In the Context of Polymorphism: Accurate Measurement, and Validation of Solubility Data

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Supporting Information

ABSTRACT: Solubility measurements for polymorphic compounds are often accompanied by solvent-mediated phase transformations. In this study, solubility measurements from undersaturated solutions are employed to investigate the solubility of the two most stable polymorphs of flufenamic acid (FFA forms I and III), tolfenamic acid (TA forms I and II), and the only known form of niflumic acid (NA). The solubility was measured from 278.15 to 333.15 K in four alcohols of a homologous series (methanol, ethanol, 1-propanol, n-butanol) using the polythermal method. It was established that the solubility of these compounds increases with increasing temperature. The solubility curves of FFA forms I and III intersect at ~315.15 K (42 °C) in all four solvents, which represents the transition temperature of the enantiotropic pair. In the case of TA, the solubility of form II could not be reliably obtained in any of the solvents because of the fast solvent-mediated phase transformation. The solubility of the only known form of NA was also determined, and no other polymorphs of NA were observed. The experimental solubility data of FFA (forms I and III), TA (form I), and NA in these four solvents was correlated using the modified Apelblat and λh model equations. The correlated and experimentally determined solubility data obtained serves to (i) guide the accurate determination of the solubility for polymorphic compounds, (ii) assess the role of the solvent in mediating transformations, and (iii) provide a route to engineer advanced crystallization processes for these pharmaceutical compounds.

INTRODUCTION

Polymorphism, a phenomenon that enables molecules to exhibit multiple crystalline phases, is estimated to occur in up to 80% of molecules that display a pharmaceutical application, affecting primarily their solubility, which correlates with bioavailability in compounds that present poor aqueous solubility. Therefore, the inadvertent occurrence of polymorphism during a pharmaceutical manufacturing process might have adverse effects on drug product properties. One parameter needed to understand and control polymorphism is the solubility of a compound in a particular solvent or solvent mixture. However, solubility measurements for polymorphic compounds are often accompanied by solvent-mediated phase transformations.

Generally, solubility measuring techniques are grouped into isothermal2–7 and polythermal methods.8–20 The former measures the solubility at preset temperatures for unspecified concentrations by adding an excess of solid, forming a slurry or suspension. The concentration of the dissolved solute is determined after prolonged agitation (typically ≥24 h) and assumes solid–liquid equilibrium has been reached. Recently, three approaches have been reviewed for the determination of the solubility for polymorphic compounds under isothermal conditions.21 These approaches can be summarized as (1) solubility measurement from undersaturated solution, (2) solubility measurement from supersaturated solution, and (3) the “bracketing” method, which visually observes the dissolution of crystals of the metastable polymorph in increasing concentrations until the dissolution of the crystals does not occur. However, the equilibration time employed in isothermal methods might hamper the accurate determination of the solubility for metastable forms because of possible solvent-mediated phase transformations.21,22 The latter represents a major issue when reviewing existing solubility

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data as emphasized in a recent editorial published by the Journal of Chemical & Engineering Data.22 On the other hand, the polythermal method determines the temperatures at which solubility is attained for suspensions with known composition at specific heating rates. This method works under the assumption that the dissolution kinetics can be neglected and quasi-equilibrium has been reached.11−13,15−20 Consequently, the polythermal method might be better suited to determine the solubility of polymorphic compounds while circumventing solvent-mediated phase transformations.

This study provides guidelines to accurately measure and validate the solubility of polymorphic compounds from an undersaturated solution employing the polythermal method. We describe the method employing two of the most polymorphic pharmaceutical substances known, thus far, flufenamic acid (FFA) and tolfenamic acid (TA, Figure 1).23,24 FFA possesses nine polymorphs, eight of which have been structurally characterized.23 FFA forms I and III are enantiotropically related with a transition temperature at 315.15 K25 and readily accessible by conventional solvent-based methods.23 TA is a pentamorphic system, of which forms I and II are the two most thermodynamically stable forms at ambient conditions and also readily accessible by conventional solvent-based methods.24 These two polymorphs are monotropically related. A third compound, niflumic acid (NA, Figure 1), a pharmaceutical compound with no other polymorphs reported, is also employed. The selected alcohols (methanol, ethanol, 1-propanol, and n-butanol) are commonly used organic solvents and classified as class 2 (methanol) or 3 (less toxic and lower health risks) solvents by the Food & Drug Administration.26 Thus, the solubility data obtained serves to (i) guide the accurate determination of the solubility for polymorphic compounds, (ii) assess the role of the solvent in mediating transformations, and (iii) provide a route to engineer advanced crystallization processes for these pharmaceutical compounds.

■ EXPERIMENTAL SECTION

**Preparation of Metastable Polymorphs.** Commercial FFA form I and TA form I were recrystallized from methanol and ethanol to produce FFA form III25 and TA form II,25 respectively. The resulting solids were filtered, vacuum-dried at room temperature, and characterized by Raman microscopy and powder X-ray diffraction to determine the phase and purity of each recrystallized form.

**Solubility Measurements.** To determine the solubility of FFA (forms I and III), TA (forms I and II), and NA in methanol, ethanol, 1-propanol, and n-butanol the polythermal method was employed, in a multiple reactor system (Crystal16, Technobis Crystallization Systems) as described elsewhere.11 Briefly, solutions with known compositions were prepared in sealed 2 mL glass vials (Fisher, Scientific). To weigh the solute, a microbalance (Mettler Toledo, MS104S) with an accuracy of ±0.002 mg was employed. The solvent was weighed using an analytical balance (Mettler Toledo, MS104S) with an accuracy of ±0.1 mg. A rare earth magnetic stir bar at 700 rpm was used to agitate the suspensions, while heated at 0.3 K/min from 278.15 to 333.15 K.25 For FFA form I, a temperature range between 318.15 and 333.15 K was employed because this form is metastable below 315.15 K.25 Any measurement attempts below the transition temperature resulted in a solvent-mediated phase transformation from FFA form I to form III during the heating profile. The temperature was kept at ≥318.15 K to avoid the transformation. The saturation temperature can be measured at the maximum transmission (turbidity measurement) using the software CrystalClear (version 1.0.1.614),11−13,15−20 if the dissolution kinetics are assumed to be negligible. To ensure accuracy, the specific compositions (Supporting Information) were measured at least twice.6,14 The measured uncertainty for the saturated temperature is ±0.1 K.

The solubility of each compound (FFA, TA, and NA) was determined at 0.3 and 0.1 K/min using 1-propanol as solvent to validate the heating rate. In the case of FFA form III, an additional heating rate (0.05 K/min) was determined using 1-propanol as solvent.

The mole fraction solubility \( x_i \) of each solute was calculated according to eq 1

\[
x_i = \frac{m_i}{M_i} \sum \frac{m_i}{M_i}
\]

where \( m_i \) and \( M_i \) represents the mass (g) and molecular weight (g/mol) of the solute and solvent. Molecular weights of FFA, TA, and NA are 281.230, 261.707, and 282.218 g/mol, respectively.

**Raman Microscopy.** Raman spectra were collected at room temperature in a Thermo Scientific DXR2 Raman microscope equipped with 532 nm laser, with 400 lines/mm grating and 25 μm pinhole as described previously.11 The spectra were determined by averaging 15 scans over the range of 650−1600 cm\(^{-1}\) with an exposure time per scan of 3 s and analyzed using the OMNIC for Dispersive Raman software (version 9.2). Prior to the solubility measurements powder samples of FFA (forms I and III), TA (forms I and II), and NA were analyzed by Raman microscopy to confirm the solid-state and purity. After the experiments all samples were characterized by Raman microscopy (Supporting Information).

**In Situ Raman Spectroscopy.** In situ Raman spectra were recorded over the range of 200−1900 cm\(^{-1}\) employing a Raman Ren2 Multichannel Raman Analyzer (Kaiser Optical Systems) equipped with an immersion probe (6.35 mm) and a 785 nm laser. For each compound, the acquisition conditions were optimized so that spectra were captured in 1 min intervals with 10 accumulations and an exposure time of 3 s for FFA form III, TA form I, and TA form II, 1 s for FFA I, and 0.5 s for NA per measurement with automatic cosmic ray filter and intensity correction using iC Raman software (version 4.1.917). The probe was immersed from the top into a multiple reactor system (Crystal16, Technobis Crystallization Systems) using sealed 8 mL glass vials (Fisher Scientific) with a 2 mL starting volume of the suspension. The samples were agitated employing a rare earth magnetic stir bar at 700 rpm to enable parallel visual measurement capabilities using the onboard camera system. All preparative and experimental procedures were applied as described for the Crystal16 in the Solubility Measurement section.

**Powder X-ray Diffraction (PXRD).** PXRD analysis was performed on 300 K using a Rigaku XtaLAB SuperNova single microfocus Cu−Kα radiation (λ = 1.5417 Å, 50 kV, and 1 mA) source equipped with a HyPix3000 X-ray detector in transmission mode. All polycrystalline samples were analyzed over an angular 2θ range of 10−50° with a step size of 0.01° using a Gandolfi move for powder experiment with an exposure time of 90 s. Powder samples of FFA (forms I and III), TA (forms I and II), and NA were analyzed by PXRD and the initial form validated prior to the solubility measurements. After the experiments all samples were characterized by PXRD (Supporting Information).

**Differential Scanning Calorimetry (DSC).** Thermograms were recorded in a TA Instruments DSC Q2000 with a single-stage refrigeration system (RCS40) and calibrated using an indium standard (\( T_m = 428.75 \) K and \( \Delta H = 28.54 \) J/g). After confirming the phase and purity by PXRD, approximately 2 mg of the powder sample were weighed in hermetically sealed aluminum pans (\( T_{\text{meas}} \))
using a microbalance (Mettler Toledo, XP26) with an accuracy of ±0.002 mg. The samples were heated from 298.15 to 573.15 K under N₂ atmosphere (50 mL/min) at a rate of 10 K/min (temperature accuracy of 0.1 K) after equilibration for 10 min at 298.15 K. The DSC analysis was performed five times (n = 5) per compound to ensure accuracy of the onset melting temperature (T_{m, onset}) determined. The average value was used in the λh model equation (Supporting Information).

THERMODYNAMIC MODELS

Thermodynamic models and empirical correlations are useful approaches to extrapolate solubility data over a wider range of temperatures. Two of the most commonly employed empirical correlations are the modified Apelblat and the λh model equations as described elsewhere.10,11,16–19

Modified Apelblat Equation. The semiempirical modified Apelblat equation correlates the solute solubility in pure solvents at various temperatures (eq 2).

\[
\ln x_i = A + \frac{B}{T} + C \ln T
\]  

(eq 2)

Parameters employed in eq 2 are the mole fraction solubility of the solute \(x_i\), the absolute temperature \(T\) in Kelvin (K), and the model parameters \(A\), \(B\), and \(C\), which represent the variation of the activity coefficient (A, B) and the temperature effect on the enthalpy of fusion (C).10,16

\(\lambda h\) Equation. The \(\lambda h\) equation is another semiempirical model commonly used to correlate solubility and temperature (eq 3).

\[
\ln \left[ 1 + \frac{\lambda(1-x_i)}{x_i} \right] = \lambda h \left( \frac{1}{T} - \frac{1}{T_m} \right)
\]  

(eq 3)

Parameters employed in eq 3 are the mole fraction solubility of the solute \(x_i\), the melting and absolute temperatures of the compound \(T_m\) and \(T\) in Kelvin (K), and the model parameters \(\lambda\) and \(h\), which represent the nonideal solution properties and excess mixture enthalpy of solution (\(h\)), respectively. The average value of \(T_{m, onset}\) was employed to determine the correlated mole fraction solubility (\(x_i^{cal}\)) using this equation (Supporting Information).

A nonlinear curve-fitting problem was solved employing the Levenberg–Marquardt algorithm within the software Origin (OriginLab Corporation, version B95.0.193) and used to model the modified Apelblat and \(\lambda h\) equations. The relative deviation (RD) and the average relative deviation (ARD\%) were calculated using the eqs 4 and 5, respectively, and used to assess the goodness of fit for the experimental and correlated solubility.

\[
RD_i = \frac{x_i^{exp} - x_i^{cal}}{x_i^{exp}}
\]  

(eq 4)

\[
ARD\% = \frac{100}{N} \sum_{i=1}^{N} \left| \frac{x_i^{exp} - x_i^{cal}}{x_i^{exp}} \right|
\]  

(eq 5)

In eqs 4 and 5, \(x_i^{exp}\) and \(x_i^{cal}\) are the \(i\)th experimental and correlated mole fraction solubility, respectively, and \(N\) is the total number of experimental values.

RESULTS AND DISCUSSION

DSC Results. For each compound the average \(T_{m, onset}\) was experimentally determined (Supporting Information) and employed in the \(\lambda h\) model equation to compute their mole fraction solubility (\(x_i^{cal}\)). The \(T_{m, onset}\) obtained within this study is in close agreement with the average peak melting point data \(T_{m, peak}\) reported in the literature (Supporting Information).20,21

Available Solubility Data and its Limitations. The solubility of FFA in methanol, ethanol, 1-propanol, and n-butanol was recently reported in a limited temperature range between 298.15 and 318.15 K using the isothermal method with an equilibration time >72 h.20 However, FFA forms I and III are enantiotropically related with a transition temperature of ∼315.15 K,23 meaning that FFA form I is not stable for most temperatures investigated.25 Additionally, no solid-state characterization was presented to evidence the polymorphic purity of the recovered material. Therefore, it is unclear whether the solubility reported is representative of FFA form I or III.23 An earlier study by Domańska et al.30 employed the polythermal method (heating rate of ∼0.1 K/min) with visual observation of the dissolution of the crystals to determine the saturation temperature for the mole fraction solubility of FFA form I and NA in various solvents, including ethanol.30 However, it is known that visual observation of the solubility is less accurate compared to techniques based on analytical principles including, attenuated total reflection-Fourier transform infrared spectroscopy, focused beam reflectance mode measurement, UV–vis spectroscopy, or turbidity.13,31–33 Moreover, most of the experimentally derived solid–liquid equilibrium temperatures for FFA form I reported by Domańska et al.30 occurred below the transition temperature, where FFA form I is metastable and thus, will undergo solvent-mediated phase transformation. In addition, no solid-state characterization was performed to evidence the phase purity.

Bustamante et al.34 reported a mole fraction solubility of \(x = 0.0163\) for NA in neat ethanol at 298 K using the isothermal method while a lower value \((x = 0.0109)\) was reported by Domańska et al.30 (extracted at 298 K with a third-order polynomial fit) employing the polythermal method (∼0.1 K/min). Besides the different solubility methods employed, the fact that no solid-state characterization was provided in either study, might hint at a possibility that the solubility for two different solid forms was reported.

The “thermodynamic solubility” of TA form I \((x = 0.0051)\) and the “apparent solubility” for TA form II \((x = 0.0056)\) were determined using the isothermal method at 310.15 K in ethanol.23 After an equilibration time of 72 h, the residual solid was identified by PXRD.35 These results yielded TA form I regardless of the initial polymorph.35 Collectively, these studies demonstrate an interest for the accurate determination of the solubility of these compounds. Moreover, they highlight a need to use more precise tools and methodologies to determine and validate the solubility of a compound, particularly when it might be prone to undergo solvent-mediated phase transformations.

Recommendations for Accurate Solubility Measurements of Polymorphic Compounds. From these studies, we have learned that the isothermal method might not be suitable to determine the solubility of compounds that undergo solvent-mediated phase transformations (polymorphs, solvates, hydrates, etc.) because of the extended time applied to reach solid–liquid equilibria, especially when not supported by solid-state characterization. In this regard, the polythermal method might be more practical. Before employing the polythermal method, the heating rate must be validated to ensure the
solubility is being measured at quasi-solid–liquid equilibrium conditions for the particular compound. Preferably, an automated system over visual examination of the saturation temperature should be employed. It is also important to determine the thermodynamic relationship of the polymorphic pair, particularly if these have a transition temperature within the temperature range of interest. For the latter, the temperature range needs to be carefully considered if the initial polymorph is metastable below or above a specific temperature. If the thermodynamic relationship is unknown several heating/cooling cycles should be observed. This practice might hint at possible solvent-mediated phase transformations as well as possible recrystallization of different forms. In the case that recrystallization of a different form occurs between heating/cooling cycles, each cycle needs to be examined to determine the solid form and validate the solubility. Solid-state characterization is essential to confirm phase purity of the starting polymorph and to monitor solvent-mediated phase transformations. These tools serve to validate that the solubility being determined corresponds to the initial and intended form. In situ monitoring of the dissolution and recrystallization processes during each cycle can support these efforts to ensure accuracy of the experimentally determined solubility, particularly when dealing with metastable forms. In the following paragraphs, we describe a method to accurately determine and validate solubility data, following the recommendations stated above.

**Solubility Data.** Prior to the solubility experiments, the applied heating rate (0.3 K/min) was validated by comparing the data obtained with slower heating rates at 0.1 K/min and also 0.05 K/min for FFA form III (Figure 2).

![Figure 2. Experimental and correlated solubility data of FFA form III in 1-propanol at different heating rates.](image)

The analysis of these results for all compounds showed that the average relative deviation of the saturation temperature for each concentration data point negligibly deviates around the null value (Supporting Information). This supports the assumption that quasi-equilibrium conditions have been reached when employing either of the heating rates, which is consistent with the literature reported for other systems. Thus, a heating rate of 0.3 K/min was used in the solubility measurements since it offers both accuracy and speed for all the solute–solvent systems under study. Typically, the solubility measurements for each compound over the temperature range from 278.15 to 333.15 K lasted about 6 h per heating/cooling cycle.

Once the heating rate was validated, it was possible to determine the experimental mole fraction solubility for the selected compounds. For FFA form III it appears that the solvent-mediated phase transformation kinetics above the transition temperature (where FFA form I is thermodynamically stable) is slower than the first cycle employed at heating rates between 0.05 and 0.3 K/min. The solubility data above the transition temperature present good correlation with the calculated solubility curves at the various heating rates (Figure 2). The lack of deviation in the solubility curve supports that no solvent-mediated phase transformation occurred. This observation was confirmed employing in situ Raman spectroscopy analysis, which allows the extrapolation of the solubility model equations. The optimized parameters were obtained using Origin, which allows the extrapolation of the solubility data for FFA forms I and III into their metastable region, using Origin, which allows the extrapolation of the solubility model equations. The optimized parameters were obtained using Origin, which allows the extrapolation of the solubility data for FFA forms I and III into their metastable region, respectively. Figure 4 shows the solubility of these two FFA polymorphs increases with increasing temperature and chain length in these four alcohols. The solubility curves for FFA forms I and III in all four solvents intersect close to the transition temperature (~315.15 K) reported for this enantiotropic pair (Supporting Information). Figures presenting the solubility data correlated with the λh model equation can be found in the Supporting Information.

This study also attempted to establish the solubility of TA forms I and II in the four alcohols selected. This polymorphic pair is monotropically related with a small free energy difference of ΔG_{1−II} < 0.04 kcal/mol. Unfortunately, the solvent-mediated phase transformation kinetics of TA form II to form I occurred fast (before the solubility determination in the first heating cycle) in all solvents over the temperature range from 278.15 to 333.15 K. This hindered the accurate determination of the metastable form. Specifically, in situ Raman spectroscopy analysis of the...
solubility data generated during multiple cycles without monitoring the dissolution process could have had adverse consequences on the accuracy and reliability of the reported solubility data. This reinforces the importance of validating the solubility data with in situ and offline solid-state characterization techniques, particularly, in systems presenting a very narrow free energy window and fast transformation kinetics, as demonstrated here in the case of TA forms I and II.24

Consequently, the first cycle was employed to determine the solubility for TA form I. The solubility of TA form I previously reported by Mattei et al.35 ($x = 0.0051$) compares very well to the value determined by the polythermal method within this study ($x = 0.0052$). Figure 5 shows that the solubility of TA form I increase with increasing temperature following the order $n$-butanol >1-propanol > ethanol > methanol. Each data point shown in Figure 5 was validated by offline Raman and PXRD measurements (Supporting Information). Figures presenting the solubility data correlated with the $\lambda h$ model equation can be found in the Supporting Information.

NA is a monomorphic system. The solubility of this compound was determined in the selected alcohols between 278.15 and 333.15 K. Dománska et al.30 reported the mole fraction solubility for NA in ethanol at $\sim$298.15 K as $x = 0.0111$ using the polythermal method. This value is comparable to the value determined within this study ($x = 0.0135$) considering the limitations of the visual method employed by Dománska et al.30. Although, our solubility data differs from that reported by Bustamante et al.34 ($x = 0.0163$) at 298 K in pure ethanol (isothermal method), the solubility data presented in this work is not heating rate dependent. The heating rate validation experiments show that quasi-equilibrium conditions are reached (Supporting Information). Moreover, the solubility determinations made by Bustamante et al.34 leave room for uncertainty in terms of phase identification and accuracy considering the lack of characterization and statistical treatment of the solubility data (only coefficient of variation is reported). Figure 6 shows that the mole fraction solubility of NA increases with increasing temperature following the order ethanol $> n$-butanol $>1$-propanol $> \text{methanol below 300 K}$ and $n$-butanol $>1$-propanol $> \text{ethanol} > \text{methanol above 300 K}$. Figures presenting correlated solubility data with the $\lambda h$ model equation are in the Supporting Information. Regardless of the solvent employed, no difference was observed after each cycle (Supporting Information), meaning that no solvent-mediated phase transformation occurred and that this form most likely represents the most thermodynamically stable polymorph for NA within the temperature range studied. This observation was corroborated during the offline characterization, as well as in situ Raman experiments (Supporting Information). Thus, no other polymorphs of NA could be accessed through solvent-based crystallization methods employing these four alcohols.

The correlation parameters for both model equations and the ARD% for the solubility of all compounds in the four pure solvents are listed in Table 1. Collectively, the correlated solubility obtained using the modified Apelblat and the $\lambda h$ model equations agree well with the experimental data, as shown by the low values of ARD% ($\leq 1.1680$) for all compounds and solvents. These model equations permit the straightforward calculation of the solubility for these compounds in methanol, ethanol, 1-propanol, and $n$-butanol. Moreover, these models help to extrapolate the solubility over a broader temperature range, as shown in the case of FFA

Figure 3. Solubility experiments of FFA form I in 1-propanol employing in situ Raman spectroscopy in a Crystalline system (A) micrographs recorded during the temperature profile (318.15–333.15 K at 0.3 K/min). (B) in situ Raman spectra, and (C) cut out of specific Raman shift: (a) prior to 1st heating cycle, (b) close to solubility point in 1st heating cycle, (c) nucleation in 1st cooling cycle, (d) close to solubility point in 2nd heating cycle, (e) nucleation in 2nd cooling cycle, (f) close to solubility point in 3rd heating cycle, and (g) nucleation in 3rd cooling cycle.

Concentration and statistical treatment of the solubility data (only coefficient of variation is reported).
where solubility data for FFA form I was extrapolated below its transition point. It can also be used to determine the transition temperature of an enantiotropic pair if the transition occurs within the measured temperature interval. This was shown here in the case of FFA forms I and III, which transition temperature compares very well to that previously reported in the literature.25

■ CONCLUSIONS

The polythermal method facilitated by a multiple reactor system (Crystal16) was successfully employed to accurately measure the solubility of two of the most polymorphic pharmaceutical compounds known, FFA and TA, in four alcohols of a homologous series with increasing chain length (methanol, ethanol, 1-propanol, n-butanol) between 278.15 and 333.15 K. The combination of in situ and offline Raman spectroscopy and PXRD, as powerful solid-state characterization methods, allowed the validation of the experimentally determined solubility data. Unlike FFA and TA, which present a high degree of polymorphism, no other polymorphs were observed during the determination of the solubility for NA. The results confirm that this form is the most thermodynamically stable polymorph under the conditions investigated. Finally, this study provides guidelines to accurately measure and validate solubility data for polymorphic compounds.
particularly when they are prone to undergo solvent-mediated phase transformations, for which the polythermal method is recommended over the isothermal method.

**ASSOCIATED CONTENT**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.9b00529.

**Materials specifications, DSC thermographs, powder X-ray diffractograms, in situ and offline Raman spectra, and solubility curves of the compounds in methanol, ethanol, 1-propanol, and n-butanol correlated using the \( \lambda h \) model equation (PDF)**

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**Table 1. Optimized Values for Parameters in the Apelblat and \( \lambda h \) Model Equations and ARD\% Used for Correlation of the Mole Fraction Solubility of FFA Forms I and III, TA Form I, and NA in Methanol, Ethanol, 1-Propanol, and n-Butanol**

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Notes

The authors declare no competing financial interest.

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**NOMENCLATURE**

A, B, C empirical parameters for Apelblat equation  
ARD\% average relative deviation  
DSC differential scanning calorimeter  
FFA flufenamic acid  
\( h \) model parameter for \( \lambda h \) equation  
\( m \) mass (g)  
\( M \) molecular mass (g·mol\(^{-1}\))  
NA niflumic acid  
PXRD powder X-ray diffraction  
RD\% relative deviation  
\( T \) absolute temperature (K)  
\( T_m \) melting temperature of the solute (K)  
TA tolfenamic acid  
\( x_1 \) mole fraction solubility of the solute (mol)

Greek Symbols

\( \lambda \) parameter for the \( \lambda h \) equation denoting nonideal properties of the system

**REFERENCES**

Crystal Growth & Design


