Accepted Manuscript

Title: Thermodynamics of Fenofibrate and Solubility in Pure Organic Solvents

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PII: S0378-3812(14)00054-5
DOI: http://dx.doi.org/doi:10.1016/j.fluid.2014.01.029
Reference: FLUID 9976

To appear in: Fluid Phase Equilibria

Received date: 8-10-2013
Revised date: 22-1-2014
Accepted date: 23-1-2014

Please cite this article as: S. Watterson, S. Hudson, M. Svärd, Å.C. Rasmuson, Thermodynamics of Fenofibrate and Solubility in Pure Organic Solvents, Fluid Phase Equilibria (2014), http://dx.doi.org/10.1016/j.fluid.2014.01.029

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Thermodynamics of Fenofibrate and Solubility in Pure Organic Solvents

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Highlights

!! Solubility data of fenofibrate FI was collected between 5–45°C in seven pure solvents.

!! Melting data and heat capacity of the solid and the melt were measured with DSC.

!! Fusion thermodynamics and ideal solubility were calculated using experimental data.

!! The heat capacity component of the enthalpy of fusion is shown to be important.

!! In some solvents the activity coefficient term controls the shape of van’t Hoff plots.

Abstract

Calorimetric data on the melting of 1-methylethyl 2-[4-(4-chlorobenzoyl)-phenoxy]-2-methylpropanoate (fenofibrate) and the heat capacity of the solid and the melt have been determined, from which the Gibbs energy, enthalpy and entropy of fusion are calculated. Solid-liquid solubility data have been collected by a gravimetric method in seven pure solvents (methanol, ethanol, 1-propanol, 2-propanol, ethyl acetate, acetonitrile, and acetone) across a range of temperatures. Fenofibrate is much more soluble in ethyl acetate, acetonitrile and acetone compared to alcohols. In the alcohols the solubility increases with aliphatic chain length. The Gibbs energy of fusion is used to estimate the activity of the solid within a Raoult’s law framework. Except for ethyl acetate solutions which are almost ideal, solutions in all evaluated solvents exhibit positive deviation from Raoult’s law, and in the alcohols the activity coefficient ranges up to 25. It is shown that the heat capacity component of the enthalpy of fusion is not negligible at room temperature, in spite of the proximity to the melting point, and furthermore that the temperature dependence of the activity coefficient in the saturated solution has a governing influence on the van’t Hoff enthalpy of solution in acetonitrile and the alcohols. Crystals obtained by two different methods from a range of solvents have been analysed by PXRD, FTIR and NMR spectroscopy, TGA and DSC, and have in all cases been shown to consist of the stable polymorph (form I).
Keywords: crystallisation; thermodynamics; solubility; activity coefficient; heat capacity
1. Introduction

Crystallisation is an important unit operation in many branches of the chemical industry where it is widely used for purification. It is of particular importance in the pharmaceutical industry, as most pharmaceutical products contain crystalline material, and it is often necessary that the process can be controlled to yield crystals of required purity and specified size, shape and polymorph. This requires a thorough control of the supersaturation during the process, and thus an understanding of the thermodynamics of solution as well as of the solid state. The ability to predict what solvents are most appropriate for a particular compound and process is highly desirable. This requires an understanding of how the compound interacts with different solvents to explain the solubility and the crystallisation behaviour. 1-methylethyl 2-[4-(4-chlorobenzoyl)-phenoxy]-2-methylpropanoate (fenofibrate) is a medium-sized, flexible, chlorinated and lipophilic molecule. The molecular structure is shown in Fig. 1. The vast majority of literature dealing with this compound concerns its clinical action, bioavailability, and formulation [1-5]. In addition there is some limited literature concerning its physico-chemical properties [6-11], including spectroscopic and analytical data [12-15], and the crystal structures of its two known polymorphs [16-18]. Some rough solubility data for a number of solvents are reported, with no mention of temperature [7]. However, at the time of writing (to the best of the knowledge of the authors), there is almost no published data of good quality on the solubility in different solvents.

![Molecular structure of fenofibrate](image_url)

**Fig. 1.** Molecular structure of fenofibrate.

In the present work, the melting properties and the heat capacity of the pure compound in the solid state and as a melt have been experimentally determined and solid phase thermodynamic properties estimated. The solid-liquid solubility has been determined in seven different solvents and is analysed within a thermodynamic framework to estimate solution activity coefficients and to examine the temperature dependence of the solubility. As thermodynamic properties of a solid phase are strongly dependent on the crystal structure, the
work includes a careful characterisation by spectroscopic and diffraction methods of the particular solid phase for which the thermodynamic data are presented.

2. Experimental work

2.1. Materials

Table 1 lists the chemicals used, where they were obtained and their listed purity. All chemicals were used as received without further purification.

Table 1. Source and mass fraction purity of chemicals.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
<th>Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenofibrate</td>
<td>AbbVie, IL., USA</td>
<td>0.997</td>
</tr>
<tr>
<td>Methanol</td>
<td>Sigma-Aldrich</td>
<td>0.997</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Sigma-Aldrich</td>
<td>0.997</td>
</tr>
<tr>
<td>1-Propanol</td>
<td>Sigma-Aldrich</td>
<td>0.997</td>
</tr>
<tr>
<td>2-Propanol</td>
<td>Sigma-Aldrich</td>
<td>0.997</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>Sigma-Aldrich</td>
<td>0.997</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>Sigma-Aldrich</td>
<td>0.997</td>
</tr>
<tr>
<td>Acetone</td>
<td>Sigma-Aldrich</td>
<td>0.997</td>
</tr>
</tbody>
</table>

2.2. Solubility

Excess solid fenofibrate was placed in 10-15 ml of solvent in 30 ml sealed vials, equipped with magnetic stirrer bars. The temperature was controlled by a water-bath (Grant GR150, stability ± 0.005 K and uniformity ± 0.02 K at 310 K). The solutions were stirred for 24 hours. Some of the supernatant liquid was extracted into pre-heated syringes and was then filtered into empty vials. The filters (0.2 μm PTFE) and syringes were pre-heated to 10 K above the dissolution temperature. The vials were sealed and weighed immediately in order to minimise evaporation. They were then left open in a fume hood for the solvent to evaporate. The vials and dry fenofibrate were weighed twice daily until no further weight change was observed (the balance was accurate to ± 0.0001 g). At least two samples for each condition were collected.

2.3. Crystallisation

Undersaturated solutions of fenofibrate in seven different solvents (methanol, ethanol, 1-propanol, acetonitrile, ethyl acetate, acetone, and toluene) were put in vials sealed with Parafilm. The seal was punctured with a number of holes to allow solvent to evaporate at a slow rate. The vials were left in a fume hood at room temperature until nucleation and crystal growth occurred.

Solutions of fenofibrate in five different solvents (methanol, ethanol, 1-propanol, acetonitrile and ethyl acetate) were also prepared in sealed, stirred vials with concentrations corresponding to saturation at 318 K. These vials were preheated in a water-bath at 328 K for over four hours, and then quickly cooled in a water-bath at 293 K until nucleation and crystal growth occurred without agitation.

2.4. Solid-state Characterisation
Dried crystal samples were spin-coated with gold and observed with a JEOL CarryScope Scanning Electron Microscope (SEM) JCM-5700. For some larger crystals photographs taken with digital camera were sufficient. Crystal samples were analysed using a Perkin-Elmer Universal ATR Sampling Accessory attached to a Perkin-Elmer Spectrum 100 Fourier-Transform Infrared (FTIR) spectrometer. Absorbance spectra were collected using 2 co-added scans in the infrared region between 600 and 4,000 cm\(^{-1}\) with the background subtracted and a resolution of 2 cm\(^{-1}\). \(^1\)H nuclear magnetic resonance (NMR) spectroscopy was carried out using a JEOL JNM-GSX 270 FT NMR spectrometer at 270 MHz. Samples were dissolved in deuterated chloroform (99.8% deuteration, 0.03% TMS, VWR BDH Prolabo). Thermo-gravimetric analysis (TA Instruments, SDT Q600) was carried out to determine at what temperature weight loss could be detected. X-ray diffraction analysis was carried out on crystals as received and samples of all recrystallised material using a Philips PANalytical X’Pert MPD Pro with PW3064 sample spinner. The recrystallised samples were ground to powder and placed on zero-background silica disks. The diffraction pattern was collected between 5 and 40° (2θ) with a step size of 0.0167°, a counting time of 29.845 s, and a sample rotation of 15 rpm using PANalytical Data Collector, version 2.0. The source was Cu K\(_\alpha\) (\(\lambda = 1.5418 \, \text{Å}\)), the accelerating voltage was 40 kV, and the anode current was 35 mA. A fixed divergence slit of ¼” and a 0.020 mm nickel filter were used.

Melting properties of the stable form I were measured with differential scanning calorimetry (DSC) using a TA Instruments MDSC 2920. Samples (5-7 mg) were encapsulated in hermetically sealed aluminium pans, and heated at 3 K/min. The (extrapolated onset) melting temperature \(T_m\) and the associated enthalpy of fusion \(\Delta_f H\) \((T_m)\) were determined by averaging over five DSC scans. The isobaric, specific heat capacity \((C_p)\) of the stable form I and of the melt was determined using the MDSC 2920 operated in modulated mode using hermetically sealed aluminium sample pans. A modulation period of 100 s and amplitude of 1.0 K were used, with an underlying constant heating rate of 3 K/min. The sample was heated past its melting point, immediately cooled to room temperature and then reheated again, and results were averaged over five scans. Calibration was carried out according to standard procedure against the melting properties of indium, and the heat capacity signal was calibrated against a sapphire sample using a linear calibration correction function based on four repeat scans. Differences in mass between sample pan and reference pan were kept within ± 0.10 mg. Repeated heating-cooling cycles were carried out using a PerkinElmer Pyris 1 differential scanning calorimeter (DSC). About 5 mg of a sample of the stable polymorph in a 40 μl aluminium pan covered by an aluminium lid with pinholes was heated from 223 K to 373 K at a rate of 10 K/min, then cooled and reheated at the same rate, and also reheated after four days storage at room temperature.

3. Results and Analysis

3.1. Solid-state Characterisation

Fig. 2 and Fig. 3 show PXRD patterns and FTIR spectra, respectively, of fenofibrate as received and recrystallised from different solvents.
Fig. 2. PXRD patterns for fenofibrate. From top to bottom: Patterns of forms I and II (Balendiran et al., 2012) calculated from the structures with CSD refcodes TADLIU01 and TADLIU02, respectively; commercial fenofibrate (as received); crystals obtained by slow evaporation from methanol, ethanol, 1-propanol, ethyl acetate, acetonitrile, acetone and toluene; and needle-shaped crystals grown by fast cooling in 1-propanol (showing a strong preferred orientation effect).
Fig. 3. FTIR spectra of fenofibrate as received and crystallised from ethanol, ethyl acetate, and acetonitrile.

Essentially no differences between samples of crystals obtained from different solvents were detected by FTIR, NMR or DSC. TGA showed no decomposition or mass loss below 469 K (not shown). It was confirmed by PXRD that the commercially available solid material consists of the stable polymorph (form I), and furthermore only form I was recrystallised from all solvents, as the peak positions were the same in all cases (Fig. 2), matching the positions predicted using the known crystal structure. Some significant variations in peak height were found, most easily explained as preferred orientation effects due to insufficient grinding and the morphology of the crystals. The crystals from the alcohols tended to be more elongated, as opposed to the others which were roughly equant or blocky. Toluene is an exception as it induced a plate-like habit. Also, fast cooling crystallisation produced elongated or needle-like crystals demonstrating the effect of high supersaturation. Grinding was deliberately restrained due to concerns about accelerating solid-state transformation of any metastable polymorph which could have been formed [16]. The FTIR spectra in Fig. 3 are consistent with the reported spectra for unsolvated fenofibrate, and the TGA curves and NMR measurements corroborate that no solvates were formed.

DSC thermograms of crystals of form I show a single endothermic peak. Immediate cooling and reheating following melting with DSC show no recrystallisation or melting peaks. However, after leaving the melted sample for 4 days at room temperature, two separate melting peaks were observed upon reheating (Fig. 4) separated by a smaller exothermic peak, likely indicating melting of the metastable form II together with recrystallisation of form I. This would be consistent with the DSC experiments from the initial discovery of the metastable form II [16].

Melting data are given in Table 2. The extrapolated onset melting temperature is somewhat lower than previously published values (353–354.8 K) [1, 4, 7-9, 13, 16] but the melting enthalpy is slightly higher (27.3–33.4 kJ/mol) than the published values [1, 4, 8, 9, 16].
Fig. 4. DSC thermograms of fenofibrate as received on heating (blue, curve 1), cooling (red, curve 2), first reheating (green, curve 3) and second reheating after 4 days of storage (purple, curve 4).

The specific heat capacity of form I was determined in the temperature interval 260–335 K and that of the melt in the temperature interval 305–395 K, each as the average of five scans. A linear regression model, Eq. (1), was fitted to the data:

\[
C_p = k_1 T + k_2
\]  

(1)

The coefficients of Eq. (1) are given in Table 2 together with scan details. Table 3 gives average values of the heat capacity of form I and the melt at different temperatures. Fig. 5 shows the average heat capacity curves and 90% confidence limits, together with extrapolated linear regression models for form I and the melt.

Table 2. Melting data and heat capacity regression coefficients (Eq. (1)) for the stable polymorph and the melt, together with scan details.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Scans</th>
<th>( T_m ) (K)</th>
<th>( \Delta_{\text{fus}}H(T_m) ) (kJ mol(^{-1}))</th>
<th>Scans</th>
<th>( T ) range (K)</th>
<th>( k_1 ) (J mol(^{-1}) K(^{-2}))</th>
<th>( k_2 ) (J mol(^{-1}) K(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid (form I)</td>
<td>5</td>
<td>352.05(^a)</td>
<td>33.53(^b)</td>
<td>5</td>
<td>260–335</td>
<td>1.2759</td>
<td>64.0</td>
</tr>
<tr>
<td>Melt</td>
<td>5</td>
<td>305–395</td>
<td></td>
<td>5</td>
<td>305–395</td>
<td>0.7567</td>
<td>371.0</td>
</tr>
</tbody>
</table>

\(^a\)Standard uncertainty \( u(T_m) = 0.0086 \) K.

\(^b\)Standard uncertainty \( u(\Delta_{\text{fus}}H) = 0.20 \) kJ mol\(^{-1}\).
Table 3. Selected values of the heat capacity of the solid and the melt, averaged over 5 runs each.

<table>
<thead>
<tr>
<th>$T$ (K)</th>
<th>$C_p$ (J mol$^{-1}$ K$^{-1}$)</th>
<th>$u(C_p)$</th>
<th>$T$ (K)</th>
<th>$C_p$ (J mol$^{-1}$ K$^{-1}$)</th>
<th>$u(C_p)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>260.0</td>
<td>396</td>
<td>6.7</td>
<td>305.1</td>
<td>602</td>
<td>3.9</td>
</tr>
<tr>
<td>265.0</td>
<td>403</td>
<td>6.7</td>
<td>310.0</td>
<td>604</td>
<td>3.8</td>
</tr>
<tr>
<td>270.0</td>
<td>411</td>
<td>6.6</td>
<td>315.0</td>
<td>608</td>
<td>3.8</td>
</tr>
<tr>
<td>275.0</td>
<td>417</td>
<td>6.0</td>
<td>320.0</td>
<td>612</td>
<td>3.9</td>
</tr>
<tr>
<td>280.0</td>
<td>422</td>
<td>5.4</td>
<td>325.0</td>
<td>616</td>
<td>3.6</td>
</tr>
<tr>
<td>285.0</td>
<td>428</td>
<td>4.9</td>
<td>330.0</td>
<td>620</td>
<td>3.5</td>
</tr>
<tr>
<td>290.0</td>
<td>433</td>
<td>4.6</td>
<td>335.0</td>
<td>625</td>
<td>3.4</td>
</tr>
<tr>
<td>294.9</td>
<td>439</td>
<td>3.8</td>
<td>340.0</td>
<td>629</td>
<td>3.4</td>
</tr>
<tr>
<td>299.9</td>
<td>444</td>
<td>3.1</td>
<td>345.1</td>
<td>634</td>
<td>3.4</td>
</tr>
<tr>
<td>304.9</td>
<td>450</td>
<td>2.8</td>
<td>350.0</td>
<td>637</td>
<td>3.0</td>
</tr>
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<td>309.9</td>
<td>456</td>
<td>2.8</td>
<td>355.0</td>
<td>641</td>
<td>3.0</td>
</tr>
<tr>
<td>314.9</td>
<td>463</td>
<td>2.6</td>
<td>360.0</td>
<td>645</td>
<td>3.1</td>
</tr>
<tr>
<td>320.0</td>
<td>472</td>
<td>2.6</td>
<td>364.9</td>
<td>648</td>
<td>2.8</td>
</tr>
<tr>
<td>325.0</td>
<td>480</td>
<td>2.5</td>
<td>370.0</td>
<td>652</td>
<td>2.8</td>
</tr>
<tr>
<td>330.0</td>
<td>489</td>
<td>2.1</td>
<td>375.0</td>
<td>655</td>
<td>2.7</td>
</tr>
<tr>
<td>335.0</td>
<td>498</td>
<td>2.1</td>
<td>380.0</td>
<td>659</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>385.1</td>
<td>661</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>390.0</td>
<td>664</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>395.0</td>
<td>667</td>
<td>3.0</td>
</tr>
</tbody>
</table>

*Standard uncertainty $u(T) = 0.11$ K.

Fig. 5. Average heat capacity of form I (blue) and the melt (red), with wrapping lines marking 90% confidence limits, dotted lines showing linear extrapolations, and the vertical dashed line marking the melting temperature.

The enthalpy and entropy of fusion at any temperature $T$ are given by:

$$
\Delta H_f = \int_{T_m}^{T} C_p\,dT \\
\Delta S_f = \int_{T_m}^{T} \frac{C_p}{T}\,dT
$$

(2)

(3)
where $\Delta C_p$ represents the heat capacity difference between the pure melt and the solid. Using extrapolated linear regression models for the heat capacities of form I and the melt (Eq. (1)), $\Delta C_p$ can be described by a linear equation:

$$
\frac{q}{T_{m}} T_{m} \left( T - T_{m} \right)
$$  \hspace{1cm} (4)

Using data in Table 2 results in values of $q = 124.3$ J mol$^{-1}$ K$^{-1}$ and $r = 0.5192$ J mol$^{-1}$ K$^{-2}$. Inserting Eq. (4) into Eq. (2) and Eq. (3) and integrating results in the following expressions for the enthalpy, entropy and Gibbs energy of fusion:

$$
\frac{q}{T_{m}} T_{m} \left( T - T_{m} \right)
$$  \hspace{1cm} (5)

$$
\ln \frac{T}{T_{m}} \left( T - T_{m} \right)
$$  \hspace{1cm} (6)

$$
\ln \frac{T}{T_{m}} \left( T - T_{m} \right)
$$  \hspace{1cm} (7)

In Fig. 6, the resulting Gibbs energy, enthalpy and entropy of fusion of form I are plotted vs. temperature. It can be seen that at room temperature, the enthalpy of fusion differs quite significantly from the value at $T_{m}$, stressing the importance of the contribution from $\Delta C_p$. However, much due to the compensation from entropy, the Gibbs energy of fusion is the fairly small sum of its larger enthalpic and entropic components, at least above room temperature.

![Fig. 6. $\Delta_{fus}G$ (solid line), $\Delta_{fus}H$ (dashed line) and $T\Delta_{fus}S$ (dotted line) of form I vs. temperature.](image)

**3.2. Solubility**

The solubility of fenofibrate form I over a range of temperatures in the seven different solvents are reported in Table 4 and illustrated in Fig. 7.
Table 4. Solubility of fenofibrate form I in seven solvents over a range of temperatures. Values are given as g fenofibrate per kg solvent together with standard uncertainties and number of samples (N).

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>Methanol</th>
<th>Ethanol</th>
<th>1-Propanol</th>
<th>2-Propanol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{eq}$ (g kg$^{-1}$)</td>
<td>$u(C_{eq})$</td>
<td>N</td>
<td>$C_{eq}$ (g kg$^{-1}$)</td>
</tr>
<tr>
<td>5.0</td>
<td>14.4</td>
<td>0.14</td>
<td>2</td>
<td>19.5</td>
</tr>
<tr>
<td>10.0</td>
<td>51.1</td>
<td>0.59</td>
<td>2</td>
<td>46.5</td>
</tr>
<tr>
<td>15.0</td>
<td>58.8</td>
<td>0.20</td>
<td>2</td>
<td>55.29</td>
</tr>
<tr>
<td>20.0</td>
<td>107.33</td>
<td>0.032</td>
<td>2</td>
<td>114.83</td>
</tr>
<tr>
<td>25.0</td>
<td>242</td>
<td>1.7</td>
<td>6</td>
<td>272</td>
</tr>
<tr>
<td>30.0</td>
<td>417.8</td>
<td>0.73</td>
<td>2</td>
<td>420.8</td>
</tr>
<tr>
<td>40.0</td>
<td>448</td>
<td>9.3</td>
<td>2</td>
<td>526</td>
</tr>
<tr>
<td>45.0</td>
<td>1725.7</td>
<td>0.83</td>
<td>3</td>
<td>3385.1</td>
</tr>
</tbody>
</table>

$^*$ Standard uncertainty $u(T) = 0.036$ K.

The solubility expressed in g/kg solvent is lowest in the alcohols and highest in acetone. The solubility curve of acetonitrile intersects that of ethyl acetate slightly above 30°C. On a mole fraction basis across all investigated temperatures, the solubility is lowest in methanol, followed by ethanol, 1-propanol, acetonitrile, acetone and ethyl acetate. The mole fraction solubility of 2-propanol is mostly between that of ethanol and methanol, and shows a decreasing trend with decreasing aliphatic chain length. In all solvents the solubility increases with higher temperature, most particularly in the alcohols.
Fenofibrate is a medium-sized aprotic hydrophobic molecule whose intermolecular forces consist of London forces and Debye interactions and therefore is expected to exhibit a higher solubility in similarly aprotic solvents [19]. This explains why the solubility of fenofibrate in the alcohols is much lower than in acetonitrile, ethyl acetate, and acetone. Solvents with both hydrogen bond donors and acceptors will preferably interact with other hydrogen bonding solvent molecules. That fenofibrate is almost insoluble in water is a good illustration of this. It also explains why fenofibrate is more soluble in alcohols with longer aliphatic chains, because when the alkyl chain is longer the hydrogen bonding alcohol group is less significant compared to the dispersion forces. A longer chain will also make the alcohol more polarisable overall. The fact that the solubility in 2-propanol is lower than that in 1-propanol corroborates this. The forces involving permanent dipoles will become weaker at higher temperatures compared to the more flexible dispersion forces. This can be seen in how the mole fraction solubility curve of 2-propanol gradually approaches that of ethanol as the temperature increases, showing that the lower polarisability due to the position of the alcohol group becomes less significant at a higher temperature. For the alcohols at 303 K the molar ratio of solvent to solute is still quite high (125–226), but at 318 K this ratio has decreased to about 12 in 1-propanol, 18 in ethanol, and 25 in methanol. Accordingly, at higher temperatures, the number of solvent molecules is below or close to that required to form the first solvation shell.

Conversely, acetonitrile, ethyl acetate and acetone, like fenofibrate, have only hydrogen-bonding acceptors and their intermolecular forces will be more similar in character to those in fenofibrate. Comparing acetone and 2-propanol, the difference in solubility due to the hydrogen bonding in the alcohol is dramatic; at 293 K on a mole fraction basis the solubility in acetone is 20 times greater than in 2-propanol. The small size of the acetonitrile molecule gives it a disadvantage with respect to dispersion forces compared to larger molecules like...
ethyl acetate. This size effect on acetonitrile’s polarisability is somewhat mitigated by the lower electronegativity of nitrogen compared to oxygen as illustrated by an increased boiling point. In the case of acetonitrile, ethyl acetate and acetone, the solvent to solute molar ratio is much lower than in the alcohols. For acetonitrile it is 22 at 293 K, and only 9 already at 303 K. The latter is clearly lower than that expected to be required for a complete first solvation shell. In acetone and ethyl acetate, the solvent to solute ratio is less than 10 at 288 K, and at 318 K in acetonitrile and ethyl acetate it is only about 2.

Our solubility data show some differences with the data published previously [7], but notably the temperature control in that work is stated as: ± 5 K. They report a solubility value in hexane which is lower than in the alcohols, and a value in chloroform that is higher than in ethyl acetate. Preliminary tests carried out at room temperature were found to approximately corroborate these observations, and in addition it was found that the solubility in toluene is also quite high (comparable to ethyl acetate). The lower solubility of fenofibrate in hexane compared to toluene demonstrates the benefit of interaction by stacking of aromatic rings. The large size of the chlorine atoms of chloroform may help to explain the particularly high solubility.

If the reference state of the activity of pure solid form I of fenofibrate is taken as the pure compound in the form of a supercooled melt at the same temperature, i.e. the same as for the solute in solution, we get:

\[ a_s = a_{eq} x_{eq} \gamma_{eq} \]  

(8)

where \( a_s \) is the activity of solid fenofibrate, \( a_{eq} \) is the activity of fenofibrate in saturated solution, and \( \gamma_{eq} \) is the corresponding activity coefficient at saturation in a solvent where the mole fraction solubility is \( x_{eq} \). \( a_s \) can now be expressed in terms of the Gibbs energy of fusion:

\[ \ln a_s = \frac{-G_{fus}}{RT} \]  

(9)

With Eq. (7), this becomes:

\[ \ln a_s = \frac{1}{R} - \frac{1}{T_m} \ln \frac{T_m}{T} - \frac{T_m}{2T} \left( \frac{T_m}{T} \right) \]  

(10)

In order to investigate the temperature dependence of solubility from the temperature range of experimental data up to the melting point, an empirical function, Eq. (11), has been derived from a simple third order polynomial with respect to \( 1/T \), altered to conform to the limiting behaviour [20] of solubility curves with decreasing \( T_m - T \) as given by Eq. (12 a) and Eq. (12 b). For each solvent, the three coefficients of Eq. (11) have been fitted to the experimental data, given in Table 5.
\[
\ln x_{eq} = \frac{1}{R} \frac{\Delta H(T_m)}{T_m} + \frac{1}{T} \left[ A + \frac{2}{T_m^2} \right] + \frac{3}{TT_m} \left[ B + \frac{2}{T_m^2} \right] \]

\[
\ln x_{eq} = 0 \text{ at } T = T_m
\]

\[
RT^2 \left[ \frac{\ln x_{eq}}{T_{eq}} \right] = \Delta H_{fus} \text{ at } T = T_m
\]

Table 5. Solubility regression coefficients (Eq. (11)) in various solvents, with associated goodness of fit.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Methanol</th>
<th>Ethanol</th>
<th>1-Propanol</th>
<th>2-Propanol</th>
<th>Ethyl acetate</th>
<th>Acetonitrile</th>
<th>Acetone</th>
</tr>
</thead>
<tbody>
<tr>
<td>(10^{-10} A (K^3))</td>
<td>-23.3449</td>
<td>-17.9477</td>
<td>-6.1444</td>
<td>-13.7633</td>
<td>0.7490</td>
<td>20.6122</td>
<td>2.7364</td>
</tr>
<tr>
<td>(10^{-3} C)</td>
<td>-24.1528</td>
<td>-18.8429</td>
<td>-7.8213</td>
<td>-14.7034</td>
<td>0.8230</td>
<td>18.3068</td>
<td>2.6811</td>
</tr>
<tr>
<td>(\chi^2)</td>
<td>0.00174</td>
<td>0.00131</td>
<td>0.00087</td>
<td>0.00019</td>
<td>0.00013</td>
<td>0.00176</td>
<td>0.00010</td>
</tr>
</tbody>
</table>

Fig. 8 shows the experimental solubility values plotted in a van’t Hoff plot (i.e. as \(\ln x\) vs. \(1/T\)) together with the respective regression curves (Eq. (11)) for each solvent, extrapolated to \(T_m\). The ideal solubility (equal to \(\ln a_{eq}\)) calculated using Eq. (10), is also shown. Frequently, in publications reporting solubility data, van’t Hoff plots are presented as straight (or almost-straight) lines, and in some cases it is even stated, implicitly or explicitly, that a van’t Hoff plot should yield a straight line. Obviously this is not the case for fenofibrate in many of the evaluated solvents. However, in ethyl acetate and acetone the van’t Hoff curves do exhibit linear behaviour, with data points falling very close to the ideal solubility line. In the case of ethyl acetate, extrapolation of a straight line fitted to experimental data to \(\ln x = 0\) leads to an estimated \(T_m\) which is just 3.3 K higher than the experimentally measured value, while for acetone the estimated value is 2.8 K lower. The solubility in the other solvents reveals clear positive deviation from Raoult’s law and the van’t Hoff curves show a markedly non-linear behaviour over the range of temperatures studied, leading to an “inverted S-shape” at extrapolation to the melting point; a combination predicted as a possibility in previous work [20].
Fig. 8. Van’t Hoff plot of fenofibrate solubility in seven solvents, with regression lines (Eq. (11)) extrapolated to $T_m$, and ideal solubility (Eq. (10)) shown in black.

Fig. 9 shows estimated activity coefficients from the experimental temperature interval to $T_m$ for form I in all investigated solvents. With the exception of ethyl acetate, showing a weak but consistent negative deviation from Raoult’s law, all solutions exhibit positive deviation, meaning that solute-solvent interactions are less favourable than solvent–solvent interactions and/or solute-solute interactions. The activity coefficient reaches values of about 25 in the alcohols within the temperature range studied. In all solvents except ethyl acetate, the activity coefficient decreases with increasing temperature to reach unity at the melting point. In ethyl acetate the activity coefficient is very close to unity over the entire temperature range.

Fig. 9. Equilibrium activity coefficients for form I in different solvents.

The slope of a van’t Hoff curve yields an enthalpic term, called the van’t Hoff enthalpy of solution [20, 21] which is not the same as the calorimetric enthalpy of solution:
It can be shown [20] with rigorous thermodynamics that the van’t Hoff enthalpy of solution consists of three component terms:

\[
\ln \frac{1}{T} \left( 1 + \frac{1}{T} \right) \frac{\partial \ln \phi}{\partial T} + \int_{T_m}^{T} \left( \frac{\partial H}{\partial T} - \frac{RT^2}{\phi} \right) dT
\]

Non-linearity in a van’t Hoff curve can originate from the heat capacity term in Eq. (14) having a significant influence on the enthalpy of fusion, which would be expected in particular at temperatures far below the melting point. As already shown in Fig. 6, for fenofibrate this term represents a significant contribution (about 30%) to the heat of fusion at room temperature, in spite of the proximity to the melting point. This contribution will affect the ideal solubility and the solubility in all solvents equally. Accordingly, the difference in van’t Hoff enthalpy of solution depending on the solvent and the corresponding difference in shape of the van’t Hoff curve depend entirely on the activity coefficient derivative term. Consequently, the temperature dependence of the saturated solution activity coefficient is the main cause for the strongly non-linear shape of the van’t Hoff curves in the alcohols and acetonitrile. Since activity coefficients depend on composition and temperature, and the solubility changes with temperature the term in Eq. (14) contains both effects. It should be noted that the heat capacity term and the activity coefficient term may compensate for one another by which a linear van’t Hoff curve can be mistakenly interpreted as showing that the solution is ideal. In addition, because of the heat capacity term, the ideal solubility curve is in general non-linear over a wider temperature range. For fenofibrate, although this might not be immediately detectable in Fig. 8, the slope of the ideal solubility line decreases by 36% from \( T_m \) down to 270 K.

4. Conclusions

The melting point and the melting enthalpy of fenofibrate form I have been determined to be 352.05 ± 0.02 K and 33.53 ± 0.42 kJ/mol, respectively. The heat capacity of the solid has been determined in the range 260–335 K, and that of the melt in the range 305–395 K, i.e. even far below the melting point. These data are used to calculate the Gibbs energy, enthalpy and entropy of fusion up to the melting point. The mole fraction solubility of fenofibrate is far higher in ethyl acetate and acetone than in acetonitrile and aliphatic alcohols. Among the alcohols, the solubility increases with aliphatic chain length. In all solvents, except ethyl acetate the deviation from Raoult’s law is positive, while in ethyl acetate the solubility is close to ideal. In the alcohols the activity coefficient reaches maximum values of 15 to 25 within the temperature range studied. It is shown that the influence of the heat capacity term on the enthalpy of fusion is not negligible at room temperature, in spite of the proximity to the melting point. It is also shown that the contribution from the temperature dependence of the activity coefficient term on the van’t Hoff enthalpy of solution is dominant in acetonitrile.
and the alcohols. All the crystals in these experiments were shown to be the stable form I by XRD. The metastable form was obtained only by recrystallisation of the melt.

5. Acknowledgements

The financial support of the Science Foundation Ireland (10/IN.1/B3038) and the donation of crystalline fenofibrate by AbbVie are gratefully acknowledged. M.S. gratefully acknowledges the financial support of the Swedish Research Council (621-2010-5391).

6. Nomenclature

\( a \) Activity
\( A \) Solubility regression coefficient
\( B \) Solubility regression coefficient
\( C \)
- \( i \) Solubility regression coefficient
- \( ii \) Concentration
\( C_p \) Heat capacity
\( \Delta C_p \) Heat capacity difference (melt – solid)
\( k_1 \) Heat capacity regression coefficient
\( k_2 \) Heat capacity regression coefficient
\( q \) Heat capacity difference regression coefficient
\( r \) Heat capacity difference regression coefficient
\( R \) Gas constant
\( T \) Temperature
\( \Delta_{\text{fus}}H \) Enthalpy of fusion
\( \Delta_{\text{fus}}S \) Entropy of fusion
\( \Delta_{\text{fus}}G \) Gibbs energy of fusion
\( \Delta_{\text{vH}}H_{\text{sol}} \) van't Hoff (apparent) enthalpy of solution
\( x \) Mole fraction
\( \gamma \) Activity coefficient

Scripts:
- \( \text{eq} \) Equilibrium
- \( \text{m} \) Melting
- \( \text{s} \) Solid

7. References