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Thermodynamics of risperidone and solubility in pure organic solvents

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ABSTRACT

The solid–liquid solubility of the thermodynamically stable form I of the drug risperidone has been determined by a gravimetric method in nine pure organic solvents in the temperature range 278.15–323.15 K. The melting temperature and associated enthalpy of fusion of risperidone form I has been determined by differential scanning calorimetry (DSC) to be 442.38 K and 43.94 kJ mol^{-1}, respectively. The heat capacity of the solid form I and the melt have been determined over a range of temperatures by temperature-modulated DSC, and extrapolated data has been used to calculate the Gibbs energy, enthalpy and entropy of fusion from ambient temperature up to the melting point. The ideal solubility within a Raoult's law framework is obtained from the Gibbs energy of fusion, and the solution activity coefficient at equilibrium in the nine solvents quantified. Solutions in all solvents exhibit positive deviation from Raoult's law, with the highest solubility (closest to ideality) in toluene, an aprotic apolar solvent. The solubility curves plotted in a van't Hoff graph show non-linear behaviour and are well-approximated by a second order polynomial.

1. Introduction

The solid–liquid solubility of an organic pharmaceutical compound is a very important property which affects its entire lifespan, from synthesis through isolation and formulation down to its bioavailability within the human body. Having access to accurate solubility data in a relevant selection of solvents is crucial for the control and optimisation of different steps of the manufacturing process. It is of particular importance in crystallisation processes, where knowledge of the solubility is needed in order to be able to control the supersaturation, particle size, desired polymorphic form and yield.

Risperidone, CAS number 106266-06-2, is an atypical benzisoxazole neuroleptic drug mainly used to treat schizophrenia, manic states associated with bipolar disorder, and schizoaffective disorder. Its main pharmacological activity is the blocking of the serotonin type 2 (5HT2) receptor and dopamine type 2 (D2) antagonism [1]. The molecular formula of risperidone is $C_{23}H_{27}FN_4O_2$ (M.W. 410.485 g mol^{-1}) and its molecular structure is shown in Fig. 1. There are two reported polymorphs with crystal structures available in the Cambridge Structural Database (CSD) [2,3]. However, very limited data is available on the solid–liquid solubility of risperidone.

In this work, we report the solubility over the temperature range 278.15–323.15 K in nine pure organic solvents of the stable polymorph of risperidone, sometimes referred to as form A but henceforth termed form I in accordance with McCrone's generally accepted standard naming conventions [4]. The melting properties and the heat capacity of the pure compound in the solid state and as a melt have been determined. Based on the thermal analysis, the thermodynamics of fusion of the solid are investigated, and the ideal solubility is estimated as a function of temperature, allowing activity coefficients in the nine solvents to be calculated.

2. Experimental work

2.1. Materials

Table 1 lists the chemicals used, together with the source and stated purity. All chemicals were used as received without further purification.

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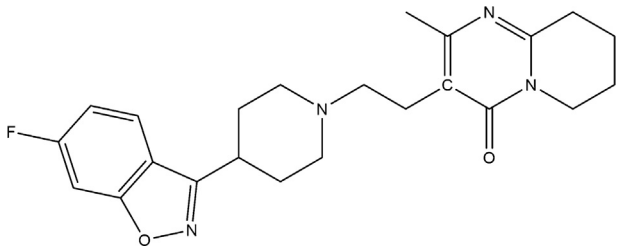

Fig. 1. Molecular structure of risperidone.

Table 1
Source and mass fraction purity of chemicals.

Compound	Source	Purity
Risperidone	Janssen Pharmaceuticals, Ireland	>0.9995
Methanol	VWR International	0.998
Ethanol	VWR International	0.998
1-Propanol	VWR International	0.998
2-Propanol	VWR International	0.998
1-Butanol	VWR International	0.998
Acetone	VWR International	0.998
Ethyl acetate	VWR International	0.998
Toluene	VWR International	0.998
Cumene	VWR International	0.998

2.2. Solubility

Solubility was determined using a gravimetric method described previously [5]. Temperature was controlled using a Grant S26 water bath equipped with a GR150 control unit (specified stability of ±0.005 K) and a Grant C2G cooling unit. A temperature uniformity of ±0.01 K was achieved by providing additional agitation to the bath using a submersible pump. A 60-point submersible magnetic stirring plate (2Mag) provided agitation at 600 rpm. Solutions were equilibrated for 24 h at each temperature in 20 ml glass vials (70 mm × 25 mm), each containing a PTFE coated magnetic stirring bar (13 mm × 3 mm) and sealed with a screw cap with a PTFE coated insert. Equilibrium was always approached from below the desired temperature point (i.e. via dissolution). After the equilibration period stirring was switched off for 1 h to allow excess solids to settle in the vials. A sample of the excess solid material in each vial was collected. Samples of the clear solution (approx. 4 ml) were extracted in triplicate using pre-heated syringes and filtered through 0.2 μm solvent-compatible (PTFE or Nylon) filters into pre-weighed glass vials (50 mm × 25 mm). The filtered solutions were then immediately capped and weighed. The caps were then removed and stored, allowing the solvent to evaporate at room temperature for a period of at least 3 days in a ventilated fume hood. When vials were visibly solvent-free they were placed in an oven at 323 K for 8 h to ensure dryness before being placed in a desiccator overnight to return to ambient temperature. The dry vials were then weighed together with the caps to determine the amount of risperidone dissolved in the solution. All weights were determined with an Ohaus Explorer balance accurate to ±0.0001 g. In each of the nine solvents listed in Section 2.1, solubility was measured in the temperature range 278.15–323.15 K with steps of 5 K. X-ray powder diffraction (XRPD, Philips PANalytical X'Pert MPD Pro with a PW3064 sample spinner) was used to analyse the sampled excess solid material. Scans in the 2θ-range 5–35° allowed identification of the polymorph by comparison with the theoretical patterns generated from the structures published in the CSD.

2.3. Thermal analysis

The melting temperature, T_m, and the associated enthalpy of fusion, $\Delta_{fus}H$, of risperidone form I were determined by differential scanning calorimetry (DSC) using a PerkinElmer Pyris 1, in six repeat runs using a constant heating rate of 1 K min^{-1} from 293 to 453 K. Samples were prepared in hermetically sealed aluminium pans with the furnace purged with nitrogen gas at a rate of 50 ml min^{-1}.

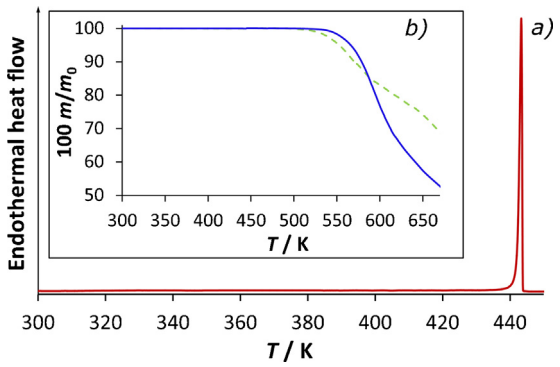

Fig. 2. (a) DSC thermogram of risperidone form I heated at a rate of 1 K min^{-1} (red solid line), and (b) TGA analysis of pure risperidone form I heated at a rate of 10 K min^{-1} under air (green dashed line) and nitrogen (blue solid line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

Heat capacity measurements were conducted using a TA Instruments MDSC 2920 operated in modulated mode using non-hermetic aluminium sample pans. A modulation period of 100 s and amplitude of 1 K were used, with an underlying constant heating rate of 3 K min^{-1}. Each powder sample (4–9 mg) was distributed evenly in the pan and covered with a lid without crimping, and the furnace was purged with nitrogen gas at a rate of 50 ml min^{-1}. The heat capacity of the solid was measured by heating the material once to just below its melting point. The heat capacity of the melt was obtained in dual scans of each sample, by heating the solid material past the melting point to 458 K, then cooling the melt to 428 K followed by heating the melt to 458 K (first scan), then cooling the melt to 423 K followed by heating the melt to 453 K (second scan), discarding scans where the melt recrystallized during cooling. Calibration of both calorimeters was carried out according to standard procedure against the melting properties of indium. Heat capacity calibration was made using sapphire and a linear calibration correction function based on three repeat scans from 273 to 473 K. Differences in mass between sample pan and reference pan were within ±0.10 mg.

Thermogravimetric analysis (TGA) was carried out using a TA Instruments SDT Q600, conducted under both air and nitrogen gas atmosphere, respectively, using a flow rate of 100 ml min^{-1}. Samples were prepared in open alumina pans and heated at a rate of 10 K min^{-1} from 298 to 773 K.

3. Results

3.1. Thermal analysis

A representative DSC thermogram of the melting of form I is shown in Fig. 2a. The average values over six DSC scans of the melting temperature (T_m) and the enthalpy of fusion at the melting temperature ($\Delta_{fus}H$) of form I are given in Table 2. The value of T_m determined in this work as the mean extrapolated onset temperature (442.4 K) is slightly less than the value reported by Silva et al. [6] (443.6 K), and slightly higher than those reported by Germann et al. [1] (441.8 K) and Shah et al. [7] (439.9 K), although it should be noted that these studies all used risperidone of unspecified or lower purity, higher heating rates (5–10 K min^{-1}), and give no estimate on the confidence of their data. The value of the melting enthalpy determined here (43.94 kJ mol^{-1}) is slightly lower than the value