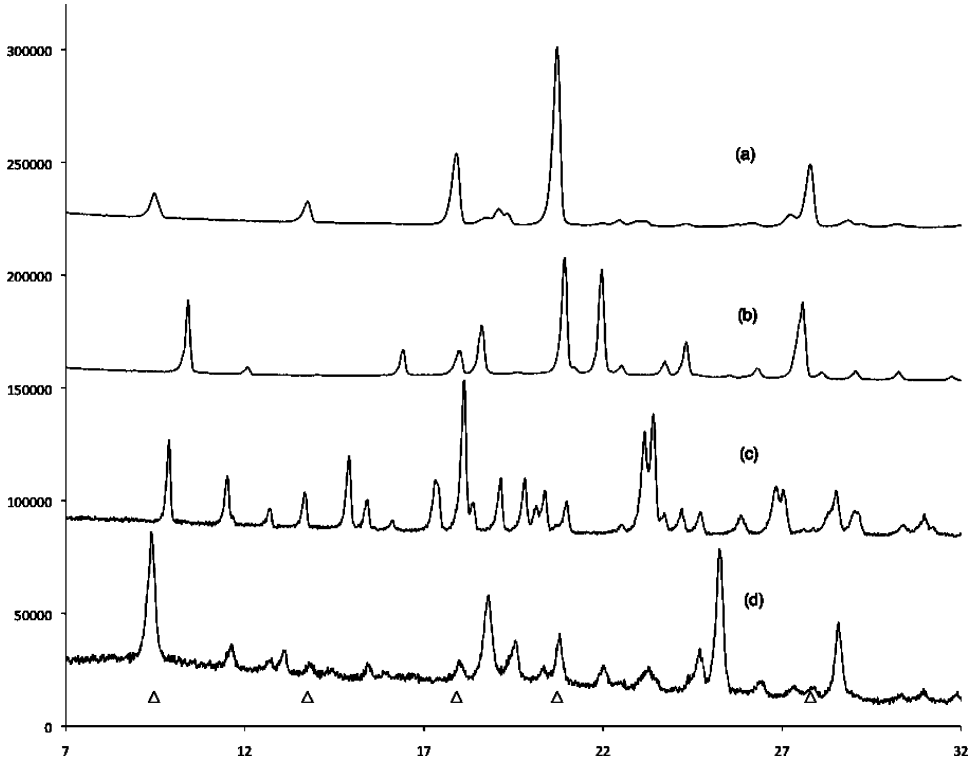


Figure 6. X-ray powder patterns showing (a) $\mathbf{1}_{\text{monoclinic}}$, (b) $\mathbf{1}_{\text{acetone}}$, (c) $\mathbf{1}_{\text{racemate}}$ and (d) $\mathbf{1}_{\text{pharma}}$. The patterns have been expanded and scaled to similar intensity for clarity. The triangular marks below (d) indicate peaks in $\mathbf{1}_{\text{pharma}}$ corresponding to peaks in the powder pattern of $\mathbf{1}_{\text{monoclinic}}$. The *y*-axis is arbitrary counts, and the *x*-axis is degrees 2θ.

diagnostic of the crystal structure. There are 11 peaks in the ^{13}C solid-state NMR spectrum of $\mathbf{1}_{\text{monoclinic}}$ (numbered in Figure 7a) that are clearly seen in the spectrum of the commercial form $\mathbf{1}_{\text{pharma}}$ (Figure 7d). This is strong evidence that duloxetine hydrochloride is present as its monoclinic form in Cymbalta. It is noteworthy that ^{13}C solid-state NMR, in this instance, is a superior technique to powder XRD for confirming structure of this pharmaceutical formulation of **1** especially if small quantities of other polymorphs are suspected.

Another notable observation in both the crystal structure and the solid-state NMR is the specific orientation of the thiophene ring in $\mathbf{1}_{\text{acetone}}$. A thiophene group is often rotationally disordered since both orientations have similar space requirements and the attractive interactions between the thiophene sulfur atoms and other atoms in the solid state are not sufficiently strong to favor one orientation over the other. In the crystal structure of $\mathbf{1}_{\text{monoclinic}}$, obtained at liquid nitrogen temperatures, the thiophene ring is disordered over two positions obtained by a 180° rotation about the C11−C12 bond with a small excess (0.58/0.42) biased toward the conformer where the thiophene sulfur is in close proximity to the ether oxygen. Further evidence for rotational motion in the solid state can be deduced from several features seen in the ^{13}C solid-state NMR spectrum of $\mathbf{1}_{\text{monoclinic}}$. CPMAS measurement of $\mathbf{1}_{\text{monoclinic}}$ at room temperature gives a spectrum which detects approximately sixteen to seventeen of the eighteen expected carbon atoms, when integrated, and these "missing" carbon atoms are in the thiophene group at ∼128 ppm. Also, the peak at 145 ppm assigned to C2 of the thiophene ring is significantly broader (100 Hz vs 35 Hz for a naphthyl carbon peak). Performing the CPMAS experiments at progressively lower temperatures achieved three things: first, the "missing" intensity from the spectrum was eventually recovered at 240 K; at this temperature, C2 at 145 ppm of the thiophene ring became two peaks, and other peaks from the thiophene ring appeared at ∼129 ppm (Figure 8); finally, the peak for the *N*-methyl group also split into two. These features can be explained by the thiophene ring adopting two conformations, thereby slowing sufficiently to allow cross-polarization, and also presenting two environments of "S" or "C−H" through space to the *N*-methyl group.

However the crystal structure of $\mathbf{1}_{\text{acetone}}$ displays only one rotational conformer, where the thiophene sulfur is in close proximity to the ether oxygen. Again, the ^{13}C solid-state NMR reveals a sharpening of the thiophene C2 peak expected for a single conformer. The sulfur−oxygen close contact is present in both crystal structures so it does not explain why the $\mathbf{1}_{\text{acetone}}$ structure displays a single rotational conformer and the $\mathbf{1}_{\text{monoclinic}}$ contains a mixture. In the absence of other attractive close contacts, we assume that the thiophene ring is comparatively sensitive to the packing arrangement. Geometric constraints permit the observed conformations in the solid state.

The observation of a rotational conformer in $\mathbf{1}_{\text{acetone}}$ suggests the intriguing possibility of a subtle type of polymorphism between $\mathbf{1}_{\text{monoclinic}}$ formed from decomposition of the solvate and $\mathbf{1}_{\text{monoclinic}}$ formed from crystallization from other solvents. However, it was not possible to determine if the rotational conformation was retained in $\mathbf{1}_{\text{monoclinic}}$ formed from decomposition of $\mathbf{1}_{\text{acetone}}$, and in any case the rotational motion of the thiophene in $\mathbf{1}_{\text{monoclinic}}$ would eventually result in the 0.58/0.42 ratio of conformers observed in the crystal structure.

Structural Transformation Kinetics of the Solvate. Several methods were employed to attempt to monitor the conversion of $\mathbf{1}_{\text{acetone}}$ to $\mathbf{1}_{\text{monoclinic}}$. The use of dynamic powder X-ray diffraction (Figure S1 in the Supporting Information),

dx.doi.org/10.1021/mp200455u | *Mol. Pharmaceutics* 2011, 8, 2454−2464

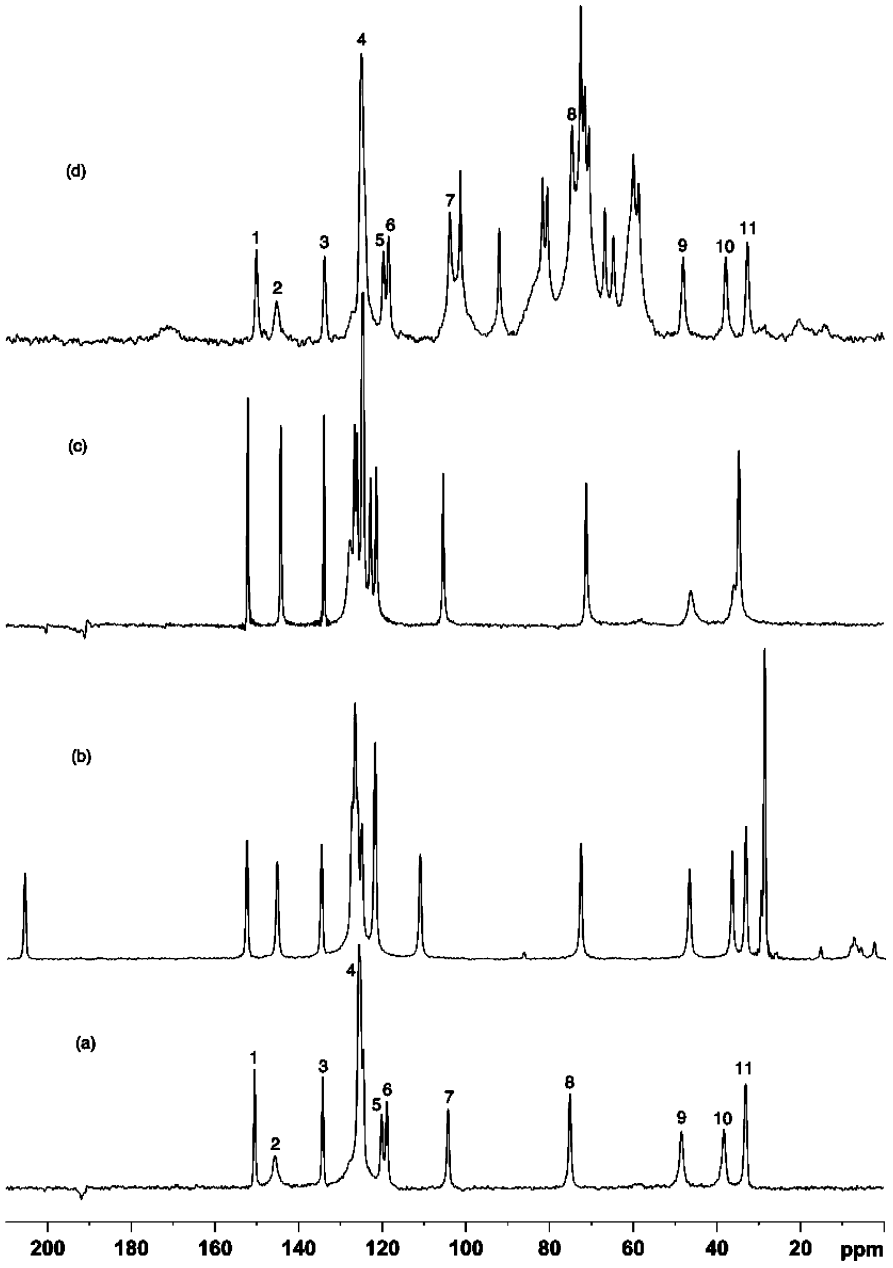


Figure 7. 75.4 MHz solid-state TOSS-CPMAS spectra of (a) $\mathbf{1}_{monoclinic}$ with peaks numbered 1 to 11; (b) $\mathbf{1}_{acetone}$; (c) $\mathbf{1}_{racemate}$; (d) $\mathbf{1}_{pharma}$ showing peaks 1 to 11 originating from $\mathbf{1}_{monoclinic}$. MAS, 8 kHz.

although initially promising, provided inconsistent desolvation rates, possibly due to packing variations of the fragile crystals of $\mathbf{1}_{acetone}$ within the sample holder. Dynamic Raman spectroscopy of the low-wavenumber region was expected to be a sensitive probe for molecular skeletal variations between the two structures. However the 785 nm diode laser induced localized heating in the sample, and there was likely to be thermally induced solvent loss as well as possible chemical degradation after repeated exposure to the laser during the analysis. Standard Raman spectroscopy did not require multiple exposures of $\mathbf{1}_{monoclinic}$ by the laser and was measured without any obvious degradation of the sample (Figure S2 in the Supporting Information).

Attenuated total reflectance Fourier-transform infrared (ATR-FTIR) provided an excellent spectrum of $\mathbf{1}_{monoclinic}$ (Figure S3 in the Supporting Information); however, the use of ATR-FTIR to monitor the desolvation of $\mathbf{1}_{acetone}$ was unsuccessful as the technique applies pressure to the sample against the ATR crystal resulting in immediate desolvation. An FTIR microspectrometer enables noncontact analysis as the incident FTIR beam can be focused and directed through a single-crystal of the sample. This technique avoids direct contact that could induce desolvation, although the FTIR beam does transfer thermal energy to the acetone that could increase the rate of desolvation. Figure 9a shows the FTIR transmission spectra of $\mathbf{1}_{acetone}$ converting to $\mathbf{1}_{monoclinic}$ and is compared to a liquid acetone spectrum (scans 1, 5, 10, 15, and 20 are displayed which correspond to 0, 5, 10, 15, and 20 min after recrystallization). Surprisingly the spectra show two carbonyl stretches that can be interpreted as acetone trapped in the lattice (1706 cm^{-1}) and bulk acetone (1736 cm^{-1}). The lattice-trapped acetone shows a large 30 cm^{-1} shift to lower energy

Table 1. ^{13}C NMR Chemical Shifts of Duloxetine Hydrochloride in Solution and the Solid State

		solid[b]		
assignment	soln[a]	$\mathbf{1}_{monoclinic}$	$\mathbf{1}_{acetone}$	$\mathbf{1}_{racemic}$
acetone C═O			205.4	
C1 α-naphthyl	152.9	150.5	152.3	152.2
C2-thiophenyl	142.4	145.7	145.0	144.3
ArC	134.9	134.2	134.5	133.9
ArH	128.0	(130−122)	(130−120)	(130−123)
ArH	127.3	(130−122)	(130−120)	(130−123)
thiophenyl CH	126.9	(130−122)	(130−120)	(130−123)
ArH	126.3	(130−122)	(130−120)	(130−123)
ArH	126.1	(130−122)	(130−120)	(130−123)
ArH	126.0	(130−122)	(130−120)	(130−123)
thiophenyl CH	125.9	(130−122)	(130−120)	(130−123)
thiophenyl CH	125.8	(130−122)	(130−120)	(130−123)
ArH	122.3	120.1	(130−120)	122.9
ArH	121.5	118.4	(130−120)	121.5
ArH	107.7	104.3	110.9	105.5
O−CH−	73.6	75.1	72.4	71.3
$-CH_2-N$	46.5	48.5	46.5	46.3
$-C-CH_2$	35.3	38.2	36.3	35.8
$N-CH_3$	33.4	33.1	33.0	34.8
acetone CH_3			29.4	
acetone CH_3			28.5	

[a] ^{1}H and ^{13}C spectra measured in as 0.56 mM $CDCl_3$ solutions; see Experimental Section for referencing. [b] ^{13}C solid-state NMR data acquired; see Experimental Section.

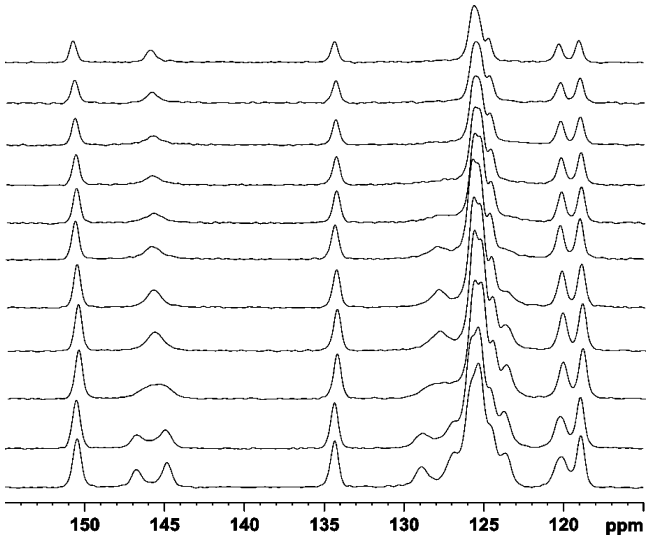


Figure 8. Variable temperature 75.4 MHz solid-state TOSS CPMAS spectra of $\mathbf{1}_{monoclinic}$ with MAS, 5 kHz showing coalescence of peaks ~145 ppm and ~128 ppm in the aromatic region. Temperature increases in 10 K increments from 235 K (bottom spectrum to top).

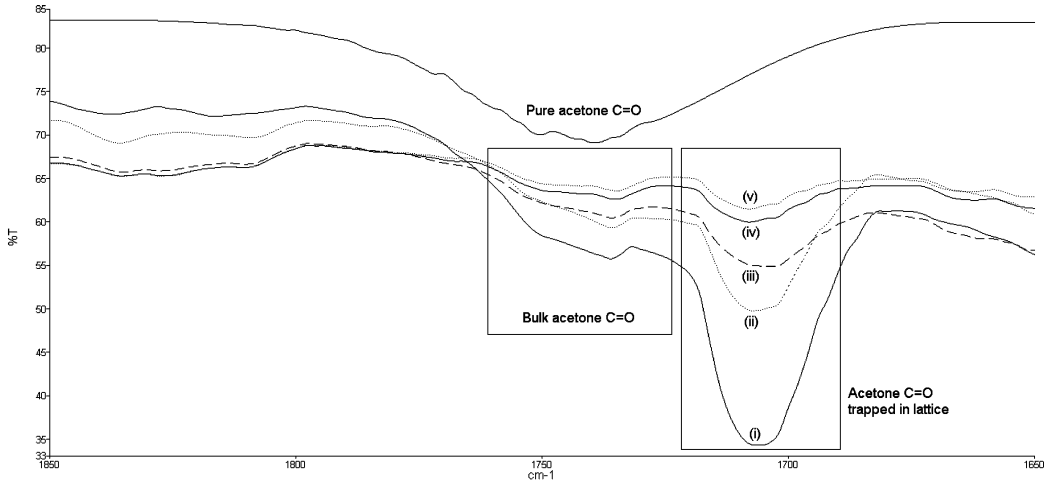
that could indicate less double-bond character in the carbonyl group[14] although it is difficult to see how the weak C−H···O hydrogen bond facilitates this change in double-bond character.

The intensity of the bound acetone carbonyl at 1706 cm^{-1} could be ratioed against the total intensity of two peaks at 1595 cm^{-1} and 1578 cm^{-1} that were found to maintain a constant intensity throughout the experiment. Figure 9b shows a plot of the fractional decomposition (alpha = [initial peak intensity] − [peak intensity]$_i$/[initial peak intensity]) over time. The desolvation data was fitted to several models to try and understand the kinetics of desolvation,[15] and there was some expectation that the contracting area model would be appropriate in this case.[16] However the best fit (R^2 = 0.9671) was achieved by assuming a first order reaction with a rate constant of k = 0.00336 s^{-1}.

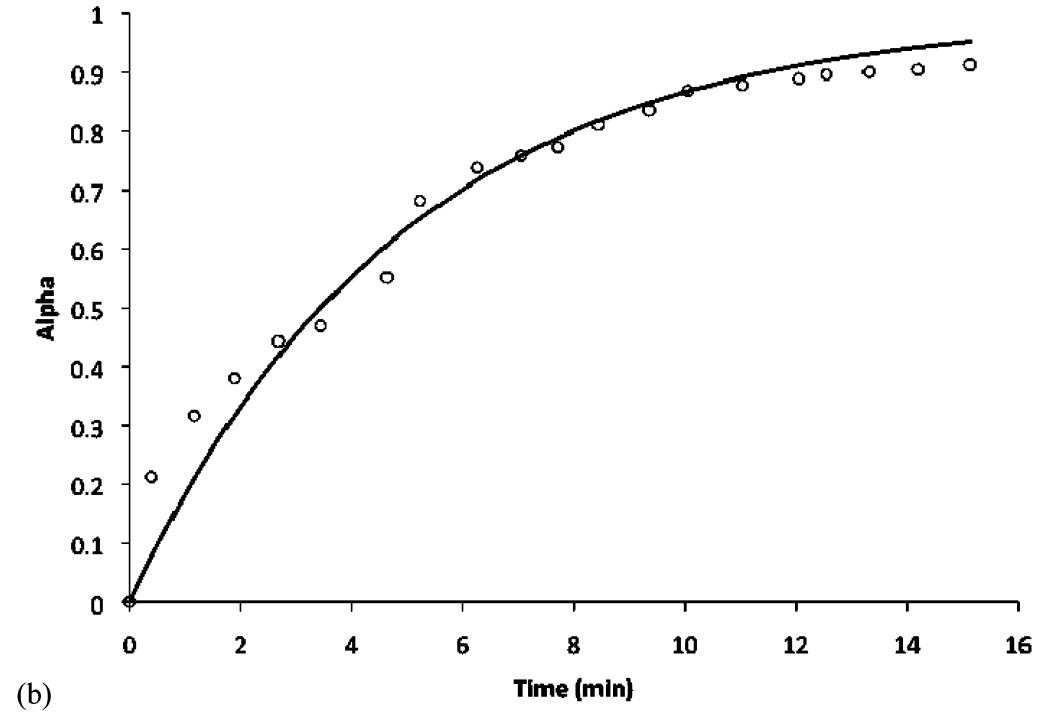
The kinetics of solvent loss could also be monitored using gravimetric analysis to follow the mass changes of $\mathbf{1}_{acetone}$ over time. Due to the low stability in open air the solvate was filtered and immediately placed on a balance. The resulting crystalline mass contained a significant proportion of bulk acetone, and Figure 10 shows the portion of the fractional decomposition (alpha = [initial acetone mass] − [acetone mass]$_i$/[initial acetone mass]) where one equivalent of acetone was calculated to remain. The evaporation rate for liquid acetone from an open 20 mm i.d. sample tube was also measured and provides a qualitative comparison to demonstrate that the evaporation rate of liquid acetone is faster than the mass loss from $\mathbf{1}_{acetone}$. Obviously the duloxetine hydrochloride host lattice is retarding the evaporation of the solvent.

Least squares fitting of the gravimetric data to a first order reaction resulted in a rate constant of 0.000978 s^{-1} (R^2 = 0.9989), 3.4 times smaller than the rate constant measured using FTIR. Although FTIR has an advantage of discriminating between acetone in different phases, which is not possible with gravimetric analysis, the incident infrared beam clearly imparts sufficient energy to increase the rate of desolvation during the measurement, influencing the kinetics. Despite the differences in rate constant, fitting to a first order reaction consistently provided the best fit to both sets of data.

The evaporation of acetone shown in Figure 10 is fast and essentially zero-order under these conditions. One proposal for a rate determining step is acetone diffusion through the channels out through an exposed crystal face. The resulting unstable empty channels would have sufficient space for duloxetine molecules to reorganize into the $\mathbf{1}_{monoclinic}$ form. Figure 11 shows overlays of the molecular conformers found in



(a)



(b)

Figure 9. (a) Spectral expansion of transmission FTIR time series showing $\mathbf{1}_{acetone}$ as it desolvates to $\mathbf{1}_{monoclinic}$ and compared to a spectrum of pure acetone. The subset of spectra are (i) 99 s, (ii) 260 s, (iii) 522 s, (iv) 761 s, (v) 1006 s. The *y*-axis is percent transmission, and the *x*-axis is wavenumbers (cm^{-1}). (b) Experimental and least-squares fitted fractional decomposition (alpha) versus time for $\mathbf{1}_{acetone}$ to $\mathbf{1}_{monoclinic}$.

each structure of duloxetine. There are a single duloxetine conformer in the unit cell of the acetone solvate and two duloxetine conformers in the $\mathbf{1}_{monoclinic}$ unit cell. Both structures show a rotation of the naphthalene group relative to the thiophene and methylamine side chains; however, the conformational changes are not large. The X-ray single-crystal and solid-state ^{13}C NMR data of $\mathbf{1}_{monoclinic}$ show that the thiophene has some rotational freedom, even in the solid state, presumably due to less restrictive packing. This freedom of motion allowing orderly repacking would account for the creation of a microcrystalline solid of $\mathbf{1}_{monoclinic}$ capable of generating a powder XRD pattern, rather than reverting to an amorphous phase.

When screening for new structures of **1** we noted its poor stability to excessive heating in solvents, and a tendency to develop a yellow coloration when exposed to air after several weeks. The chemical nature of the decomposition was not explored; however, the phenomenon of poor chemical stability and the potential for epimerization of the *S*-enantiomer stand as warning to future investigators looking for new polymorphic forms of **1**. When a new polymorph of duloxetine hydrochloride is detected, it is necessary to confirm its chemical purity by the usual methods (solution NMR, HPLC for example) as well as comparing it to the solid-state NMR and powder XRD. The powder XRD of the racemic duloxetine hydrochloride presented in this study may be useful to ensure that epimerization has not occurred during crystallization, avoiding the requirement of optical rotation measurements or chiral HPLC. The only polymorphic behavior observed in this study was the formation of the 1:1 acetone solvate that was

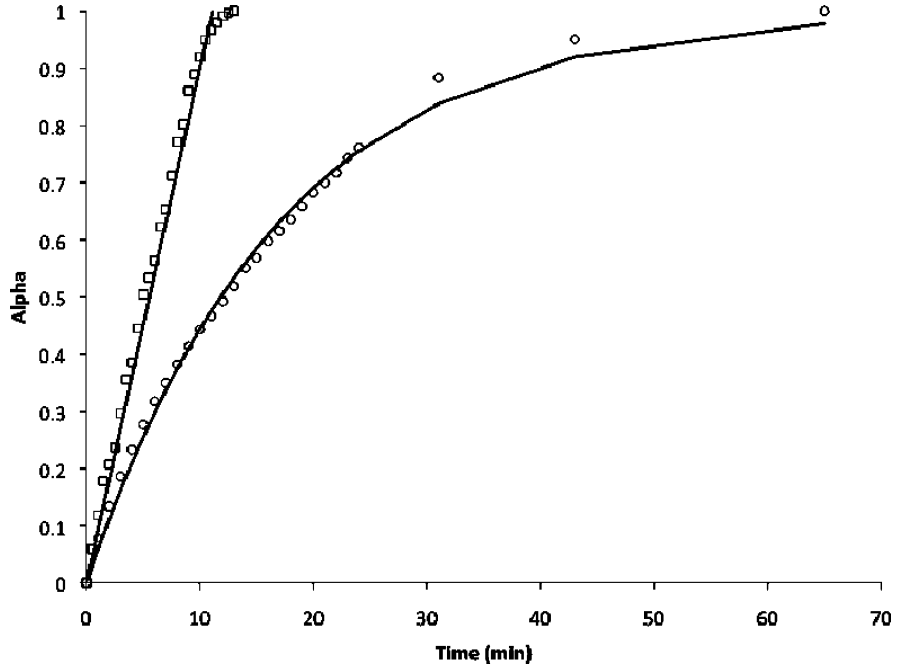


Figure 10. Gravimetric analysis of the desolvation of $\mathbf{1}_{acetone}$ to $\mathbf{1}_{monoclinic}$ (circles) and evaporation of liquid acetone (squares). The line is the least-squares fit to a zero order reaction (liquid acetone) and a first order reaction ($\mathbf{1}_{acetone}$ to $\mathbf{1}_{monoclinic}$). The *y*-axis shows the mass fraction, alpha, and the *x*-axis shows minutes elapsed.

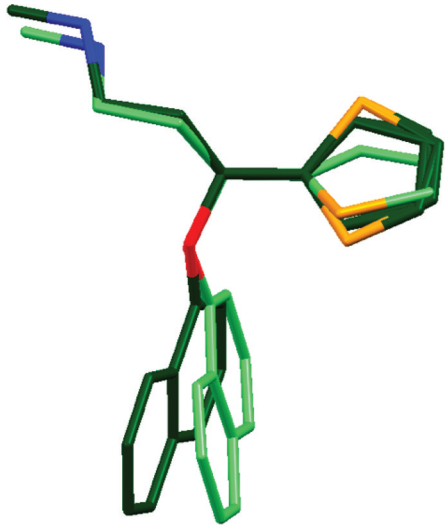


Figure 11. Overlap of conformations of duloxetine hydrochloride in crystals of $\mathbf{1}_{monoclinic}$ and of $\mathbf{1}_{acetone}$. The dark green structure found in $\mathbf{1}_{monoclinic}$ shows two orientations of thiophene, and the light green structure found in $\mathbf{1}_{acetone}$ shows a single thiophene orientation. The notable conformational differences are the orientation of the naphthalene moiety and the orientation of the thiophene ring.

stable when sealed, but spontaneously desolvated within a few hours to the standard monoclinic form $\mathbf{1}_{monoclinic}$ when open to the atmosphere. This was conclusively demonstrated by powder XRD and solid-state NMR. This structural transformation may be entropically driven by release of solvent from the crystal since comparison of the intermolecular interactions in X-ray crystal structures show only van der Waals bonds and weak hydrogen bonds and no new strong intermolecular interaction is present in $\mathbf{1}_{monoclinic}$. Only slight changes in the molecular conformation of duloxetine were observed in each crystal structure, so reduction of molecular strain in the host lattice is not a factor. The acetone carbonyl stretch in the FTIR was found to be significantly different to the free acetone carbonyl stretch, perhaps due to weak interactions from close contacts in the crystal.

CONCLUSIONS

This study highlights the importance of collecting thorough structural and chemical characterization data when searching for polymorphic forms of a new pharmaceutical like duloxetine hydrochloride. Our findings imply that true polymorphs and solvates of **1** are probably rare, or at the least quite challenging to prepare, and data presented here will help to avoid any spurious assignments of polymorphism in **1** for future studies. The structural form of **1** in a common commercial formulation of duloxetine hydrochloride, Eli Lilly's Cymbalta, was confirmed as $\mathbf{1}_{monoclinic}$ by solid-state NMR and powder XRD. The discovery of the unstable solvate $\mathbf{1}_{acetone}$ provides a new route to $\mathbf{1}_{monoclinic}$ that may possess unique physical properties such as higher surface area and bioavailability, or compressibility during tablet formulation. An investigation of the physical properties of $\mathbf{1}_{monoclinic}$ prepared in this way will be the subject of future work on this important new pharmaceutical.

ASSOCIATED CONTENT

Supporting Information

Crystallographic details, additional XRD, Raman and FTIR spectra and comprehensive solution state NMR analysis of duloxetine hydrochloride. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

The authors are grateful to Dr. Qing Hong Lin of Arrow Pharmaceuticals Pty Ltd in Melbourne Australia for the donation of duloxetine hydrochloride, to Mr. John Arthur for performing the DSC measurements, to Mrs. Hilda Stender for expertise with the solution state NMR measurements, and to the Mark Wainwright Analytical Centre for provision of an ARGC Grant to M.B. and A.M.R.

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