Thermodynamic Stability Analysis of Tolbutamide Polymorphs and Solubility in Organic Solvents

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ABSTRACT: Melting temperatures and enthalpies of fusion have been determined by differential scanning calorimetry (DSC) for two polymorphs of the drug tolbutamide: FI^H and FV. Heat capacities have been determined by temperature-modulated DSC for four polymorphs: FI^L, FI^H, FII, FV, and for the supercooled melt. The enthalpy of fusion of FII at its melting point has been estimated from the enthalpy of transition of FII into FI^H through a thermodynamic cycle. Calorimetric data has been used to derive a quantitative polymorphic stability relationship between these four polymorphs, showing that FII is the stable polymorph below approx. 333 K, above which temperature FI^H is the stable form up to its melting point. The relative stability of FV is well below the other polymorphs. The previously reported kinetic reversibility of the transformation between FI^L and FI^H has been verified using *in situ* Raman spectroscopy. The solid-liquid solubility of FII has been gravimetrically determined in five pure organic solvents (methanol, 1-propanol, ethyl acetate, acetonitrile and toluene) over the temperature range 278 K – 323 K. The ideal solubility has been estimated from calorimetric data, and solution activity coefficients at saturation in the five solvents determined. All solutions show positive deviation from Raoult's law, and all van't Hoff plots of solubility data are non-linear. The solubility in toluene is well below that observed in the other investigated solvents. Solubility data has been correlated and extrapolated to the melting point using a semi-empirical regression model.

INTRODUCTION

The solid-liquid solubility of a crystalline, pharmaceutically active compound is a very important property, directly affecting its therapeutic effectiveness. Knowledge of the temperature dependence of the solubility of different solid forms of a drug is a prerequisite for the successful design of suitable dosage forms and optimization of the manufacturing process. The solubility is particularly important in crystallization processes, where it is a key to controlling the supersaturation, the particle size, shape and yield, as well as polymorphic form.

The prevalence among organic compounds of polymorphs, having the same elemental composition but different crystal structures, is well documented. There is a vast number of physicochemical properties that can differ between polymorphs,[1] most importantly solubility[2] and dissolution rate (and thence bioavailability of an API,) and physical and chemical stability. As a consequence of this, there are strict regulations for identification of possible polymorphs and careful process control.[3] Another aspect is the fact that the majority of drug candidates are abandoned at an early stage, frequently because of poor solubility.[4] Finally, an important role of polymorphs in the pharmaceutical industry is that they can form the basis for intellectual property rights.[5] A thorough investigation into the polymorphism of a drug substance, including an evaluation of the thermodynamic stability relationship of the different solid forms, is thus always called for.

Tolbutamide (*N*-[(Butylamino)carbonyl]-4-methylbenzenesulfonamide; 1-butyl-3-(4-methyl-phenylsulfonyl) urea; CAS number 64-77-7) is a first-generation sulfonylurea oral hypoglycemic drug compound, which has been used e.g. under the market name Orinase in the treatment of type II diabetes as a complement to a controlled diet. It acts through stimulating pancreatic insulin secretion.[6] The molecular structure of tolbutamide is provided as supporting information. Because of its significant conformational flexibility, tolbutamide has a high propensity for polymorphism. At least six polymorphs of tolbutamide are reported to exist.[7,8] At ambient conditions FII is reported to be the stable solid form, followed by FI^{L} and then the more metastable forms FIII and FIV.[7] FV is reported to be 1D-isostructural with FIV and to rapidly convert into FI^{L} at ambient conditions.[8] On heating the pure solid, at approx. 313 K FI^{L} is reported to transform reversibly into FI^{H}.[7] The structural similarity of FI^{L} and FI^{H}, and the reported kinetic reversibility of the interconversion, are the reasons for the peculiar naming of these two polymorphs. At higher temperatures FI^{H} is the stable polymorph with a high melting point of 401 K.[7] The thermodynamic transition temperature between FII and FI^{H} is verified to be below 390 K (the reported melting point of FII) and, based on a comparison of solubility data in ethanol, should be located near 353 K.[7]

In this work, we report the solubility of the low-temperature stable polymorph FII between 278 K and 313 K in 5 pure organic solvents: methanol, 1-propanol, ethyl acetate, acetonitrile and toluene. Based on a comprehensive thermodynamic analysis of calorimetric data, the Gibbs energy, enthalpy and entropy of fusion are calculated as functions of temperature for polymorphs FI^{L}, FI^{H}, FII and FV, allowing a more comprehensive and accurate establishment of the stability relationship than previously reported. By comparing solubility data with the activity of pure solid FII, activity coefficients at saturation have been calculated in the five

solvents at different temperatures. The activity coefficients and the solubility have been modelled using a thermodynamically robust semi-empirical regression model.

EXPERIMENTAL SECTION

Materials

Tolbutamide was obtained from Sigma-Aldrich at a specified mass fraction purity of 99.7% and confirmed to be FI^L by X-ray powder diffraction (XRPD). Methanol (99.9%), acetonitrile (99.9%), ethyl acetate (99.7%) and toluene (99.9%) were obtained from Sigma-Aldrich, and 1-propanol (99.5%) from VWR. All solvents were used as received with no further purification.

Preparation of FII

For preparation of FII, FI^L as received from the supplier was partly dissolved in toluene and the slurry agitated for 7 days at ambient temperature in a sealed bottle. The solvent was then evaporated in a fume hood and the phase identity of the dry powder verified to be pure FII using XRPD and Raman spectroscopy.

Spectroscopic characterization

Raman spectra were collected using a Kaiser Raman Rxn2 analyser equipped with a 785 nm excitation laser and a CCD-based detector. A non-contact optic probe was used to collect spectra with a minimum exposure time of 10 s and 5 accumulations over the spectral region of 1750-200 cm^{-1}. Raman spectra of FI^L, FI^H and FII are provided as supporting information.

Thermal analysis

Differential scanning calorimetry (DSC) analyses were carried out using a TA Instruments MDSC 2920. Powder samples (3–8 mg) were encapsulated in hermetically sealed aluminum pans, and the furnace was purged with nitrogen gas at a rate of 50 ml min^{-1}. The extrapolated onset temperature and associated enthalpy changes of phase transitions were determined using a constant heating rate of 5 K min^{-1}. A subset of samples were cooled and reheated once after melting. Heat capacity measurements were conducted using the same instrument operated in temperature-modulated mode. A modulation period of 100 s and an amplitude of 1 K were used, with an underlying constant heating rate of 5 K min^{-1}. The heat capacity of the solid was measured by heating the solid material until it melted. The heat capacity of the melt was obtained by cooling the resulting melt inside the pan to a temperature below the melting point without recrystallization occurring, followed by a heating scan of the supercooled melt. Calibration of the temperature and the calorimetric response of the instrument 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 function of the temperature. Differences in weight between sample and reference pans were limited to ±0.10 mg.

Solubility measurement

The solid-liquid solubility was measured using a gravimetric method. Saturated solutions with excess crystals were prepared in capped vials. The temperature was controlled using a Grant

S26 thermostatic bath equipped with a GR150 control unit (specified temperature stability of ±0.005 K) and a Grant C2G cooling unit. Agitation of solutions was provided by magnetic stir bars, rotated at a rate of 600 min^{-1} using a 2Mag 60-point submersible stirring plate. Before sampling, stirring was switched off to allow excess crystals to settle for approx. 3 h. Samples of approx. 5 mL of clear solution were collected from the bulk of each solution using pre-heated syringes, and filtered through 0.2 µm PTFE filters into glass vials (50 mm × 25 mm). The vials were immediately capped and weighed. The caps were removed and solutions were placed in a fume hood for two weeks in order to evaporate all solvent. The vials containing visibly dry solids were then further dried in an oven at 50 °C for 24 h. The mass of each vial were recorded by repeated weighing, verifying complete dryness. The solution concentration *C* was determined from the masses of the empty vials, the capped vials containing solution, the caps and the vials containing the dry solids, according to:

$$C = \frac{m_{\text{dry vial}} - m_{\text{empty vial}}}{m_{\text{full capped vial}} - m_{\text{cap}} - m_{\text{empty vial}}} \quad (1)$$

Samples were collected in triplicate from each solution at temperatures ranging from 278 K to 313 K in increments of 5 K. The solutions were kept under agitation for 24 h before sampling at each temperature. All syringes and filters were preheated to the solution temperature prior to sampling. The establishment of equilibrium after 24 h was verified within experimental limitations in all solvents at 5°C by comparison with concentrations re-measured after 48 h. In order to ensure that equilibrium was always attained by dissolution, pure solvents were pre-cooled to 278 K before solid tolbutamide was added. The specified error of the balance used is 0.0001 g. The identity of the polymorph present at equilibrium with each sampled solution was verified by XRPD, once during solution preparation and again at 313 K after completed sampling.

RESULTS AND DISCUSSION

Thermodynamic stability relationship of tolbutamide polymorphs

On heating FI^L powder in a DSC pan, it was observed to transform into FI^H at 311 K with an associated enthalpy change (endothermic) of 2.5 kJ mol^{-1}. Upon further heating, FI^H was observed to melt at 400 K with an enthalpy of fusion of 27.6 kJ mol^{-1}. On heating FII, an unexplained, very faint endotherm (0.1 kJ mol^{-1}) was observed at 311 K, and at 376 K FII invariably transformed into FI^H with an enthalpy change (endothermic) of 3.1 kJ mol^{-1}. On cooling the melt inside the pan it recrystallised at approx. 350 K, and on subsequent heating the resulting solid was observed to melt at 376 K with an associated enthalpy of fusion of 19.7 kJ mol^{-1}. This new solid was verified to be FV by IR spectroscopy, using a Perkin Elmer Spectrum One with an ATR cell, and by comparison with spectra of all the known polymorphs.[8] Typical DSC thermograms are shown in Figure 1, and numerical data for the observed phase transitions is reported as means of four runs in each case, with associated standard errors, in Table 1.

The heat capacities of FI^L, FI^H, FII, FV and the supercooled melt were successfully measured over different temperature ranges. Figure 2 shows averaged values of heat capacities together with 90% confidence bands. For FV only one scan was carried out. The curves have been

truncated at the points where they start to deviate from linear behavior close to the onset of phase transitions, and averaged data has been used to fit the coefficients of Eq. 2 (*T* in units of K):

$$C_p = k_1 T + k_2 \quad (2)$$

Resulting regression coefficients are given in Table 2 together with goodness of fit, and experimental heat capacity data is available as supporting information. The FII curve shown in Figure 2 has a small peak at 311 K, corresponding to the faint endotherm observed on heating FII, Figure 1. The origin of this peak has not been verified, but a likely source is traces of FI^L in the FII powder (not detected by XRPD or Raman spectroscopy) which transforms into FI^H. A comparison of the enthalpies of the respective peaks suggests that the FI^L content in the FII material should be below 5%. The selection of a linear regression equation, in the fitting of which data over the temperature range 304 K – 320 K was not used, should render the impact of this error negligible.

The calorimetric data appears to support the reported observation[7] with regard to the stability relationship of FI^L and FI^H. In the DSC pan, the transformation between FI^L and FI^H repeatedly and kinetically reversibly occurred at 311 K. This results in the complete inaccessibility of FI^H below this temperature and of FI^L above it. Indeed, for purposes of a thermodynamic analysis, the results suggest that these two phases could be treated as a single polymorph, with discontinuous heat capacity, enthalpy and entropy curves but with a continuous Gibbs energy curve.

For further verification of the reversibility of the transformation $FI^L \leftrightarrow FI^H$, the phenomenon was investigated using *in situ* Raman spectroscopy. FI^L crystal powder was placed in a flask together with a Raman probe and sealed with Parafilm. The flask was placed in a cryostatic bath (Grant GR150 with a C2G cooling unit). The bath temperature was then linearly raised and lowered according to a specific program, and Raman spectra recorded regularly (1/min). The Raman spectra (available as supporting information) of the two phases are very similar, but FI^L has increased intensity at some wavenumbers, notably at 1451, 1149 and 960 cm^{-1} while FI^H has increased intensity at 1300 and 1122 cm^{-1}. The first three of these peaks were designated as indicative of FI^L and the latter two as indicative of FI^H. The intensities at these respective wavenumbers were averaged and normalized for all spectra collected as the sample was heated and cooled. The peaks of the transformation events, taken as the points where the two averaged intensity values become equal, occur at bath temperatures of approx. 318 K (on heating) and 314 K (on cooling), respectively. The onset temperatures would show even less hysteresis, but are difficult to define. Notably, there is a systematic difference of several K compared to the transformation temperature observed using DSC (311 K), which we attribute to the experimental setup involving a flask with a probe partly submerged in a water bath. Figures showing the normalized intensity profiles and Raman spectra in the fingerprint region during the experiment are provided as supporting information.

The DSC data also verifies that FI^H is more stable than FII and FV at high temperatures. However, the consistently observed $FII \rightarrow FI^H$ transformation precluded observation of a

melting peak of FII. Thirunahari *et al*.[7] were able to observe the onset of melting prior to polymorphic transformation, and report the melting point to be 390 K. An estimate of the enthalpy of fusion of FII at this temperature was obtained from the enthalpy of the transition FII → FI^H, the enthalpy of fusion of FI^H at $T_{m,FIH}$ and integrated heat capacities (using Eq. 2 and coefficients in Table 2) according to the thermodynamic cycle 1-7 outlined in Figure 3.

The resulting enthalpy of fusion at $T_{m,FII}$ was obtained as:

$$\Delta^{fus}_{FII} H(T_{m,FII}) =$$

$$\Delta^{trans}_{FII \rightarrow FI^H} H(T_{trans}) + \Delta^{fus}_{FI^H} H(T_{m,FI^H}) + \int_{T_{trans}}^{T_{m,FII}} (C_{p,FI^H} - C_{p,FII}) dT + \int_{T_{m,FI^H}}^{T_{m,FII}} (C_{p,L} - C_{p,FI^H}) dT \quad (3)$$

Having access to melting data as well as experimentally determined heat capacities of a solid form and its supercooled melt allows the thermodynamics of fusion to be estimated as functions of temperature. Approximating the difference in heat capacity between the melt and the solid by a linear function:

$$\Delta C_p = q + r(T_m - T) \quad (4)$$

the equations for the Gibbs energy of fusion and its enthalpic and entropic component terms become:[9]

$$\Delta^{fus} G(T) = \Delta^{fus} H(T) - T\Delta^{fus} S(T) \quad (5)$$

$$\Delta^{fus} H(T) = \Delta^{fus} H(T_m) + q(T - T_m) - \frac{r}{2}(T - T_m)^2 \quad (6)$$

$$\Delta^{fus} S(T) = \frac{\Delta^{fus} H(T_m)}{T_m} + q \ln\left(\frac{T}{T_m}\right) + r\left[T_m \ln\left(\frac{T}{T_m}\right) - T + T_m\right] \quad (7)$$

In Figure 4, the resulting thermodynamic functions of fusion are shown for the four polymorphs FI^L, FI^H, FII and FV. For the purpose of constructing this figure, FI^L and FI^H are treated as one polymorph with discontinuous enthalpy and entropy curves and a thermodynamic transition temperature equal to the kinetic transition temperature of 311.1 K (as observed with DSC).

Qualitatively, the polymorphic stability relationship agrees with previously reported findings.[7] The Gibbs energy estimates of FI^H and FII become equal at a temperature of 333 K. This value is somewhat below the estimate of Thirunahari *et al*.[7] of 353 K, which is based on a simplified extrapolation of solubility data in methanol. However, it should be noted that there is also a significant uncertainty associated with our estimated value, mainly resulting from the closeness of the two Gibbs energy isobars, but also from the lack of calorimetric data on the fusion of FII. The diagram also shows that FV is significantly less stable than the other polymorphs, and that this fact is maintained throughout the entire investigated temperature range. Furthermore, it is worth mentioning that, as a result of the considerable difference in the heat capacity between

FI^L and FI^H shown in Figure 2, the enthalpy and entropy curves of these polymorphs exhibit significant differences. Due to enthalpy-entropy compensation, however, the resulting effect on the slope of the Gibbs energy curve of FI is almost undetectable.

Solubility of FII in pure organic solvents

The solubility of FII between 278 K and 313 K is reported in Table 3 as mass fraction on solvent basis. Each value is taken as the mean of three samples, and given together with its associated standard error. The solubility of other polymorphs could not be measured within this temperature range with the gravimetric method used, due to transformation into the stable FII. In Figure 5 a), the experimental solubility data is shown as g solute per kg of solvent. In Figure 5 b) the same data is shown in a van't Hoff plot, *i.e.* as $\ln x_{eq}$ *vs.* T^{-1}, where x_{eq} is the solubility mole fraction. Van't Hoff plots are often used to linearly extrapolate solubility values to higher temperatures, and even for predicting melting points. However, linearity in a van't Hoff plot is not to be expected,[10] and when it is occasionally observed it is the result of a cancelling out of the temperature dependences of the enthalpy of fusion of the pure solid and the solution activity coefficient.[11] The van't Hoff curves of the solubility of FII in all investigated solvents are visibly non-linear.

The solubility mole fraction, x_{eq}, has been modelled with two functions. The first is a simple empirical function of three parameters, where T is the temperature (in units of K), Eq. 8. This empirical model is a conveniently simple method for obtaining solubility data by interpolation within the experimental temperature range, where it gives a good fit.

$$\ln x_{eq} = \frac{c_1}{T^2} + \frac{c_2}{T} + c_3 \tag{8}$$

The second model is a recently-proposed semi-empirical solubility regression equation,[10] the principle of which is the separation of the temperature dependence of the activity of the pure solid from that of the activity coefficient of the saturated solution. The solubility then becomes:

$$\ln x_{eq} = \ln a_{eq} - \ln \gamma_{eq} = \ln a^s - \ln \gamma_{eq} \tag{9}$$

a_{eq} is the activity of the solute in a saturated solution, which becomes equal to the activity of the pure solid, a^s, provided that the same reference state is used. Choosing the pure, supercooled melt at the same temperature as the reference state, and modelling the heat capacity difference between the supercooled melt and the solid by Eq. 4, leads to:

$$\ln a^s = \frac{\Delta^{fus}H(T_m)}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) - \frac{q}{R}\left(\ln\frac{T_m}{T} - \frac{T_m}{T} + 1\right) - \frac{r}{R}\left(T_m \ln\frac{T_m}{T} - \frac{T_m^2}{2T} + \frac{T}{2}\right) \tag{10}$$

The activity coefficient in the saturated solution is expressed as:

$$\ln \gamma_{\mathrm{eq}} = \frac{c_4}{T}\left(1 - e^{-\left(\frac{c_5}{T} - \frac{c_5}{T_{\mathrm{m}}}\right)^{c6}}\right) \quad \{c_6 \geq 2\} \tag{11}$$

Eq. 11 obeys thermodynamic boundary conditions at the melting point.[10]. Consequently, the combination of Eq. 10 and Eq. 11 according to Eq. 9 results in an expression which obeys thermodynamic boundary conditions for the solubility mole fraction at the melting point. This makes it an appropriate model for correlating solubility data for purposes of extrapolation outside the experimental temperature range.[10] The regression coefficients of Eq. 8 and Eq. 11, obtained from a least-squares fit using the software OriginPro 8 (Origin Lab), are provided in Table 3.

In Figure 5 c), the activity coefficients obtained using experimental solubility data and the activity of the pure solid are shown together with the regression curves obtained using Eq. (11) and the coefficients in Table 3. In all solvents at all investigated temperatures, the activity coefficient at saturation is well above unity. This considerable positive deviation from Raoult's law indicates that none of the solvents is able to form sufficiently favorable interactions with the tolbutamide molecule. Tolbutamide is able to both donate and accept hydrogen bonds. Indeed, in the FII structure, each tolbutamide molecule participates in six hydrogen bonds with its neighbors, showing the importance of this kind of interaction. The departure from ideal behavior is by far the greatest in toluene, with the other four solvents resulting in approximately equal values of the activity coefficient at saturation. All the solvents are able, at least to some extent, to accept hydrogen bonds, although acetonitrile is a comparatively weak electron donor, as is the aromatic ring of toluene.[12] Neither toluene nor ethyl acetate are able to donate protons, however. Out of these two solvents, ethyl acetate shares a stronger chemical similarity with the tolbutamide molecule, having a polar group in the center surrounded by non-polar regions. Toluene is also unique in being the only essentially non-polar solvent evaluated. This, together with its poor ability to take part in hydrogen bonding with the solute molecules, is likely the explanation for the relatively high values of the activity coefficient observed in toluene.

CONCLUSIONS

The melting temperature and the associated enthalpy of fusion of tolbutamide FI^H have been determined to be 400.3 ± 0.14 K and 27.56 ± 0.092 kJ/mol, respectively. The enthalpy of transition from FI^L to FI^H at 311.1 K has been measured to be 2.52 ± 0.010 kJ/mol. The melting temperature and the associated enthalpy of fusion of FV have been determined to be 375.73 ± 0.051 K and 19.66 ± 0.088 kJ/mol, respectively. The heat capacities of FI^H, FI^H, FII and the supercooled melt are well described by linear functions of temperature. Through a thermodynamic cycle the enthalpy of fusion of FII at its reported melting point of 390 K has been calculated to be 28.3 kJ/mol. Through a comprehensive and quantitative analysis of experimental calorimetric data, the Gibbs energy, enthalpy and entropy of fusion are calculated for FI^L+FI^H, FII and FV up to the respective melting points. This data shows that the Gibbs energy of FII is the lowest of the evaluated polymorphs below approx. 333 K, above which

temperature FI^H is the stable polymorph until its melting point. The relative stability of FV is below that of the other forms throughout the investigated temperature range.

The solubility mole fraction of FII is significantly lower in toluene than in the evaluated aliphatic alcohols, ethyl acetate and acetonitrile. In all these solvents there is a positive deviation from Raoult's law, with activity coefficients at saturation ranging between 33 and 80 in toluene and between 3 and 10 in the other four solvents, over the evaluated temperature range. It is shown that the contribution from the difference in heat capacity between the solid and the melt to the enthalpy of fusion of all the polymorphs, and to the ideal solubility of FII, is non-negligible.

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SUPPORTING INFORMATION

This article contains supplementary material available from the authors upon request or via the Internet at http://onlinelibrary.wiley.com/.

REFERENCES

1. Brittain HG. 2009. Theory and principles of polymorphic systems. In *Polymorphism in pharmaceutical solids, 2nd ed*; Brittain HG, Ed. New York, NY: Informa.
2. Pudipeddi M, Serajuddin ATM. 2005. Trends in solubility of polymorphs. *J Pharm Sci* **94**(5):929-939.
3. Yu LX, Furness MS, Raw A, Outlaw KPW, Nashed NE, Ramos E, Miller SPF, Adams RC, Fang F, Patel RM, Holcombe FO, Chiu Y-y, Hussain AS. 2003. Scientific considerations of pharmaceutical solid polymorphism in abbreviated new drug applications. *Pharm Res* **20**(4):531-536.
4. Gardner CR, Walsh CT, Almarsson O. 2004. Drugs as materials: valuing physical form in drug discovery. *Nat Rev Drug Discov* **3**(11):926-934.
5. Vure P. 2011. Polymorph patents; how strong they are really? *Int J Intellectual Property Management* **4**(4):297-306.
6. Skillman TG, Feldman JM. 1981. The pharmacology of sulfonylureas. *Am J Med* **70**(2):361-372.
7. Thirunahari S, Aitipamula S, Chow PS, Tan RBH. 2010. Conformational polymorphism of tolbutamide: A structural, spectroscopic, and thermodynamic characterization of Burger's forms I–IV. *J Pharm Sci* **99**(7):2975-2990.
8. Nath NK, Nangia A. 2011. Novel form V of tolbutamide and a high Z' crystal structure of form III. *CrystEngComm* **13**(1):47-51.
9. Watterson S, Hudson S, Svärd M, Rasmuson ÅC. 2014. Thermodynamics of fenofibrate and solubility in pure organic solvents. *Fluid Phase Equilib* **367**:143-150.
10. Svärd M, Rasmuson ÅC. 2014. (Solid + liquid) solubility of organic compounds in organic solvents – correlation and extrapolation. *J Chem Thermodyn* **76**:124-133.
11. Kuhs M, Svärd M, Rasmuson ÅC. 2013. Thermodynamics of fenoxycarb in solution. *J Chem Thermodyn* **66**:50-58.
12. Brinkley RL, Gupta RB. 2001. Hydrogen bonding with aromatic rings. *AlChE J* **47**(4):948-953.