Solubility of Form III Piracetam in a Range of Solvents

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The polymorph known as Form III of 2-oxo-1-pyrrolidine acetamide (piracetam) was isolated by cooling crystallization from methanol and characterized by X-ray diffraction (XRD), scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC). Form III is the thermodynamically stable polymorph of piracetam in the range of this solubility study. The solubility of Form III was determined by gravimetrically measuring the amount of Form III which was contained in a volume of saturated solution over the temperature range (278 to 323) K, following evaporation of the solvent. Five solvents were examined: methanol, ethanol, 2-propanol, acetone, and 1,4-dioxane. The results showed that the solubility values correlated positively with solvent polar characteristics from a qualitative point of view; an increase in solubility of Form III was observed with increasing solvent polarity and solvent acidity. As the number of carbons in the *n*-alcohols increases, the polarity of the solvent and its hydrogen donation ability decreases and so does the solubility of Form III in the solvent. 1,4-Dioxane and acetone are relatively nonpolar and non-hydrogen bond donating solvents compared to the *n*-alcohols, and accordingly Form III is much less soluble in these.

Introduction

The crystallization of an active pharmaceutical ingredient is a very important step in the manufacturing of a drug product. Crystalline molecular solids, either pure or in solvate form, can exist in different crystal arrangements. Polymorphism in crystalline solids is defined as materials having the same chemical composition but different lattice structure orientations and/or different molecular conformations and, therefore, different physicochemical properties.[1,2] The difference in properties (e.g., solubility) between different polymorphs of a drug has led to a tight regulation of polymorphism in the pharmaceutical industry, as they have a direct impact on drug substance processability, drug product manufacturability, and drug product quality or performance, including stability, dissolution, and bioavailability.[3]

As solubility and drug dissolution rate are related to drug processing in the body, a lot of work has been carried out investigating the effect of polymorphism on solubility and dissolution.[4] Solubility data are very important for any polymorphic system, as they give information on the relative stability of the polymorphs in that system. The most stable polymorph in a system will have the lowest solubility, while the least stable polymorph will have the highest solubility, irrespective of the solvent.[5]

2-Oxo-1-pyrrolidine acetamide (piracetam) (Figure 1) is a nootropic drug, which is an agent that acts on cognitive dysfunction without causing sedation or stimulation.[6] Cognitive dysfunction is one of the main symptoms accompanying aging, stroke, head injury, and neurodegenerative diseases such as Alzheimer's.[7] Throughout the literature there is some confusion over the nomenclature of the different polymorphs. In this work the system used for naming polymorphs is simply the form number followed by the *a* lattice parameter reported for the particular polymorph in the Cambridge Crystallographic Data Centre[12] (CCDC) in parentheses, so that Form III is referred to below as FIII(6.525).[8] The reference code for the polymorphic entries of piracetam in the CCDC is BISMEV, while the entry that corresponds to FIII(6.525) is BISMEV01.

Five polymorphs of piracetam have been reported, but two of these [FIV(8.9537) and FV(6.3903)] are obtained in high pressure (> 0.5 GPa) conditions only.[9,10] Another polymorph, FI(6.747), is only seen when FII(6.403) or FIII(6.525) are heated to 400 K and then quenched to room temperature.[9,11] However, FI(6.747) transforms back to FII(6.403) within a few hours at room temperature and so is not of practical relevance. The other two polymorphs, FII(6.403) and FIII(6.525), have been identified and structurally characterized under ambient conditions.[11] Conflicting views on the stability hierarchy of the polymorphs in the system are presented in the literature.[11,13,14] While it is well agreed that FI(6.747) is the stable polymorph at higher temperatures, there is some confusion as to which polymorph is stable at lower temperatures. Analysis of the polymorphs in solution and in the solid state suggest that FIII(6.525) is the thermodynamically stable polymorph at lower temperatures until it transforms to FI(6.747) at approximately 393 K. This is in agreement with the work published by Kuhnert-Brandstaetter et al.[14]

To date, there are no published solubility data for the polymorphs of piracetam. In this study, the solubility of FIII(6.525) was determined in a range of five solvents, at increments of 5 K, over the range of (278 to 323) K.

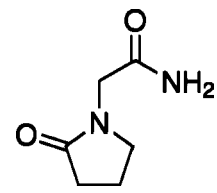

Figure 1. Molecular structure of piracetam.

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Table 1. List of Solvents Used along with Their Specification and CAS Registry Number

solvent	specification/mass %	CAS No.
methanol	ACS reagent, > 99.8 %	67-56-1
ethanol	ACS reagent, > 99.5 %	64-17-5
2-propanol	ACS reagent > 99.5 %	67-63-0
1,4-dioxane	spectrophotometric grade, > 99 %	123-91-1
acetone	ACS reagent, > 99.5 %	67-64-1

Experimental Section

Piracetam was supplied by UCB Pharma SA and complies with European Pharmacopoeia standards (CAS Number: 7491-74-9). The five solvents listed in Table 1 were obtained from Sigma-Aldrich and were used without further purification.

FIII(6.525) was produced using a HEL PolyBLOCK parallel synthesis reactor. Eighty grams of piracetam were dissolved in 200 mL of methanol at 333 K with agitation of 200 rpm. The solution was then cooled to 283 K at a rate of 1 K·min^{-1}. Solids were sampled periodically before harvesting the FIII(6.525) crystals by vacuum filtration after 24 h. X-ray diffraction (XRD) analysis (Phillips PANalytical X'Pert MPD Pro with PW3064 sample spinner) was used to analyze the composition of the sampled solids. The solids were dried in an oven at 318 K. Fifty-nine grams of FIII(6.525) were obtained per batch and characterized by XRD, optical microscopy (Zeiss Axioscope Axio-Imager MAT reflected-light microscope), scanning electron microscopy (SEM, JEOL CarryScope scanning electron microscope JCM-5700), attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR, PerkinElmer precisely Spectrum 100 FT-IR spectrometer with a PerkinElmer precisely Universal ATR sampling accessory) and differential scanning calorimetry (DSC, PerkinElmer instruments Pyris 1 differential scanning calorimeter).

The experimental setup for the solubility measurements of FIII(6.525) consisted of a thermostatic water bath (Grant GR150 with S38 stainless steel water bath; 38 L; 690 × 300 × 200 mm; @ 310 K; stability ± 0.005 K and uniformity ± 0.02 K) with a serial magnetic stirrer plate placed on the base. Five test tubes (150·25 mm) with a Teflon-coated magnetic stirrer were charged with each of the five solvents and placed in a rack in the water bath which was set at the desired temperature. After 1 h (temperature of solvent had reached the temperature of the water bath) excess FIII(6.525) was added to each of the five test tubes. The test tubes were agitated at 500 rpm for at least 48 h to allow the equilibrium concentration to be reached. The stirring was then turned off, and excess FIII(6.525) was allowed to settle for 2 h. Samples of the clear saturated solution (approx 4 mL) were transferred from each of the test tubes to three 50 × 25 mm clean dry weighed vials (mass of dry vial + cap = m_{empty}) using a preheated syringe. A 0.2 μm, 15 mm membrane diameter syringe filter was attached to the head of the syringe before the saturated solution was passed into the vials to ensure that there was no suspended solid present. Caps were put on the vials immediately after solution had been filtered into them, to prevent solvent evaporation, and then reweighed (mass = m_{liq}). The caps were then removed, and the solvent was allowed to evaporate at room temperature in the fume hood for approximately 1 week. At this point only a solid residue remained in the vials, and the drying process was completed by placing the vials in an oven at 333 K for 3 days (Lenton Thermal Designs oven). The vials were then allowed to return to room temperature in the fume hood before reweighing with their caps (mass = m_{dry}). All weighing was carried out using a Mettler Toledo AX054 with a weighing capacity of up to 520 g and readability of 0.1 mg. A typical mass of solid residue was approximately 0.1 g. The solubility of FIII(6.525) in the solvent, C_s, could then be calculated as shown in eq 1, expressed as g FIII(6.525)/g solvent. The solubility was measured at every 5 K in the temperature range (278 to 323) K. Three samples were taken for each solvent at each temperature. The freezing point of 1,4-dioxane is 284.8 K so the solubility of FIII(6.525) in this solvent was not measured below 288 K.

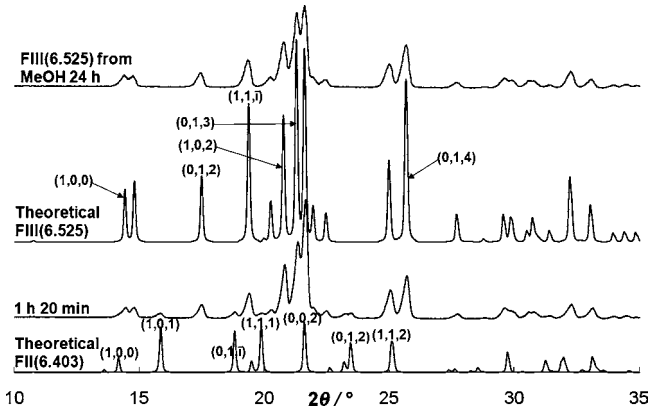

Figure 2. Theoretical XRD patterns of FII(6.403) and FIII(6.525) from CCDC[12] compared to the XRD patterns of the crystals harvested from methanol after 1 h 20 min and 24 h.

$$C_s = \frac{(m_{dry} - m_{empty})}{(m_{liq} - m_{dry})} \quad (1)$$

At each temperature as the clear saturated solution sample was taken from the test tube, a sample of the excess solid was also taken. XRD was carried out on the solid sample to verify that the composition was indeed FIII(6.525). The reproducibility of the solubility results was examined in methanol by repeating the solubility measurements at each temperature in a separate test tube.

An experiment was carried out to examine the time it took for the equilibrium saturation to be reached in methanol at 298 K. Samples of the clear solution were taken every hour for 12 h and after that once every 12 h up to 48 h. The samples were dried in the same manner as outlined, and the resulting curve showed that the solubility point was reached after (5 to 6) h. The concentration in solution then remained at that same value for the duration of the analysis.

The drying procedure used in this work was verified by weighing certain amounts of solvents (methanol and acetone) and FIII(6.525) into vials and subjecting them to the drying procedure. The vials were then reweighed and the percentage weight loss calculated. FIII(6.525) showed a percentage weight loss of 0.04 %. This drop in the weight may be a result of any residual moisture that is present during storage evaporating off during drying. No detectable residue was found after the drying of the pure solvents.

Results and Discussion

XRD demonstrated the commercial piracetam to consist mostly of FIII(6.525) but with traces of FII(6.403). Pure FIII(6.525) was crystallized by cooling crystallization in methanol. Figure 2 shows the XRD of the pure FIII(6.525) crystals that were harvested after 24 h from methanol. This XRD pattern is identical to that of the FIII(6.525) entry in the CCDC.[12] Looking at the XRD of the crystals harvested after 1 h 20 min

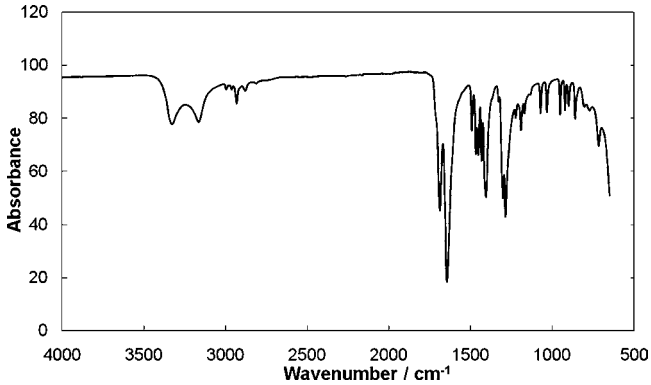

Figure 3. FTIR spectrum of pure FIII(6.525).

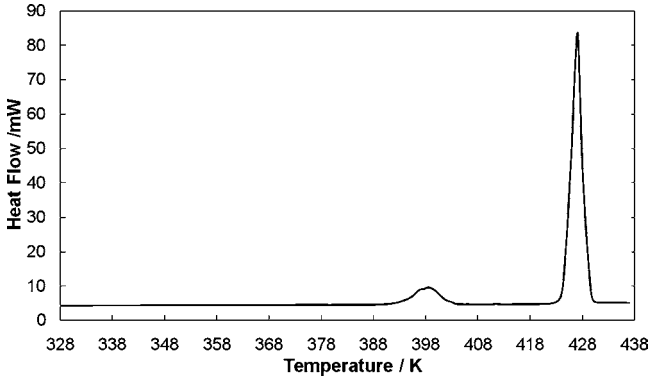

Figure 4. DSC scan of pure FIII(6.525); heating rate of 5 K·min^{-1}. Endothermic peaks indicating the transformation to FI(6.747) at 393 K and melting of FI(6.747) at 425 K.

in Figure 2, some FII(6.403) peaks are present, such as the (1,0,1) peak at 16.0 2θ and the (0,1,$\bar{1}$) peak at 18.5 2θ. All peaks related to FII(6.403) have clearly disappeared after 24 h agitation at 283 K, at which time pure FIII(6.525) was harvested.

After isolation, FIII(6.525) was characterized. The FTIR spectrum obtained is shown in Figure 3. The regions unique to FIII(6.525) are (1100 to 1250) cm^{-1} and (2850 to 3050) cm^{-1} as outlined by Pavlova[13] and Kuhnert-Brandstaetter et al.[14] The DSC scan in Figure 4, using a heating rate of 5 K·min^{-1}, shows that FIII(6.525) is stable until heated to 393 K where it transforms to FI(6.747) with an endothermic peak. The melting of FI(6.747) gives an endothermic peak at approximately 425 K. It is the stable polymorph of piracetam from 393 K to its melting point (425 K). The SEM images of the FIII(6.525) crystals from methanol after 24 h in Figure 5 shows that the crystals have a hexagonal habit, with very well-defined faces.

Table 2 gives the mean values of the three samples of the experimental results obtained for the solubility of FIII(6.525) in the five solvents over the range of (278 to 323) K. The standard deviation between the three samples taken at each temperature for each solvent is also shown in brackets. The standard deviation is quite low (less than 1.50·10^{-3} in all cases) indicating little variance and reproducible results. The solubility graph for FIII(6.525) in the five solvents of choice is presented in Figure 6. The solubility in methanol increases from 7.96·10^{-2} g FIII(6.525)/g solvent at 278 K to 48.04·10^{-2} g FIII(6.525)/g solvent at 323 K. As can be seen in all five solvents analyzed in this work, the solubility of FIII(6.525) in the solvents increases with temperature. By examining Figure 6 and Table 2, it can be said that the solubility of FIII(6.525) in methanol (one carbon) is greater than that of ethanol (two carbons), which is greater than that of 2-propanol (three carbons) across the range of the study. The solubility decreases as the number of carbons in the *n*-alcohols increases, which reflects a decreasing solubility with decreasing solvent polarity and hydrogen bond donor ability. 1,4-Dioxane and acetone are relatively nonpolar solvents when compared to alcohols, and accordingly FIII(6.525) is much less soluble in these solvents. In addition, 1,4-dioxane and acetone are aprotic solvents and cannot hydrogen bond to the proton-accepting carbonyl oxygen of the solute molecule. Alcohols are protic and can interact not only with the hydrogen bond donating amino groups but also with the carbonyl oxygen of the solute.

Along with the low standard deviation values, Figure 6 shows that the solubility results are reproducible. The solubility determination was repeated at all temperatures in methanol. As can be seen on the graph, the two solubility curves for FIII(6.525) in methanol are almost identical, indicating that the data obtained is reliable.

Figure 7 shows a van't Hoff plot where the mole fraction solubility (ln(x)), eq 2, of FIII(6.525) in the five solvents is plotted against temperature:

$$\ln(x) = \ln\left(\frac{n_{\mathrm{FIII(6.525)}}}{(n_{\mathrm{FIII(6.525)}} + n_{\mathrm{solvent}})}\right) \qquad (2)$$

where n is the number of moles. In addition it is noted that the van't Hoff enthalpy of solution:

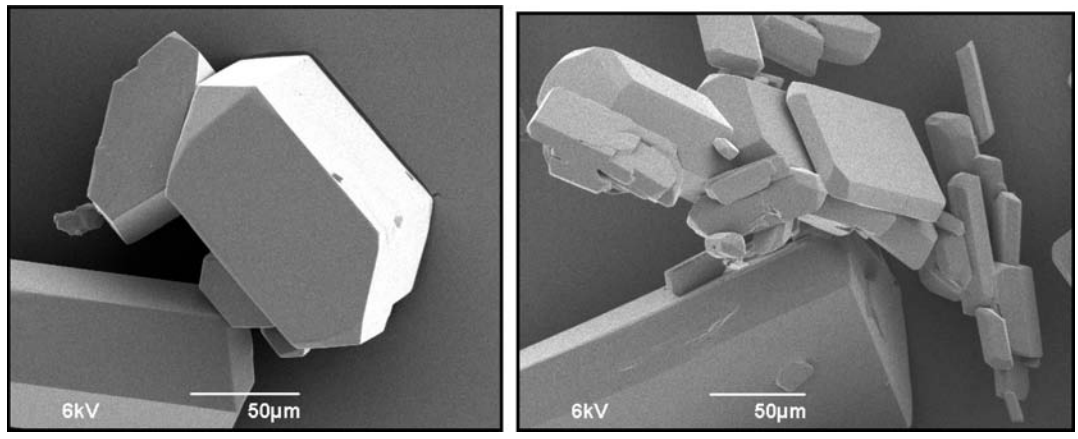

Figure 5. SEM images of pure FIII(6.525) crystals.

Table 2. Solubility Data (C_s) (g FIII(6.525)/g Solvent) and Standard Deviation in Brackets (Std. Dev.) Obtained for FIII(6.525) in the Five Solvents over the Range (278 to 323) K

temperature	methanol C_s (std. dev.)	methanol rpt C_s (std. dev.)	ethanol C_s (std. dev.)	2-propanol C_s (std. dev.)	1,4-dioxane C_s (std. dev.)	acetone C_s (std. dev.)
K	g FIII(6.525)/g solvent	g FIII(6.525)/g solvent	g FIII(6.525)/g solvent	g FIII(6.525)/g solvent	g FIII(6.525)/g solvent	g FIII(6.525)/g solvent
278	$7.96\cdot10^{-2}$ ($1.17\cdot10^{-3}$)	$7.98\cdot10^{-2}$ ($1.32\cdot10^{-3}$)	$1.61\cdot10^{-2}$ ($2.12\cdot10^{-4}$)	$0.73\cdot10^{-2}$ ($1.02\cdot10^{-3}$)	n/a[a]	$0.38\cdot10^{-2}$ ($1.89\cdot10^{-4}$)
283	$9.72\cdot10^{-2}$ ($1.80\cdot10^{-4}$)	$9.78\cdot10^{-2}$ ($1.02\cdot10^{-3}$)	$2.05\cdot10^{-2}$ ($7.87\cdot10^{-5}$)	$0.91\cdot10^{-2}$ ($2.21\cdot10^{-4}$)	n/a[a]	$0.42\cdot10^{-2}$ ($1.30\cdot10^{-4}$)
288	$11.95\cdot10^{-2}$ ($9.80\cdot10^{-5}$)	$12.00\cdot10^{-2}$ ($1.21\cdot10^{-3}$)	$2.60\cdot10^{-2}$ ($1.26\cdot10^{-3}$)	$1.20\cdot10^{-2}$ ($1.16\cdot10^{-3}$)	$2.56\cdot10^{-3}$ ($1.09\cdot10^{-3}$)	$0.51\cdot10^{-2}$ ($2.53\cdot10^{-4}$)
293	$14.81\cdot10^{-2}$ ($1.96\cdot10^{-4}$)	$14.82\cdot10^{-2}$ ($1.74\cdot10^{-4}$)	$3.24\cdot10^{-2}$ ($2.27\cdot10^{-4}$)	$1.50\cdot10^{-2}$ ($1.78\cdot10^{-4}$)	$2.91\cdot10^{-3}$ ($9.11\cdot10^{-5}$)	$0.63\cdot10^{-2}$ ($1.59\cdot10^{-4}$)
298	$17.96\cdot10^{-2}$ ($1.19\cdot10^{-3}$)	$18.01\cdot10^{-2}$ ($1.53\cdot10^{-4}$)	$4.08\cdot10^{-2}$ ($7.90\cdot10^{-4}$)	$1.90\cdot10^{-2}$ ($4.18\cdot10^{-4}$)	$3.45\cdot10^{-3}$ ($4.07\cdot10^{-4}$)	$0.77\cdot10^{-2}$ ($3.33\cdot10^{-5}$)
303	$21.60\cdot10^{-2}$ ($1.95\cdot10^{-4}$)	$21.58\cdot10^{-2}$ ($1.03\cdot10^{-3}$)	$5.11\cdot10^{-2}$ ($1.29\cdot10^{-3}$)	$2.45\cdot10^{-2}$ ($1.33\cdot10^{-3}$)	$4.23\cdot10^{-3}$ ($1.19\cdot10^{-3}$)	$0.94\cdot10^{-2}$ ($1.25\cdot10^{-3}$)
308	$26.31\cdot10^{-2}$ ($1.32\cdot10^{-3}$)	$26.26\cdot10^{-2}$ ($1.01\cdot10^{-3}$)	$6.31\cdot10^{-2}$ ($3.94\cdot10^{-4}$)	$3.12\cdot10^{-2}$ ($2.69\cdot10^{-4}$)	$5.26\cdot10^{-3}$ ($4.16\cdot10^{-4}$)	$1.16\cdot10^{-2}$ ($3.89\cdot10^{-4}$)
313	$32.30\cdot10^{-2}$ ($6.01\cdot10^{-3}$)	$32.29\cdot10^{-2}$ ($1.43\cdot10^{-3}$)	$7.92\cdot10^{-2}$ ($1.19\cdot10^{-3}$)	$4.00\cdot10^{-2}$ ($8.49\cdot10^{-4}$)	$6.74\cdot10^{-3}$ ($5.25\cdot10^{-4}$)	$1.41\cdot10^{-2}$ ($5.23\cdot10^{-4}$)
318	$39.47\cdot10^{-2}$ ($1.06\cdot10^{-3}$)	$39.39\cdot10^{-2}$ ($1.04\cdot10^{-3}$)	$9.82\cdot10^{-2}$ ($1.25\cdot10^{-3}$)	$5.13\cdot10^{-2}$ ($1.14\cdot10^{-3}$)	$8.36\cdot10^{-3}$ ($1.21\cdot10^{-3}$)	$1.66\cdot10^{-2}$ ($1.36\cdot10^{-3}$)
323	$48.04\cdot10^{-2}$ ($3.16\cdot10^{-4}$)	$48.01\cdot10^{-2}$ ($1.50\cdot10^{-3}$)	$12.48\cdot10^{-2}$ ($1.19\cdot10^{-3}$)	$6.49\cdot10^{-2}$ ($2.46\cdot10^{-4}$)	$10.45\cdot10^{-3}$ ($2.93\cdot10^{-4}$)	$2.00\cdot10^{-2}$ ($1.78\cdot10^{-4}$)

[a] "n/a" refers to temperatures where the solubility of FIII(6.525) could not be measured as it was below the freezing point of the particular solvent.

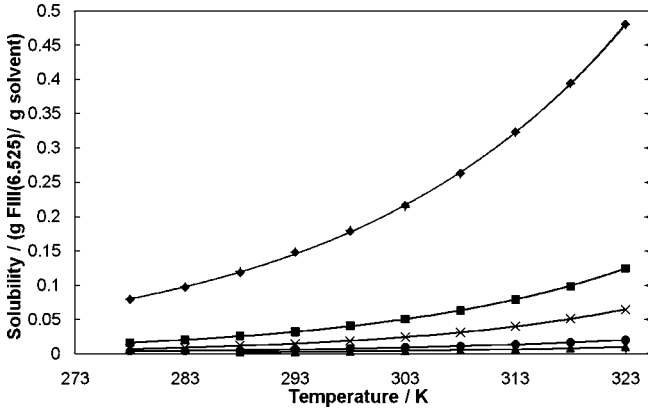

Figure 6. Solubility of FIII(6.525) versus temperature in a range of solvents from (278 to 323) K. ◆, methanol; +, methanol repeat; ■, ethanol; ×, 2-propanol; ●, acetone; ▲, 1,4-dioxane.

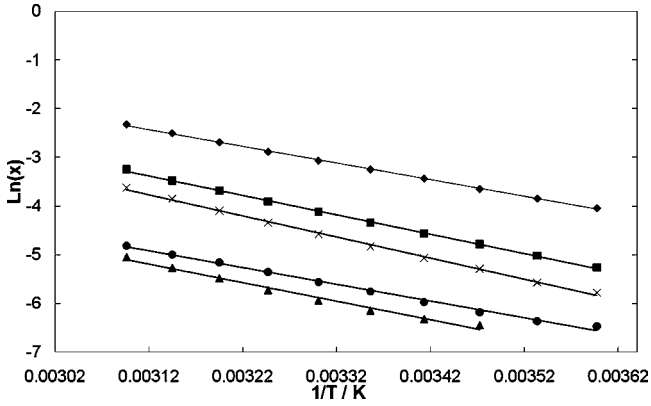

Figure 7. A van't Hoff plot of the mole fraction solubility (ln(x)) of FIII(6.525) in different solvents against 1/T over the range of (278 to 323) K with a straight line fitted to the data. ◆, methanol; ■, ethanol; ×, 2-propanol; ●, acetone; ▲, 1,4-dioxane.

$$\Delta H^{\mathrm{vH}}_{\mathrm{soln}} = -R\frac{d\ln x}{d(1/T)} \tag{3}$$

is essentially constant over the temperature range studied. From the data, values of $\Delta H^{vH}_{\mathrm{soln}}$ were calculated for methanol, ethanol, 2-propanol, acetone, and 1,4-dioxane to be (28.4, 33.1, 36.0, 29.5, and 31.8) kJ·mol^{-1}, respectively.

Nordström and Rasmuson[15] evaluated a series of "regression equations" for the correlation of experimental solubility data and for extrapolation to the melting point. For the latter purpose, the two most successful equations were:

$$\ln(x) = A + BT \tag{4}$$

$$\ln(x) = AT^{-1} + B + CT \tag{5}$$

In the present work, both equations were successfully fitted to the solubility data using Microsoft Office Excel 2003 and Matlab 6.5. R^2 values of greater than 0.9990 were obtained for the data in every solvent. The obtained coefficient values for eq 4 are given in Table 3.

Since FIII(6.525) transforms to FI(6.747) at about 393 K, the determination of melting data for FIII(6.525) becomes uncertain. Pavlova et al.[16] stated that the melting point of FIII(6.525) is in the region of (418 to 426) K. Kuhnert-Brandstaetter et al.[14] determined the melting point of FIII(6.525) to be 413 K using DSC analysis after the commercial product was stored for one year. In the present work, DSC analysis of recrystallized FIII(6.525) as well as the commercial product after one year of storage did not give a solitary peak indicating the melting point of FIII(6.525) (Figure 8). While issues arose with the polymorphic transformation seen in Figure 4, the analysis established that the true value of the melting point appears to be very close to that published by Kuhnert-Brandstaetter et al.[14] Using a heating rate of 2 K·min^{-1}, a small endothermic peak could be seen at 412 K indicating the melting of FIII(6.525). Figure 8 shows a scan with a heating rate of 300 K·min^{-1}. An analysis of this scan shows that there has been a partial transformation to FI(6.747), indicated by the broad endothermic peak at approximately 380 K. A melting peak can be seen for both FIII(6.525) and FI(6.747) at (415 and 427) K, respectively. Variations in exact temperatures of the thermal event are caused by different heating rates employed for the DSC analysis. Because the amount of FIII(6.525) that contributed to the melting peak cannot be quantified, it is impossible to calculate important values such as the melting enthalpy. As put forward by Nordström and Rasmuson,[15] at increasing temperature solubility data should gradually approach the conditions at the melting temperature where ln(x) = 0 and the van't Hoff enthalpy of solution equals the melting enthalpy. Table 4 shows the values of melting temperature, calculated according to Nordström and Rasmuson.[15] Equation 5 appears to give a better prediction of

Table 3. Calculated A and B Coefficients for a Regression Equation (eq 4) Fitted to the Solubility Data Obtained for FIII(6.525) in Each Solvent in the Range (278 to 323) K

	equation ln(x) = A + BT	
solvent	A	B
methanol	−14.609	0.0381
ethanol	−17.571	0.0444
2-propanol	−19.198	0.0482
acetone	−17.143	0.0382
1,4-dioxane	−18.377	0.0412

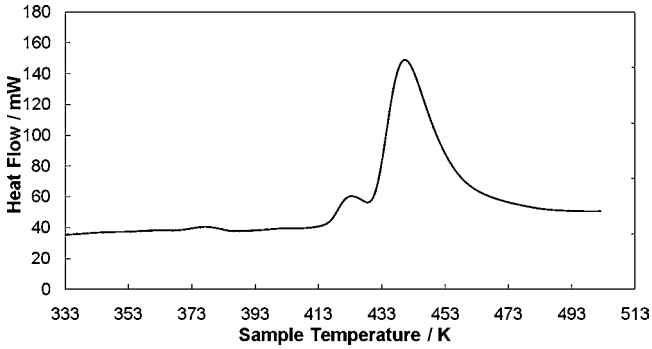

Figure 8. DSC scan of FIII(6.525); heating rate of 300 K·min^{-1}. Endothermic peaks indicating the partial transformation to FI(6.747) at 380 K and melting of remaining FIII(6.525) and transformed FI(6.747) at (415 and 427) K, respectively.

Table 4. Estimated Melting Temperature (K) Calculated by Extrapolation of Equations 4 (Left) and 5 (Right)

	equation $\ln(x) = A + BT$	equation $\ln(x) = AT^{-1} + B + CT$
solvent	melting point/K	melting point/K
methanol	383	392
ethanol	396	405
2-propanol	398	298
acetone	449	426
1,4-dioxane	446	391
mean	414	402

the melting temperature of FIII(6.525). In all solvents except for 2-propanol, the predicted melting temperature is within approximately ± 20 K of the true value, with the average being 402 K. This level of error is approximately equal to the error reported for the predictions by Nordström and Rasmuson.[15] Equation 4 is a straight line. While the melting temperatures predicted using the straight line are not as good as those for eq 5, the mean (414 K) is closer to the true value. The melting enthalpies were calculated using the predicted melting temperatures, but in this instance the values obtained were almost double the value published by Kuhnert-Brandstaetter et al.[14] (29.3 kJ·mol^{-1}), and there is a significant variation especially in the data estimations by eq 5.

Conclusion

FIII(6.525) piracetam displays a wide range of solubility in the five solvents studied. The solubility of FIII(6.525) is influenced by the polarity of the solvent in question and the hydrogen-bonding capacity of the solvent. In this work it was shown that FIII(6.525) is most soluble in the alcohol with the shortest aliphatic chain, methanol. As the polarity and acidity of the alcohol decrease through ethanol and 2-propanol with the increasing number of carbons, so too does the solubility of FIII(6.525) in these solvents. Acetone and 1,4-dioxane are relatively nonpolar when compared to the *n*-alcohols, and accordingly the solubility of FIII(6.525) is much lower in these solvents. By fitting certain regression equations to the solubility data according to Nordström and Rasmuson,[15] the approximate melting temperature can be estimated for FIII(6.525) piracetam, by extrapolation to $\ln(x) = 0$.

Acknowledgment

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