



The solubility behaviour and thermodynamic relations of the three forms of Venlafaxine free base

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ABSTRACT

The polymorphic and solubility behaviour of the active pharmaceutical ingredient Venlafaxine free base, which is used as an antidepressant, is studied. Using differential scanning calorimetry and slurry experiments, an enantiotropic relation between the three forms was found. Transition temperatures were determined using solubility data and compared with calculated transition temperatures based on the melting enthalpies and temperatures of the different forms. The solubility of Venlafaxine in heptane, toluene and methanol shows a large deviation from ideal behaviour. The deviations are to a large extent determined by the temperature dependence of the difference in fusion enthalpy of the undercooled melt and the solid.

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1. Introduction

Polymorphism is a major concern for the pharmaceutical industry during the development of a new drug (Brittain, 1999; Bernstein, 2002). Polymorphism is the ability of substances to crystallize in two or more crystalline phases. Each of these crystal structures, or modifications, has the same chemical composition, but differs in the arrangement and/or conformation of the molecules in the crystal lattice. As a result, polymorphic forms have different physical properties, e.g. melting point, solubility, dissolution rate, habit and stability. These different physical properties may affect the therapeutic efficacy, toxicity, bio-availability, pharmaceutical processing and stability of the drug product. An important part of the investigation of a new form of a pharmaceutical product is the comprehensive study for polymorphs. Firstly, because it may prevent patenting problems (Byrn et al., 1995) and secondly, it is recommended by regulatory bodies (Guidance for Industry, 2007).

Two distinct types of polymorphic systems are known; monotropic and enantiotropic systems. When the free energy curves of the stable polymorph and any other observed polymorph do not cross as a function of temperature, and consequently only one polymorph is stable below the melting point, one deals

with a monotropic system. When the free energy curves as a function of temperature of two polymorphs do cross below the melting point, different polymorphs are stable below and above the transition point, and one speaks of an enantiotropic system. Knowing the number of phases and their thermodynamic relationships in the context of crystallization is a basic prerequisite in understanding the phase diagram of a polymorphic system.

During crystallization it is possible that a less stable form crystallizes out first, which can be transformed to a more stable one later. This is known as Ostwald's rule of stages (Ostwald, 1897). The formation of metastable polymorphic crystals is a kinetic effect, which is usually attributed to the nucleation stage (Deij et al., 2006; Davey, 1982). Nevertheless, examples are known for which the metastable phase is formed heterogeneously on the stable phase crystals either in a random orientation (Yu, 2003; Ferrari et al., 2004) or epitaxially (Boistelle and Rinaude, 1981; Stoica et al., 2005).

Interconversion of polymorphs can be accomplished via solvent or gas phase-mediated transformation or directly via a solid–solid phase transformation. Depending on the kinetic barriers, the transformation time can range from instantaneous to infinitely long. Determination of the precise polymorph transition temperature for an enantiotropically related system is often a laborious task. For such a system the solubility of two polymorphs is, however, equal at the transition point. Therefore solubility data can be used to determine the transition temperature and the stability region of the polymorphs. Assuming that the solution shows more or less ideal mixing behaviour for the solute and solvent, solubil-

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ity data will show up as nearly linear curves in a van't Hoff plot (Brittain, 1999). If the polymorphic transition rate is low, it is possible to determine the solubility of both polymorphs even in the region in which the polymorphs are metastable (Park et al., 2003).

In the following we report a study of the phase behaviour of the free base of the drug Venlafaxine. The polymorphic phase diagram as well as the thermodynamic relations between the three forms were investigated using X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), slurry experiments and solubility measurements. The solubility of Venlafaxine was studied in different solvents, with the emphasis on deviations of the solubility with respect to the van't Hoff equation for ideal behaviour. The deviations turn out to be such that the assignment of the stability regions of polymorphs I and II of Venlafaxine, on the basis of solubility data, would lead to a contradiction. This is due to a concave form of the solubility curves, a shape that was recently described in detail in terms of a thermodynamic treatment of solubility (Bennema et al., 2008). In that paper an equation to calculate the transition temperature of two enantiotropically related polymorphs was published. For this equation only the melting point and the melting enthalpy, which are relatively easy to determine using DSC, are necessary. The resulting transition temperatures for Venlafaxine free base are compared with those derived from the solubility data and the shape of the curves is interpreted in terms of the mixing properties in the solution. The concave shape is explained by a non-negligible difference in the temperature dependence of the enthalpy of fusion.

2. Venlafaxine

Venlafaxine is the common name for the compound 1-[2-(dimethylamino)-1-(4-methoxyphenyl)-ethyl]cyclohexanol. The molecular structure is given in Fig. 1. The product is marketed as the hydrochloric acid salt. It is used for treating depression and thymoanaleptic and anxiolytic disorders. Especially because Venlafaxine hydrochloride is relatively aggressive towards handling equipment and it is irritating to the skin, it would be beneficial to have other forms of Venlafaxine at one's disposal. The free base is one of the promising candidates.

Until a few years ago, little was reported regarding Venlafaxine free base, the information being restricted to patents (US Patent, 1985, 2001). In these disclosures Venlafaxine was never precipitated as a free base, but obtained as an oily/solid residue in the synthesis, after evaporation of the solvent. This procedure generally does not lead to a useful pharmaceutical solid form, as impurities and the solvent are likely to be present. Later, Venlafaxine free base was isolated as a solid via evaporation of the solvent and the resulting residue was recrystallized from hexane or heptane (WO Patent, 2000). The fact that it can be isolated in multiple forms was recently described (WO Patent, 2003). According to this publication, two polymorphs, A and B, of the free base of Venlafaxine exist. The crystal structures were not known and the thermodynamic behaviour was only poorly understood.

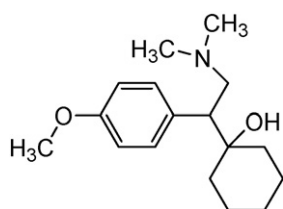


Fig. 1. The molecular structure of Venlafaxine.

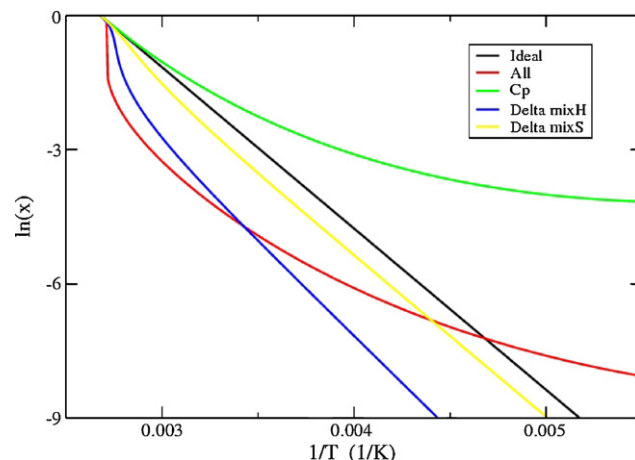


Fig. 2. Overview of the shapes solubility curves can adopt when various thermodynamic parameters are included in the calculations. The black curve represents the ideal case, Eq. (1); the green curve represents the case for which a temperature dependence of $\Delta_{\text{fus}}h^*(T)$ is included, Eq. (3); the blue curve represents the case for which only $\Delta_{\text{mix}}^{\text{reg}}h$ is included, Eq. (4); the yellow curve represents the case for which both $\Delta_{\text{mix}}^{\text{reg}}h$ and a $\Delta_{\text{mix}}^{\text{qu-reg}}s$ are included, Eq. (5) and the red curve represents the case for which all parameters are included; Eq. (6). The following parameters are used for the calculations: $T_{\text{fus}} = 373 \text{ K}$, $\Delta_{\text{fus}}h = 30 \text{ kJ/mol}$, $\Delta c_p^0 = 150 \text{ J/(mol K)}$, $\Delta c_p^1 = 0$, $\Delta_{\text{mix}}h = 5 \text{ kJ/mol}$ and $\Delta_{\text{mix}}s = -5 \text{ J/(mol K)}$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

Polymorph A was expected to be the stable form at room temperature.

Very recently it was reported that three forms, labelled I, II and III, of Venlafaxine free base exist and their crystal structures were determined using single crystal X-ray diffraction (van Eupen et al., 2008). This showed that in case of polymorphs I and II one deals with racemic compounds; form I is composed of alternating layers of R and S enantiomers, in case of form II the crystal is composed of alternating bi-layers of R and S enantiomers. Form III, a racemic conglomerate, is composed of a stacking of thick layers of R and S enantiomers, in other words, form III crystallizes as an epitaxial conglomerate. We will use the same labels as in van Eupen et al. (2008).

3. Solubility theory

In the following we summarize some of the theoretical considerations concerning solubility of (molecular) crystals (Bennema et al., 2008) that are relevant for the present study. The solubility curve of crystals, as a function of the temperature T , in case of an ideal mixing behaviour of the solute and the solvent and assuming that the fusion enthalpy of the pure solute, $\Delta_{\text{fus}}h^*$, is independent of the temperature follows:

$$\ln x^{\text{ideal}} = \frac{\Delta_{\text{fus}}h^*}{R} \left[\frac{1}{T_{\text{fus}}} - \frac{1}{T} \right], \quad (1)$$

where x is the mole fraction of the solute in the solution. If $\ln x$ is plotted versus $1/T$, this leads to a linear solubility curve, often referred to as a van't Hoff curve. In practice, however, there will be a temperature dependence of $\Delta_{\text{fus}}h^*$, which results, even for an ideal mixing in solution, in a deviation of the linear curve. Fig. 2 presents an overview of the different shapes solubility curves can adopt. When $\Delta_{\text{fus}}h^*(T)$ is expressed in terms of a linear temperature dependence of the molar heat capacity according to:

$$\Delta c_p(T) = c_p^l(T) - c_p^s(T) = \Delta c_p^0 - \Delta c_p^1 (T - T_{\text{fus}}), \quad (2)$$

where the superscript *l* denotes the (undercooled) melt and superscript *s* the solid phase, the solubility becomes

$$\ln x^{C_p} = \frac{\Delta_{\text{fus}} h^*}{R} \left[\frac{1}{T_{\text{fus}}} - \frac{1}{T} \right] + \frac{\Delta c_p^0}{R} \left[\frac{T_{\text{fus}}}{T} - \ln \frac{T_{\text{fus}}}{T} - 1 \right] + \frac{\Delta c_p^1 T_{\text{fus}}}{2R} \left[\frac{T}{T_{\text{fus}}} - \frac{T_{\text{fus}}}{T} + 2 \ln \frac{T_{\text{fus}}}{T} \right]. \quad (3)$$

If $\Delta c_p(T)$ is positive, the solubility is larger than the ideal solubility, if $\Delta c_p(T)$ is negative the solubility is lower. As a result, the solubility curve changes from a straight line for the ideal case, to a nonlinear curve; concave in case $\Delta c_p(T)$ is positive and convex in case $\Delta c_p(T)$ is negative. Note that this deviation is independent of the solvent used.

Deviations from ideal behaviour are usually expressed in terms of excess parameters, $\Delta_{\text{mix}}^E H$ and $\Delta_{\text{mix}}^E S$. In case of a regular solution (Hildebrand et al., 1970), for which $\Delta_{\text{mix}}^E S = \Delta_{\text{mix}}^{\text{reg}} S = 0$, and $\Delta_{\text{mix}}^E H = nx(1-x)\Delta_{\text{mix}}^{\text{reg}} h$, the solubility is:

$$\ln x^{\text{reg}} = \frac{\Delta_{\text{fus}} h^*}{R} \left[\frac{1}{T_{\text{fus}}} - \frac{1}{T} \right] - \frac{\Delta_{\text{mix}}^{\text{reg}} h}{R} \left[\frac{(1-x^{\text{reg}})^2}{T} \right]. \quad (4)$$

If the regular solution model is extended to include an excess mixing entropy, $\Delta_{\text{mix}}^E S = \Delta_{\text{mix}}^{\text{qu-reg}} S$, a quasi-regular solution model results for which the solubility is given by:

$$\ln x^{\text{qu-reg}} = \frac{\Delta_{\text{fus}} h^*}{R} \left[\frac{1}{T_{\text{fus}}} - \frac{1}{T} \right] - \left[\frac{\Delta_{\text{mix}}^{\text{reg}} h - T \Delta_{\text{mix}}^{\text{qu-reg}} s}{R} \right] \left[\frac{(1-x^{\text{qu-reg}})^2}{T} \right]. \quad (5)$$

The parameters $\Delta_{\text{mix}}^{\text{reg}} h$ and $\Delta_{\text{mix}}^{\text{qu-reg}} s$ are assumed to be independent of the temperature in the range of interest. An important conclusion from Fig. 2 is that for a negligible Δc_p value the solubility curves adopt a linear behaviour well below the melting temperature of the solute, as long as $\Delta_{\text{mix}}^E h$ and $\Delta_{\text{mix}}^E s$ are independent of the temperature, whereas a non-negligible (positive) value of Δc_p leads to a concave shaped curve. If all parameters are included, $\Delta c_p(T)$, $\Delta_{\text{mix}}^E H$ and $\Delta_{\text{mix}}^E S$, the solubility equation becomes:

$$\ln x^{\text{all}} = \frac{\Delta_{\text{fus}} h^*}{R} \left[\frac{1}{T_{\text{fus}}} - \frac{1}{T} \right] + \frac{\Delta c_p^0}{R} \left[\frac{T_{\text{fus}}}{T} - \ln \frac{T_{\text{fus}}}{T} - 1 \right] + \frac{\Delta c_p^1 T_{\text{fus}}}{2R} \left[\frac{T}{T_{\text{fus}}} - \frac{T_{\text{fus}}}{T} + 2 \ln \frac{T_{\text{fus}}}{T} \right] - \left[\frac{\Delta_{\text{mix}}^{\text{reg}} h - T \Delta_{\text{mix}}^{\text{qu-reg}} s}{R} \right] \left[\frac{(1-x)^2}{T} \right]. \quad (6)$$

In case of an enantiotropic polymorphic system the transition temperature, T_{trs} , is given by the following equation:

$$T_{\text{trs}} = \frac{\Delta_{\text{trs}} h^*}{\Delta_{\text{trs}} s^*}, \quad (7)$$

where $\Delta_{\text{trs}} h^*$ and $\Delta_{\text{trs}} s^*$ are the enthalpy and the entropy change, respectively, for the transition between the polymorphic forms at the transition temperature. Assuming ideal behaviour, according to Eq. (2), this temperature can be approximated by the following equation (Bennema et al., 2008):

$$T_{\text{trs}} = \frac{\Delta_{\text{fus}} h_{\alpha}^* - \Delta_{\text{fus}} h_{\beta}^*}{(\Delta_{\text{fus}} h_{\alpha}^*/T_{\text{fus},\alpha}) - (\Delta_{\text{fus}} h_{\beta}^*/T_{\text{fus},\beta})}, \quad (8)$$

where $\Delta_{\text{fus}} h_{\alpha}^*$ and $\Delta_{\text{fus}} h_{\beta}^*$ are the melting enthalpy of forms α and β , respectively, and $T_{\text{fus},\alpha}$ and $T_{\text{fus},\beta}$ are the respective absolute fusion temperatures.

4. Experimental procedures

Venlafaxine with a purity of 99.9%, according to high-pressure liquid chromatography (HPLC), was supplied by Synthron BV. The solvents used (pa) were purchased from Aldrich and were used without further purification.

All the solubility experiments were started using polymorph I. Crystals were obtained by dissolving Venlafaxine in heptane at reflux temperature, crystallizing the different polymorphs by cooling the clear solution to the desired temperature, and isolating the formed crystals at that temperature.

For the determination of the solubility two different techniques were used. The most accurate, but time consuming, approach is an in situ method. For that a closed thermostated glass cell was filled with a known amount of solute and solvent. The growth and dissolution of the crystals was observed using an optical transmission microscope (Zeiss Axioplan 2). By varying the temperature, the saturation temperature for different concentrations was determined; after nucleation at low temperatures all the crystals were dissolved by increasing the temperature except for one very small one, in order to minimize the effect on the solute concentration (Boerrigter et al., 2002). This crystal was subsequently grown and etched a few times to determine the saturation temperature of the solution. Besides being a time consuming method a disadvantage of the method is that it is difficult to determine the polymorphic form of the crystal studied.

A fast, but less accurate, method is the saturation shaken flask method. For that, a slurry of a given polymorph and a saturated solution was stirred for several days at a well-defined temperature, allowing the appropriate polymorph to be formed. The residue was filtered off and the polymorph obtained was determined using X-ray powder diffraction. A certain amount of the clear solution was weighed and the solvent was evaporated using a rotary evaporator. From the weight of the residue and the weight of the solution the amount of solvent and solute was determined.

Differential scanning calorimetry was performed using a Mettler Toledo DSC 822^e. Nitrogen was used as an inert purge gas. The samples were analyzed using 40 μl aluminium pans with a pierced lid. The heating rate varied between 0.1 and 10 $^{\circ}\text{C}/\text{min}$. Further calorimetric measurements were performed using a Setaram C-80 micro-calorimeter. In this case a heating rate of 0.01 or 0.001 $^{\circ}\text{C}/\text{min}$ was used. The heat capacity of polymorphs I, II and III was determined using a Mettler DSC 822^e apparatus. The thermograms were recorded using 40 μl aluminium pans with a heating rate of 10 $^{\circ}\text{C}/\text{min}$. Sapphire was used as standard.

X-ray powder diffraction patterns were recorded using a Bruker Vario-1 diffractometer in a Bragg-Brentano geometry. The patterns were collected in the range from 2 $^{\circ}$ to 35 $^{\circ}$ 2 θ using a VANTEC detector. Samples were measured in reflection mode using a silicon zero background wafer or a sampleholder with a silicon cavity. Cu K α -2 radiation was used at a voltage of 40 kV and a current of 40 mA.

5. Results and discussion

5.1. X-ray powder diffraction

Fig. 3 shows the X-ray powder diffractograms of the three forms of Venlafaxine. Comparing these with the diffractograms given in the patent, of the forms called A and B by van Eupen et al. (2008), we notice that polymorph I is identical to polymorph A. The XRPD pattern of form III resembles the pattern of form B, although extra peaks are visible in the pattern of form B. After careful comparison of the pattern of form B with the patterns of forms II and III, we conclude that form B is a mixture of forms II and III.

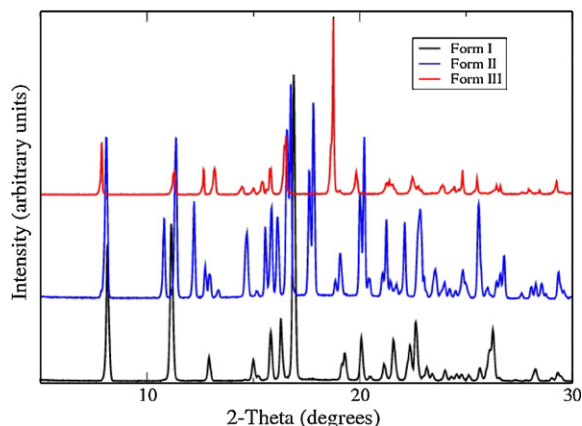


Fig. 3. XRPD patterns of forms I, II and III of Venlafaxine free base.

Table 1

Results of the slurry experiments.

Starting polymorph	Isolated polymorph	Conditions
I	II	Stirring at 42 °C, for 7 days
II	I	Stirring at 20 °C, for 7 days
I	III	Stirring at 55 °C, for 7 days
III	II	Stirring at 42 °C, for 7 days
III	I	Stirring at 20 °C, for 7 days
II	III	Stirring at 55 °C, for 7 days

5.2. Slurry experiments

To obtain a first impression of the mutual stability of the three forms at different temperatures, slurry experiments were performed, starting with different forms. For the results of these experiments see Table 1. Under the right conditions, in a slurry, all the different forms can be converted into each other. It can be concluded from these slurry experiments that an enantiotropic relation exists between all the three forms. The stability regions are as follows; below ~20 °C form I is stable, above ~55 °C form III is stable. In a region somewhere between these temperatures, form II is stable.

In Section 5.4 we will compare these estimated phase transition temperatures with more precise transition temperatures determined using solubility data.

5.3. Thermographic analysis

A DSC study was performed to determine the thermodynamic behaviour of the polymorphs. A DSC thermogram of Venlafaxine free base, polymorph I, with the usual heating rate of 10 °C/min showed one broad melting peak at 76 °C. There was no sign of a solid–solid transformation. Because solid–solid transformations can be difficult due to kinetic barriers, the DSC measurements of polymorph I, were repeated at lower heating rates. For the resulting thermograms, see Fig. 4. When the heating rate is lowered from 10 to 1 °C/min, two endothermic peaks are visible in the DSC thermogram, of which the first can be attributed to the melting of polymorph I, and the second one is the result of the melting of another polymorph. In between these two endotherms, a small

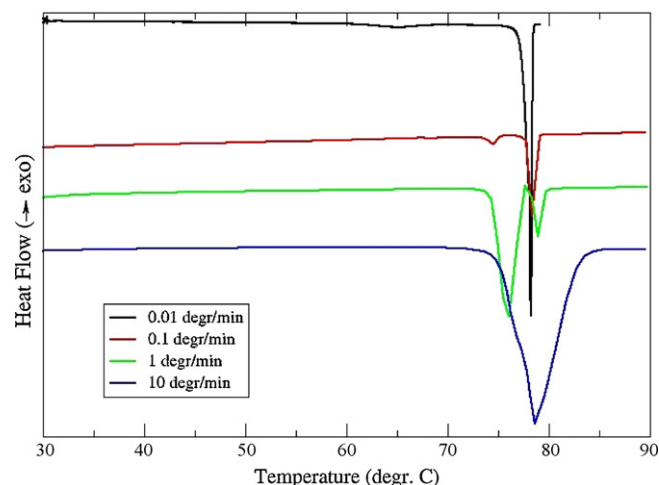


Fig. 4. DSC thermograms of polymorph I heated at 10, 1, 0.1 and 0.01 °C/min; for the sake of clarity the vertical axis of the traces have been enlarged; by a factor of 20 for the 0.01 °C/min trace, by a factor of 10 for the 0.1 °C/min trace and by a factor of 5 for the 1 °C/min trace.

exothermic recrystallization peak is visible. Lowering the heating rate to 0.1 °C/min yields a small endothermic peak and a small exothermic peak, separated by only 0.3 °C; the melting and the recrystallization processes now take place almost simultaneously. The complete sample is thus converted to another polymorph, which melts at ~78.7 °C, with a melting enthalpy comparable to that of the fast run; for data see Table 2.

An experiment with an even lower heating rate of 0.01 °C/min, performed with a C-80 Setaram calorimeter, resulted in a considerable shift of the first endotherm to 60 °C with a heat of 2.9 J/g. The sign and the magnitude of the first endotherm are in accordance with the value of a solid–solid phase transition to an enantiotropically related polymorph (Burger and Ramberger, 1979). To verify this assumption, a sample was heated to 70 °C in the C-80 Setaram calorimeter, as described above (0.01 °C/min), and cooled to room temperature, after which an XRPD was recorded of the sample. The XRPD pattern showed that form III was isolated.

A DSC heating run of polymorph II with a heating rate of 10 or 1 °C/min showed only a melting endotherm at 78 °C. For an overview of the thermograms of polymorph II, see Fig. 5. Lowering the heating rate to 0.1 °C/min did not show any further peaks, only the onset of the melting peak was shifted to 77 °C. Further lowering of the heating rate to 0.01 °C, using the C-80 Setaram calorimeter, did not lead to a well-resolved recrystallization exotherm and no solid–solid transformation is visible. The XRPD pattern of a sample of polymorph II, heated to 75 °C with 0.01 °C/min and then cooled to room temperature, was identical with the pattern of the starting polymorph II, showing that no transformation had taken place. Starting with form III, the thermograms show only the melting peak of that polymorph, whatever heating rate was used.

The results given above show that a precise determination of the melting points and the melting enthalpies is difficult, especially for polymorph I. The result is an overestimation of the melting temperatures of polymorph I when a high heating rate is used. If a lower

Table 2

Thermal data obtained from the DSC scans of Fig. 4, the most right column states the sum of the thermic events.

Heating rate (°C/min)	<i>T</i> onset first peak (°C)	ΔH (J/g)	<i>T</i> onset second peak (°C)	ΔH (J/g)	<i>T</i> onset melting peak (°C)	$\Delta_{\text{fus}}H$ (J/g)	Total ΔH (J/g)
10					76.0	100.9	100.9
1	74.5	87.9	77.5	−0.5	78.3	14.6	102
0.1	74.4	7.4	74.7	−1.9	78.1	93.2	98.7

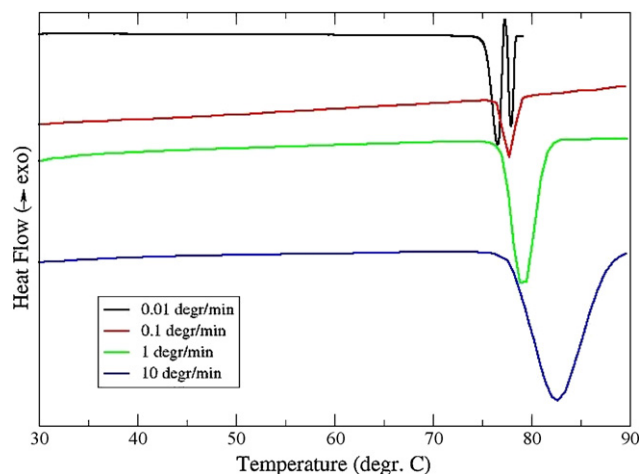


Fig. 5. DSC thermograms of polymorph II heated with different heating rates, 10, 1, 0.1 and 0.01 °C/min; for the sake of clarity the vertical axis of the traces have been enlarged; by a factor of 20 for the 0.01 °C/min trace, by a factor of 10 for the 0.1 °C/min trace and by a factor of 5 for the 1 °C/min trace.

heating rate is used, the endothermic melting peak overlaps the exothermic crystallization peak of form III and as a result of that, it is not possible to determine the melting enthalpy accurately. To find a compromise with a reasonable accuracy, a heating rate of 3 °C/min for polymorph I was used which resulted in the formation of only small amounts of form III. Likewise, overlapping peaks make it difficult to determine the melting enthalpy of polymorph II. The melting points and the melting enthalpies of all three polymorphs, thus obtained, are summarized in Table 3. Table 3 shows that the melting point of polymorph II is higher than that of polymorph I. Using the Burger and Ramberger thermodynamic “rules” for polymorphs [21], this suggests that polymorph II has a lower free energy than polymorph I, at least near the melting point. The same reasoning is valid for forms III and II. These conclusions are in accordance with the results found in the slurry experiments.

5.4. Solubility experiments

5.4.1. Solubility of Venlafaxine in heptane

Heptane is used in the large scale purification of Venlafaxine free base, and was therefore included in this study. The polymorphic transition rate in this solvent is too high to determine the solubility of the polymorphs in their metastable regions. The solubilities of all three forms were determined using the saturation shaken flask method and are presented in Fig. 6. A transition temperature between polymorphs I and II, of 35.7 °C and between forms II and III at 51 °C was determined by extrapolating the trendlines, assuming a linear relation. Surprisingly, the extrapolated solubility line of polymorph I, which is stable at low temperatures according to the slurry experiments, shows that polymorph I has the lowest solubility above the transition temperature. For polymorph II a similarly surprising result is found for temperatures below that temperature. To investigate the cause of this anomalous behaviour, the solubil-

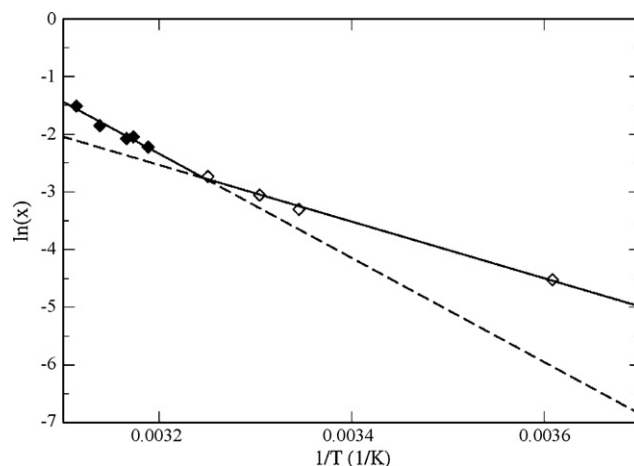


Fig. 6. van't Hoff solubility plots of polymorphs I (open symbols) and II (closed symbols) in heptane, determined using the saturation shaken flask method, with extrapolated dashed trend lines.

ity of Venlafaxine was determined over a wider temperature range, from –76 to 60 °C and compared with the van't Hoff solubility curve for ideal solutions. To test the reliability of the saturation shaken flask method, solubility data for polymorph II were also determined using the in situ method. The combined solubility data are presented in Fig. 7 in a van't Hoff plot. In this figure the solubility of VFX is presented together with the various solubility curves calculated using the measured parameters presented in Table 3, for polymorphs I (solid curves) and II (dashed curves). From the determined solubility of Venlafaxine free base it is obvious that except for temperatures just below the melting point of the solute, the data deviate considerably from the ideal solubility behaviour. The observed lower than ideal solubility could be accounted for by less favourable interactions between solvent and solute molecules. If the solubility data would be fitted using Eq. (5), which includes mixing terms only, the agreement would still not be very good, because as

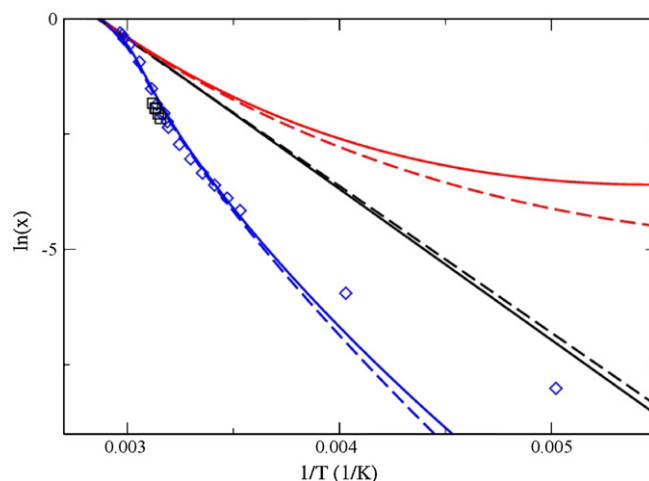


Fig. 7. Solubility data of the three forms of Venlafaxine in heptane, determined down to 197 K; diamond symbols: data determined using saturation shaken flask method; square symbols: data determined using the in situ method; the solid and dashed black curves, represent the ideal solubility curves for polymorphs I and II, respectively (Eq. (1)), the red curves represent the solubility curves for polymorphs I and II, respectively for which a temperature dependence of $\Delta_{\text{fus}} h'(T)$ is included using the data of Table 3; the blue curves represent a fit for which all parameters are included, combining Eq. (6), the data of Table 3 and $\Delta_{\text{mix}} h = 26.5 \text{ kJ/mol}$ and $\Delta_{\text{mix}} s = 72 \text{ J/(mol K)}$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

Table 3

Melting temperatures, melting enthalpies and heat capacity data of forms I, II and III of Venlafaxine. Δc_p is determined from measurements between T_{fus} and 40 °C (Section 5.4).

	T_{fus} (°C)	$\Delta_{\text{fus}} H$ (J/g)	Δc_p^0 (J/(mol K))	Δc_p^1 (J/(mol K))
Polymorph I	74.9	98.1	136.4	–0.3355
Polymorph II	76.5	95.3	100.1	–0.3283
Form III	78.1	87.9	96.0	–0.109

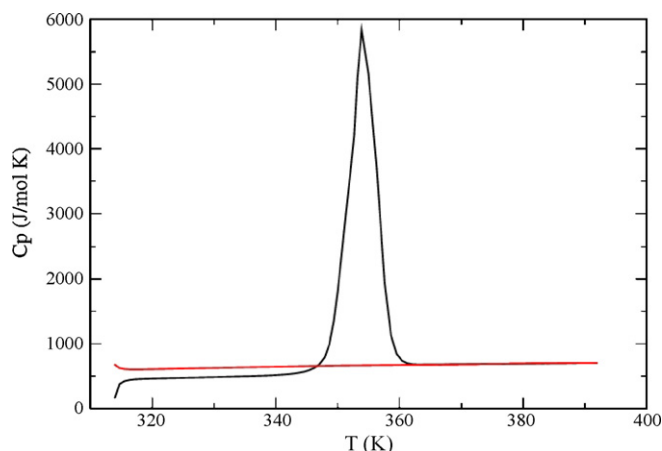


Fig. 8. c_p -curves of Venlafaxine. Heating run for the crystal (black curve), and heating run for the undercooled liquid (red curve). Deviations in the curves at low temperatures are artefacts of the measurement. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

is shown in Fig. 2, the mixing terms in the equation cannot account for the observed concave shaped curve in the solubility at lower temperatures. The concave shape suggests an effect of a temperature dependent $\Delta_{\text{fus}}h^*$. To determine $\Delta_{\text{fus}}h^*$, the difference of the molar heat capacity of the undercooled liquid and the crystal was measured. For most compounds it is rather difficult to determine this difference, because the undercooled liquid can usually be maintained only in a limited temperature range below the melting point. For Venlafaxine, determination of Δc_p turned out to be quite well possible down to 40 °C for the undercooled liquid. For that, a sample of Venlafaxine was heated to a temperature 10 °C above the melting point, cooled to 40 °C (without crystallization of the liquid) and the undercooled liquid was again heated to 10 °C above its melting point. As an example the resulting curves for polymorph I are shown in Fig. 8. Fitting the c_p -data to Eq. (2) resulted in parameters Δc_p^0 and Δc_p^1 for the three forms as presented in Table 3. Including a temperature dependence for $\Delta_{\text{fus}}h^*$ in the solubility equation, results in the red curves in Fig. 7. Combining the effect of the measured temperature dependence of $\Delta_{\text{fus}}h^*$, an enthalpy of mixing and an excess entropy, as parameters to fit the solubility data, and using Eq. (6), the agreement between the calculated and the measured solubility is reasonable (blue curves in Fig. 7). The fit parameters used for these curves are presented in Table 4. Note that the mixing parameters in the solution are independent of the forms I, II or III. The agreement between the calculated and the observed solubility is especially good from 40 up to ~60 °C. Below 40 °C the observed solubility shows a higher solubility than calculated. The positive deviation of the solubility could be the result of a more complex temperature dependence of Δc_p at lower temperatures. After all it was not possible to measure Δc_p below 40 °C. Although the concave shape of the solubility curves is described rather well by the temperature dependence of the heat of fusion difference, the order of the curves for polymorphs I and II is swapped on including this difference.

Table 4

Fit parameters found for the different solvents using Eq. (6) and data of Table 3.

	$\Delta_{\text{mix}}h$ (kJ/mol)	$\Delta_{\text{mix}}s$ (J/(mol K))
Heptane	26.5	72
Toluene	0.5	1
Methanol	1.6	10

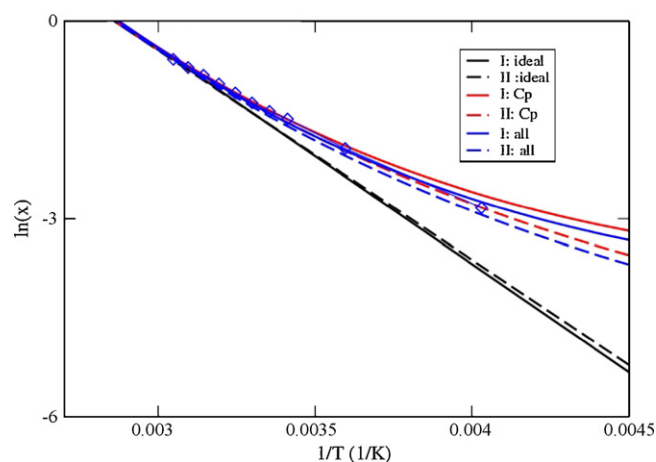


Fig. 9. Solubility of Venlafaxine free base in toluene. Open diamond symbols represent data determined using the saturation shaken flask method, the solid and dashed black curves, represent the ideal solubility curves for polymorphs I and II respectively, the red curves represent the solubility curves for polymorphs I and II, respectively for which a temperature dependence of $\Delta_{\text{fus}}h^*(T)$ is included and the blue curves represent the case for which all parameters are included. For the calculations data from Table 2 were used and $\Delta_{\text{mix}}h = 0.5$ kJ/mol and $\Delta_{\text{mix}}s = 1$ J/(mol K) were obtained from the fit. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

5.4.2. Solubility of Venlafaxine in toluene

To investigate the effect of different solvents on the solubility behaviour of Venlafaxine free base, the solubility was also determined in toluene, a solvent with physical parameters comparable to heptane, in particular a small difference in dipole moment and boiling point. The solubility of Venlafaxine free base was determined in toluene using the saturation shaken flask method, in the temperature range of –25 to 60 °C, see Fig. 9. In case of toluene it was very difficult to measure the solubility at temperatures below –25 °C, because the solution became so viscous, that it was almost impossible to filter the solution keeping it at the right temperature. Like for heptane, the solubility behaviour of Venlafaxine in toluene deviates considerably from ideal behaviour, but this time the deviation is positive compared to the ideal linear van't Hoff curve. The shape of the solubility curve is still concave, as expected for a temperature dependent contribution of $\Delta_{\text{fus}}h^*$ to the solubility. When Eq. (6) is used as a model to fit the solubility data, the agreement is very good. The fit parameters found, using the data from Table 3, are presented in Table 4. Over the complete experimental temperature range the measured solubility follows the calculated curve very well. As for heptane, however, the order of the solubility curves of polymorphs I and II is swapped.

5.4.3. Solubility of Venlafaxine in methanol

To study the behaviour of Venlafaxine free base in a polar solvent, the solubility was measured in methanol. The results are presented in Fig. 10. The data show that the solubility behaviour is not ideal, but the deviation from ideal behaviour is not large, besides the data point at low temperature, which deviates considerably, like in the case of heptane. Using Eq. (6), to fit the data, the results are in a reasonable agreement between the observed and the calculated solubility. The fit parameters using the data from Table 3, are presented in Table 4.

5.4.4. Discussion

From the comparison between the measured and the calculated solubility of Venlafaxine it is clear that the temperature dependence of $\Delta_{\text{fus}}h^*$ has a large effect on the solubility. That this effect is independent of the solvent used, is clear from the fact that

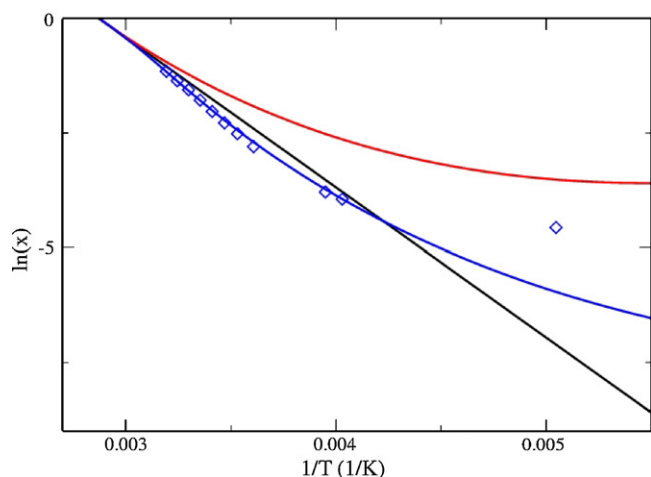


Fig. 10. Solubility data of the three forms of Venlafaxine in methanol, open diamond symbols, data determined using the saturation shaken flask method; the solid black curve represents the ideal solubility curves for polymorph I the red curve represents the solubility curve for polymorph I for which a temperature dependence of $\Delta_{\text{fus}}h^*(T)$ is included; and the blue curves represent the case for which all parameters are included. For the calculations data from Table 2 were used and $\Delta_{\text{mix}}h = 1.6 \text{ kJ/mol}$ and $\Delta_{\text{mix}}s = 10 \text{ J/(molK)}$ were obtained from the fit. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

the resulting concave shape of the solubility curve was observed both for polar and apolar solvents. For Venlafaxine it was possible to measure Δc_p down to 35°C undercooling. For polymorph I the measurement of Δc_p is less accurate because during the first heating cycle part of the solid can transform to polymorph II via a melt-recrystallization process. The same effect makes it difficult to determine the precise melting temperature and melting enthalpy for polymorph I. Together with the instrumental errors, these effects might account for the observed swap of the position of calculated ideal solubility curves of polymorphs I and II on including the effect of Δc_p .

A solution of Venlafaxine free base in toluene behaves almost as an ideal solution when including the temperature dependence of the fusion enthalpy, which means that the solvent–solute interactions are very similar to the solvent–solvent and the solute–solute interactions. In case of heptane, a solvent molecule without a significant dipole moment, the intermolecular interactions are due to van der Waals forces. For Venlafaxine free base, a more polarizable molecule, the dipole moment is larger, but it also forms an intra-molecular hydrogen bond between the OH and the dimethylamino group. These two effects can account for the large $\Delta_{\text{mix}}h$ (26.5 kJ/mol) found from the solubility data fit. The solvent–solvent and solute–solute interactions are preferred compared to the interaction between solvent and solute molecules. In other words, the mixing energy is positive and large.

For methanol, a solvent with a hydrogen bonded structure, the molecular properties are more similar to those of Venlafaxine free base; the solvent–solute interactions are more comparable to the solvent–solvent and the solute–solute interactions, resulting in a smaller $\Delta_{\text{mix}}h$ (1.6 kJ/mol) to fit the solubility data.

Remarkably, the solution of Venlafaxine free base in toluene, a molecule without a significant dipole moment and no possibility to form hydrogen bonds, behaves almost as an ideal solution; the observed and the calculated solubility fit very well and only a small $\Delta_{\text{mix}}h$ (0.5 kJ/mol) was necessary to fit the data, suggesting a strong π – π interaction between the solvent and solute molecules.

By extrapolating solubility trendlines of the respective polymorphs in the ideal van't Hoff plots, transition temperatures can

be calculated. This temperature for the transition of polymorphs I to II is 35.7°C. For the transition of polymorph II to form III this temperature is 51°C. When we apply Eq. (8) to calculate the transition temperatures for our system, using the thermodynamic data of Table 3, we find a temperature for the transition of polymorphs I to II of 28, and 56°C for the transition of polymorph II to form III. Given the assumption of ideal behaviour made for Eq. (8) and the far from ideal behaviour found for heptane, these calculated transition temperatures agree reasonably well with the results of the solubility experiments.

6. Conclusions

The three forms of the free base of Venlafaxine were studied. All three forms were isolated and characterized using different techniques; DSC and X-ray powder diffraction and solubility experiments. From slurry experiments it was found that all the three forms have a distinct temperature range where they are stable, in other words there exists an enantiotropic relation between the three forms. The results of measuring DSC thermograms of a compound with different heating rates of 10°C/min and lower, show that several phenomena can be missed like solid–solid transitions and/or melt–recrystallizations. Although this is a well-established fact, it is still common practice to measure DSC thermograms with heating rates of 10°C/min or more.

The solubility curves of Venlafaxine free base in different solvents could be only described when the temperature dependence of $\Delta_{\text{fus}}h^*$ was included. This term, which is independent of the solvent, was determined by measuring the difference in heat capacity of the solid and undercooled melt of the solute. It was shown that using solubility data in the form of van't Hoff curves to draw conclusions about the stability regions of two enantiotropic-related polymorphs can lead to paradoxical situations if the temperature dependence of $\Delta_{\text{fus}}h^*$ is not considered. Although this temperature dependence is almost always neglected, the present results show that care should be taken in doing so, especially in the case of pharmaceutical compounds. These often have a large number of degrees of freedom due to the complex structure of the molecules, and consequently a non-negligible Δc_p can be expected between the undercooled melt and the solid phase.

Finally, a recently derived expression for the transition temperature of two enantiotropic forms in terms of the heat of fusion and the melting temperatures of the forms, as determined by for example DSC measurements, was validated for Venlafaxine. The results agree reasonably with the experimental transition temperatures. This is remarkable because in case of the calculated transition temperatures the non-negligible temperature dependence of $\Delta_{\text{fus}}h^*$, as was found for Venlafaxine, was not taken into account.

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