

# Solubility Measurements and Correlation of Modafinil in Neat Solvents and Binary Solvent Mixtures

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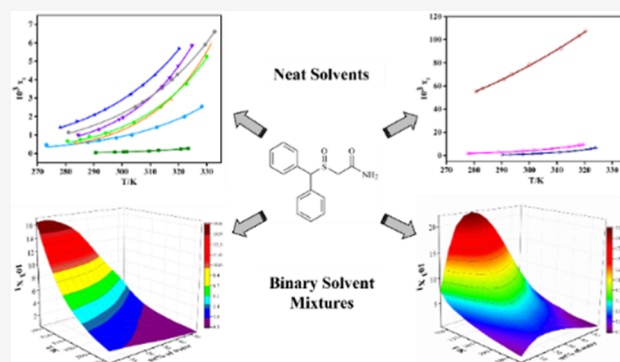
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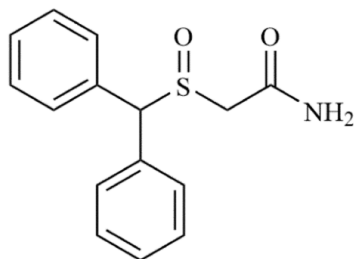
**ABSTRACT:** The solubility of modafinil (MOD) form I, an antinarcotic drug, was measured at temperatures ranging from 278.15 to 333.15 K in ten neat solvents (acetone, acetonitrile, dimethylformamide, ethanol, ethyl acetate, methanol, methylethylketone, 1-propanol, 2-propanol, and water) and two binary solvent mixtures (acetone + water and methanol + water). The results employing the polythermal method demonstrate that the solubility increases with increasing temperature in the neat solvents and at constant composition in the binary solvent mixtures. Moreover, the MOD solubility decreases with an increasing mass fraction of water (antisolvent) in the binary solvent mixture methanol + water. In the binary solvent mixture acetone + water, the solubility exceeds its solubility in neat acetone and water, reaching a maximum at a water mass fraction of ~20 wt %. Based on the calculated average relative deviation (ARD %), the experimental solubility data agree with the correlated data using the modified Apelblat and  $\lambda h$  equations. Additionally, powder X-ray diffraction confirms that the recrystallized solid in the neat and binary solvent mixtures was the commercial MOD form I, except for 2-propanol. Thus, the presented solubility data provide a pathway to engineer crystallization processes for MOD toward integrated manufacturing from flow synthesis to crystallization.



## INTRODUCTION

Modafinil (MOD) or diphenylmethylsulfinylacetamide, CAS number: 68693-11-8, is an antinarcotic active pharmaceutical ingredient (API) prescribed to treat, e.g., narcolepsy, obstructive sleep apnea, or shift work disorder.<sup>1–6</sup> It is sold in its racemic form under the trade names Provigil, Alertec, or Modavigil. Owing to its cognitive enhancing properties,<sup>7</sup> MOD is made available to astronauts onboard the International Space Station.<sup>8</sup>

MOD (Figure 1) was first synthesized in 1976.<sup>9</sup> Numerous alternative synthetic routes have been reported in the following



**Figure 1.** Molecular structure of MOD (drawn using ChemBioDraw, Ultra 12.0).

years aimed at increasing yield,<sup>10</sup> limiting the formation of impurities,<sup>11</sup> decreasing the number of synthetic steps,<sup>1,12</sup> or developing a greener synthesis method.<sup>13</sup>

To address the need for developing more sustainable synthetic procedures with a lower environmental footprint, a 3-step flow synthesis of MOD was recently reported.<sup>13</sup> This flow synthesis represents the first step toward the development of an integrated end-to-end continuous manufacturing process for MOD.<sup>14–17</sup> To take advantage of these process intensification developments, MOD needs to be purified by continuous crystallization.<sup>15,18,19</sup> MOD can crystallize in seven known polymorphic forms (I–VII), two hydrates (monohydrate, dihydrate), and two solvates (acetonitrile, chloroform),<sup>20–22</sup> but only form I is the solid form needed in the solid dosage formulation.<sup>2,5,11</sup> To advance the development of a continuous crystallization process for MOD, its solubility in neat and solvent mixtures needs to be understood. Solubility is

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Table 1. Supplier and Mass Fraction Purity of Materials with the Corresponding Analysis Method

chemical name	CAS registry number	supplier	purity (%) <sup>a</sup>	purification method	analysis method	solvent classification <sup>32</sup>
MOD	68693-11-8	Yick-Vic Chem. & Pharma. (HK) LTD	99.5	none	HPLC <sup>b</sup>	
acetone	67-64-1	Millipore Sigma	99.9	none	LC-MS <sup>c</sup>	class 3
acetonitrile	75-05-8	Millipore Sigma	99.9	none	LC-MS <sup>c</sup>	class 2
DMF	68-12-2	Millipore Sigma	99.8	none	GC <sup>d</sup>	class 2
ethanol	64-17-5	Millipore Sigma	99.5	none	GC <sup>d</sup>	class 3
ethyl acetate	141-78-6	Fisher Scientific	99.5	none	HPLC <sup>b</sup>	class 3
methanol	67-56-1	VWR	99.8	none	GC <sup>d</sup>	class 2
MEK	78-93-3	Millipore Sigma	99.0	none	GC <sup>d</sup>	class 3
1-propanol	71-23-8	Alfa Aesar	99.5	none	GC <sup>d</sup>	class 3
2-propanol	67-63-0	Millipore Sigma	99.5	none	GC <sup>d</sup>	class 3

<sup>a</sup>Provided by the supplier in mass fraction. <sup>b</sup>High-performance liquid chromatography. <sup>c</sup>Liquid chromatography–mass spectrometry. <sup>d</sup>Gas chromatography.

a fundamental parameter needed to engineer the crystallization process (e.g., cooling, antisolvent) for this or other compounds.<sup>18,19</sup>

Upon reviewing the available literature, the solubility data for MOD are very limited.<sup>23,24</sup> For instance, it has been reported that MOD form I (white crystalline powder) is practically insoluble in aqueous solutions and moderately soluble in alcohol, ester, and ketone solvents without providing quantifiable values.<sup>24</sup> Thimmasetty et al.<sup>23</sup> reported the solubility of MOD in water and water-cosolvent mixtures with ethanol, glycerin, and liquid polyethylene glycol at two temperatures, 298.15 and 310.15 K. To our knowledge, there is no account of reported temperature-dependent solubility of MOD in any of the neat solvents and solvent mixtures used in the present study.<sup>25</sup> Specifically, the MOD solubility was determined in ten neat solvents [acetone, acetonitrile, dimethylformamide (DMF), ethanol, ethyl acetate, methanol, methylethylketone (MEK), 1-propanol, 2-propanol, and water] in the temperature range from 278.15 to 333.15 K using the polythermal method.<sup>26–30</sup> These solvents have been reported to lead to the commercial form I of MOD upon crystallization, except ethanol and 2-propanol, which should result in form II.<sup>11,31</sup> The temperature range represents the expected crystallization process application. In addition, the present study also determined the MOD solubility in two binary solvent mixtures (acetone + water and methanol + water), with water acting as the antisolvent. Referring to the Food and Drug Administration solvent classification system,<sup>32</sup> the majority of solvents studied are categorized as class 3 solvents (less toxic and lower risk to human health), with the exception of acetonitrile, DMF, and methanol, which are class 2 solvents. However, acetonitrile, DMF, and methanol are commonly used as (anti)solvents in pharmaceutical crystallization processes.<sup>33,34</sup> The experimental solubility data were correlated using the modified Apelblat and  $\lambda h$  equations,<sup>35–37</sup> allowing to extrapolate and interpolate MOD solubility within and beyond the selected temperature ranges. Ultimately, the MOD solubility data presented in this study provide guidance on the choice of solvent or solvent mixture for the development of crystallization processes for this API.

## EXPERIMENTAL SECTION

**Materials.** Table 1 summarizes the CAS number, supplier, purity (provided by the chemical supplier), and analytical method for the API (solute) and solvents (including the solvent classification<sup>32</sup>) used in this study. Ultrahigh purified water (18.23 M $\Omega$ /cm, pH = 5.98, and mV = 57.3) from a

water purification system (Aries Filter, Gemini) was utilized for aqueous solutions. All materials were used “as-received” without further purification.

**Solubility Measurements.** To measure the solubility of a solute in a solvent or solvent mixture, isothermal<sup>23,36–38</sup> and polythermal<sup>26,28,29,39–44</sup> methods are commonly employed. The main difference is that the isothermal method determines the unknown concentration of a solute in a solvent at known constant temperatures, while the polythermal method uses the known concentration to determine the temperature at which solubility is achieved by applying a constant heating rate.<sup>26,28,30,39,42</sup>

In this study, the polythermal method was used, employing the automated multiple reactor system Crystal16 from Technobis Crystallization Systems as described elsewhere.<sup>26,28,29,39</sup> Briefly, suspensions composed of MOD and a neat solvent or a solvent mixture were prepared in 2 mL sealed glass vials (Fisher Scientific) at predetermined concentrations. An analytical balance (MS104S,  $\pm 0.1$  mg) and a microbalance (XPE26,  $\pm 0.002$  mg), both from Mettler Toledo, were used to weigh the solvent and solute, respectively. Rare earth magnetic stir bars at 700 rpm were used to agitate the resulting suspension while heating at 0.3 K/min from 278.15 to 333.15 K. The temperature range for acetone needed to be adjusted to 278.15–323.15 K because of the low boiling point of acetone (329.15 K).<sup>45</sup> Assuming that the kinetics of the solute dissolution can be neglected,<sup>40,41</sup> the transmission of light through the suspensions can be utilized to determine the clear point using the CrystalClear software (version 1.0.1.614).<sup>15,26,28,29,39,40</sup> The clear point is defined as the temperature at which the solution is free of crystals and thus saturated. The measured uncertainty of the saturation temperature is within  $\pm 0.1$  K. To validate the heating rate and prove the reliability of the polythermal method within this work, the solubility of MOD was determined at 0.05, 0.1, and 0.3 K/min using methanol as solvent.<sup>26,28,29,39</sup> Details of the experimental procedure for the isothermal method conducted for additional validation of the polythermal method are provided in the [Supporting Information](#).

The mole fraction solubility ( $x_i$ ) was calculated employing eq 1

$$x_i = \frac{m_i/M_i}{\sum_{i=1}^n m_i/M_i} \quad (1)$$

In eq 1,  $m_i$  represents the mass (g) and  $M_i$  the molecular weight (g/mol) of component  $i$ , which refers to MOD (MW = 273.35 g/mol),<sup>4,10,13</sup> neat solvents, or binary solvent mixtures.

**Powder X-ray Diffraction.** A Rigaku XtaLAB SuperNova single microfocus Cu K $\alpha$  radiation ( $\lambda = 1.5417 \text{ \AA}$ , 50 kV, 1 mA) source equipped with a HyPix3000 X-ray detector in transmission mode was used to collect powder diffractograms of samples at 298.15 K. Powders were affixed in MiTeGen microloops with a small amount of paratone oil. All microcrystalline samples were collected over an angular  $2\theta$  range of  $6\text{--}50^\circ$  with a step size of  $0.01^\circ$  employing the fast phi mode with an exposure time of 300 s. Before and after concluding the solubility experiments, MOD (“as-received”) and the recovered solid were analyzed by powder X-ray diffraction (PXRD) to validate the initial form and confirm the solid state of the yielded material<sup>34,46</sup> (Figures S6–S12 in the Supporting Information).

**Differential Scanning Calorimetry.** A differential scanning calorimetry (DSC) (Q2000, TA Instruments Inc.) instrument equipped with an RCS40 single-stage refrigeration system was used to record DSC thermograms. The DSC was calibrated using an indium standard (melting temperature,  $T_m = 429.75 \text{ K}$  and enthalpy of fusion,  $\Delta H_{\text{fus}} = 7.8 \text{ kJ/mol}$ ). MOD samples of  $\sim 3.500 \text{ mg}$  were weighed in hermetically sealed Tzero aluminum pans using a microbalance (XPE26, Mettler Toledo  $\pm 0.002 \text{ mg}$ ). After equilibration of the samples for 5 min at 298.15 K, they were heated at 5 K/min to 523.15 K (temperature accuracy of 0.1 K) under a N<sub>2</sub> atmosphere (50 mL/min). The resulting thermograms were analyzed using the linear peak integration function of the TA Universal Analysis 2000 software (version 4.5A) to determine the onset melting temperature ( $T_{m,\text{onset}}$ ) and  $\Delta H_{\text{fus}}$ . The DSC measurements were performed five times ( $n = 5$ ) to ensure accuracy. The average value of  $T_{m,\text{onset}}$  was used in this work. A representative DSC thermogram and summarized DSC data are shown in Figure S1 and Table S1 in the Supporting Information, respectively.

**Thermogravimetric Analysis.** Thermogravimetric analysis (TGA) (Q500, TA Instruments Inc.) was employed to record the TGA thermogram of MOD to evaluate the degradation (weight loss) of MOD before and during melting. The TGA analyzer was calibrated with a calcium oxalate monohydrate (CaC<sub>2</sub>O<sub>4</sub>·H<sub>2</sub>O) standard. MOD samples of  $\sim 5 \text{ mg}$  were equilibrated at 303.15 K for 5 min and heated at 5 K/min to 523.15 K (temperature accuracy of 0.1 K) under a N<sub>2</sub> atmosphere (60 mL/min). The data were analyzed with TA Universal Analysis 2000 Software (version 4.5). The TGA thermogram is shown in Figure S1 in the Supporting Information.

## ■ THERMODYNAMIC MODELS

Thermodynamic models allow the interpolation and extrapolation of solubility data within and beyond the temperatures studied, which facilitates the broader understanding of the solubility behavior of a solute.<sup>29,30,47,48</sup> The modified Apelblat and  $\lambda h$  equations are two of the most commonly used empirical correlations to interpret the solubility behavior of solutes.<sup>26,28,29,39,47</sup> In this study, the solute refers to MOD.

**Modified Apelblat Equation.** The modified Apelblat eq 2 is a semiempirical model that allows to correlate solubility data as a function of temperature.<sup>26,28,29,39,47,49–51</sup>

$$\ln x_1 = A + \frac{B}{T} + C \ln T \quad (2)$$

In eq 2,  $x_1$  represents the mole fraction solubility of the solute (in this study MOD),  $T$  is the absolute temperature in

K, and  $A$ ,  $B$ , and  $C$  are empirical model parameters. The parameters  $A$  and  $B$  represent the variation in the solution activity coefficient, while  $C$  represents the effect of temperature on the enthalpy of fusion.<sup>50,52</sup>

**$\lambda h$  Equation.** Proposed by Buchowski et al.,<sup>53</sup> the  $\lambda h$  model (eq 3) correlates the solubility of solutes with temperature.<sup>26,28,29,39,47,49</sup>

$$\ln \left[ 1 + \lambda \frac{1 - x_1}{x_1} \right] = \lambda h \left( \frac{1}{T} - \frac{1}{T_m} \right) \quad (3)$$

In eq 3,  $x_1$  represents the mole fraction solubility of the solute (in this study MOD),  $T$  and  $T_m$  are the absolute temperature of the system and melting temperature of the solute in K, while  $\lambda$  and  $h$  are model parameters that depict the nonideal properties of the solution and the excess mixture enthalpy of solution, respectively. The average value of  $T_{m,\text{onset}}$  (Table S1 in the Supporting Information) was used to calculate  $x_1$  in eq 3.

To correlate the modified Apelblat and  $\lambda h$  equations, the nonlinear curve fitting was solved using the Levenberg–Marquardt algorithm within the software Origin (OriginLab Corporation, version 10.00.154). To estimate the difference between the experimental and calculated solubility data, the relative deviation (RD) and the percent average relative deviation (ARD %) were determined by employing eqs 4 and 5, respectively.

$$\text{RD}_i = \frac{x_{1,i}^{\text{exp}} - x_{1,i}^{\text{cal}}}{x_{1,i}^{\text{exp}}} \quad (4)$$

$$\text{ARD \%} = \frac{100}{N} \sum_{i=1}^N \left| \frac{x_{1,i}^{\text{exp}} - x_{1,i}^{\text{cal}}}{x_{1,i}^{\text{exp}}} \right| \quad (5)$$

In eqs 4 and 5,  $x_{1,i}^{\text{exp}}$  and  $x_{1,i}^{\text{cal}}$  are the  $i$ th experimental and calculated mole fraction solubility, respectively, and  $N$  represents the total number of experiments.

## ■ RESULTS AND DISCUSSION

**DSC and TGA Results.** In this work, the DSC analysis of MOD was performed in quintuplicate. The average value for  $T_{m,\text{onset}}$  of the first endothermic peak is  $437.54 \pm 0.18 \text{ K}$  (Table S1 in the Supporting Information). The obtained  $T_{m,\text{onset}}$  is within the range of the reported literature values for MOD form I ( $437.15\text{--}439.15 \text{ K}$ ).<sup>20,22</sup> The endothermic event is followed by an exothermic event, indicating chemical decomposition after melting (Figure S1 in the Supporting Information). This is supported by TGA analysis, revealing no weight loss of MOD until 437.74 K, indicating that MOD did not decompose before and during melting (Figure S1 in the Supporting Information). Thus, the obtained  $T_{m,\text{onset}}$  in this work is not impacted by degradation and can be reliably used to calculate  $x_1$  in the  $\lambda h$  eq (eq 3).

**Validation of Heating Rate.** Before conducting the solubility experiments, the applied heating rate of 0.3 K/min was validated by comparing the results of MOD in methanol measured with slower heating rates (0.05 and 0.1 K/min).<sup>26,28,29,39</sup> Due to the limited solubility data documented for MOD at only two temperatures, 298.15 and 310.15 K,<sup>23,24</sup> it was decided to employ 0.05 K/min as the reference to calculate the RD of the experimentally measured saturated temperatures obtained at 0.1 and 0.3 K/min.<sup>26,39</sup> The three

**Table 2. Experimental and Correlated Mole Fraction Solubility of MOD  $x_1$  in Neat Solvents at Different Temperatures  $T$  and at Pressure  $p = 101.3$  kPa<sup>a</sup>**

$T/K$	$10^3 x_1^{\text{exp}}$	Apelblat		$\lambda h$		$T/K$	$10^3 x_1^{\text{exp}}$	Apelblat		$\lambda h$	
		$10^3 x_1^{\text{cal}}$	$10^2$ RD	$10^3 x_1^{\text{cal}}$	$10^2$ RD			$10^3 x_1^{\text{cal}}$	$10^2$ RD		
Acetone						Acetonitrile					
278.2	1.412	1.435	-1.742	1.345	4.448	286.3	0.684	0.690	4.761	0.765	7.209
284.0	1.749	1.720	1.702	1.674	4.336	293.1	0.981	0.954	2.803	0.942	3.956
290.4	2.099	2.110	-0.489	2.109	-0.433	297.9	1.318	1.298	1.474	1.306	0.918
294.1	2.389	2.379	0.462	2.401	-0.468	301.4	1.632	1.622	0.589	1.645	-0.827
303.2	3.210	3.209	0.024	3.267	-1.806	304.4	1.950	1.960	-0.531	1.997	-2.427
307.5	3.713	3.704	0.156	3.761	-1.404	311.1	2.917	2.979	-2.098	3.039	-4.18
311.8	4.256	4.280	-0.476	4.318	-1.383	322.0	5.779	5.802	-0.402	5.800	-0.350
320.2	5.702	5.693	0.131	5.615	1.484	326.4	7.291	7.292	0.543	7.293	1.288
DMF						Ethanol					
280.7	55.229	55.236	-0.021	55.591	-0.657	280.6	0.668	0.663	0.669	0.550	22.873
283.3	57.873	57.949	-0.137	58.183	-0.526	285.2	0.755	0.786	-4.081	0.698	8.842
290.8	65.615	66.285	-1.023	66.180	-0.861	288.4	0.917	0.887	3.358	0.820	3.462
293.6	70.227	69.597	0.897	69.385	1.194	294.2	1.106	1.112	-0.503	1.090	1.712
300.1	78.417	77.717	0.894	77.341	1.377	304.2	1.672	1.676	-0.210	1.738	-4.206
311.5	92.589	93.471	-0.952	93.179	-0.642	313.7	2.535	2.521	0.544	2.641	-4.007
318.0	103.210	103.355	-0.139	103.452	-0.234	322.8	3.770	3.785	-0.376	3.865	-1.170
320.4	107.630	107.170	0.421	107.501	0.120	330.0	5.270	5.265	0.090	5.162	1.418
Ethyl Acetate						Methanol					
273.2	0.460	0.440	4.295	0.319	30.699	277.9	1.894	1.918	-0.937	1.646	13.386
288.0	0.602	0.630	-4.959	0.590	1.663	289.0	2.803	2.814	-0.494	2.727	2.598
291.9	0.709	0.704	0.895	0.688	3.167	297.5	3.936	3.860	1.035	3.921	-0.543
298.0	0.844	0.847	-0.865	0.868	-3.249	301.8	4.586	4.558	0.911	4.679	-1.711
303.5	1.000	1.014	-1.362	1.063	-6.228	308.4	5.900	5.928	-0.482	6.084	-3.123
312.3	1.414	1.379	2.203	1.453	-3.003	314.0	7.437	7.458	-0.787	7.547	-1.993
322.2	2.000	2.003	-0.172	2.035	-1.720	318.2	8.908	8.891	0.100	8.835	0.726
328.3	2.549	2.554	-0.160	2.488	2.444	319.7	9.455	9.474	0.278	9.339	1.691
MEK						1-Propanol					
281.0	1.140	1.187	-4.086	1.031	9.552	284.5	1.000	0.935	6.981	0.888	11.718
304.7	2.533	2.563	-1.171	2.559	-1.008	291.9	1.308	1.323	-1.163	1.299	0.697
307.3	2.777	2.795	-0.637	2.807	-1.061	299.0	1.839	1.838	0.062	1.840	-0.057
314.1	3.537	3.512	0.699	3.556	-0.529	300.4	1.951	1.959	-0.454	1.967	-0.835
317.8	4.014	3.981	0.822	4.032	-0.452	314.3	3.616	3.673	-1.587	3.707	-2.531
319.6	4.287	4.231	1.293	4.283	0.097	316.9	4.106	4.124	-0.447	4.151	-1.114
329.4	5.904	5.913	-0.151	5.906	-0.047	319.9	4.754	4.710	0.923	4.721	0.690
332.8	6.612	6.644	-0.492	6.586	0.387	324.8	5.849	5.841	0.140	5.798	0.865
2-Propanol <sup>b</sup>						Water					
283.2	0.603	0.702	-17.044	0.484	19.382	290.7	0.054	0.055	-1.527	0.054	0.881
287.9	0.860	0.818	9.158	0.639	28.987	297.5	0.081	0.078	3.876	0.078	4.489
295.8	1.056	1.091	0.784	1.001	8.987	300.5	0.088	0.091	-2.793	0.091	-2.672
299.8	1.294	1.282	1.394	1.246	4.183	301.7	0.103	0.097	5.801	0.097	5.753
308.5	1.925	1.876	1.283	1.970	-3.490	309.5	0.130	0.142	-9.661	0.143	-10.340
317.6	2.911	2.908	-0.272	3.091	-6.594	312.9	0.177	0.168	4.759	0.169	4.182
323.5	3.885	3.940	-1.040	4.094	-4.973	320.8	0.242	0.246	-1.587	0.246	-1.630
331.5	6.065	6.082	0.293	5.909	3.128	323.4	0.281	0.278	0.980	0.277	1.261

<sup>a</sup>Standard uncertainties  $u$  are  $u(T) = 2$  K. Relative standard uncertainties  $u_r$  are  $u_r(p) = 0.1$  and  $u_r(x_1) = 0.02$ .  $x_1^{\text{exp}}$  refers to the experimental mole fraction solubility.  $x_1^{\text{cal}}$  refers to the calculated solubility data using the modified Apelblat and  $\lambda h$  equations. RD represents the corresponding relative deviation. <sup>b</sup>Recovered crystalline material shows concomitant polymorphs<sup>54</sup> (detailed in the section Results and Discussion).

resulting solubility curves revealed that the averaged RD (to maintain the positive or negative impact compared to ARD %) <sup>26,39</sup> negligibly deviated from the null value (Figure S2 and Tables S2 and S3 in the Supporting Information). Thus, it can be assumed that quasi-equilibrium conditions were reached at 0.3 K/min.<sup>26,39</sup> These results are coherent with documented studies for other solutes proving the reliability of  $x_1$  measured with the polythermal method within this work.<sup>26,28,30,39</sup> To further validate the polythermal method, the MOD solubility

was determined at the saturated temperatures measured with the polythermal approach by employing the isothermal method. The low values for RD and ARD % (0.772) between the measured concentrations using the isothermal method compared to the concentrations employed in the polythermal method prove the reliability of the experimental approach employed in this work (Figure S2 and Tables S2 and S3 in the Supporting Information).

**Table 3.** Experimental and Correlated Mole Fraction Solubility of MOD  $x_1$  in Binary Solvent Mixture of Acetone (2) + Water (3) at Different Temperatures  $T$  and at Pressure  $p = 101.3$  kPa<sup>a</sup>

$T/K$	$10^3 x_1^{\text{exp}}$	Apelblat		$\lambda h$		$T/K$	$10^3 x_1^{\text{exp}}$	Apelblat		$\lambda h$	
		$10^3 x_1^{\text{cal}}$	$10^2$ RD	$10^3 x_1^{\text{cal}}$	$10^2$ RD			$10^3 x_1^{\text{cal}}$	$10^2$ RD	$10^3 x_1^{\text{cal}}$	$10^2$ RD
$w_3 = 0.12$											
273.2	3.617	3.495	2.902	3.147	12.509	279.0	3.578	3.597	0.096	3.426	4.847
281.0	4.438	4.526	-2.822	4.325	1.699	283.4	4.312	4.297	0.078	4.181	2.753
286.9	5.389	5.517	-2.163	5.442	-0.782	287.8	5.155	5.127	-0.532	5.073	0.523
292.0	6.554	6.556	0.666	6.594	0.093	292.6	6.339	6.210	1.417	6.225	1.181
297.3	7.978	7.854	1.830	8.001	-0.009	298.3	7.731	7.783	-1.077	7.875	-2.262
303.2	9.599	9.615	-0.156	9.856	-2.663	302.6	9.215	9.217	-0.186	9.353	-1.658
314.8	14.278	14.353	-0.368	14.578	-1.944	312.7	13.745	13.653	0.342	13.778	-0.568
324.9	20.438	20.385	0.074	20.150	1.222	321.2	18.931	18.915	-0.078	18.783	0.618
$w_3 = 0.36$											
280.3	2.859	2.907	-0.258	2.704	6.85	279.3	1.550	1.441	7.001	1.356	12.511
284.4	3.364	3.422	-0.622	3.287	3.359	284.9	1.962	1.912	2.437	1.852	5.527
288.6	4.055	4.052	1.187	3.993	2.638	290.7	2.398	2.551	-6.307	2.525	-5.215
292.6	4.763	4.766	0.709	4.782	0.381	292.6	3.051	2.801	8.147	2.788	8.591
298.5	5.999	6.071	-1.190	6.187	-3.122	297.9	3.790	3.628	4.279	3.651	3.663
302.3	7.105	7.105	-0.078	7.268	-2.370	305.6	4.866	5.249	-7.776	5.317	-9.179
311.1	10.290	10.265	0.343	10.409	-1.061	312.3	7.172	7.196	-0.370	7.269	-1.387
318.8	14.191	14.210	-0.073	14.050	1.058	321.8	11.249	11.159	0.809	11.095	1.378
$w_3 = 0.57$											
278.2	0.858	0.887	1.506	0.693	22.991						
285.5	1.075	1.172	-6.742	1.047	4.820						
291.0	1.389	1.468	-4.896	1.410	-0.691						
293.9	1.772	1.661	7.851	1.642	8.736						
301.0	2.269	2.277	1.027	2.357	-2.499						
306.3	2.902	2.913	-0.436	3.055	-5.341						
316.3	4.698	4.742	-0.898	4.876	-3.748						
323.6	6.858	6.882	0.267	6.748	2.208						

<sup>a</sup>Standard uncertainties  $u$  are  $u(T) = 2$  K. Relative standard uncertainties  $u_r$  are  $u_r(p) = 0.1$ ,  $u_r(x_1) = 0.02$ , and  $u_r(w_3) = 0.0001$ .  $x_1^{\text{exp}}$  refers to the experimental mole fraction solubility.  $x_1^{\text{cal}}$  refers to the calculated solubility data using the modified Apelblat and  $\lambda h$  equations. RD represents the corresponding relative deviation.  $w_3$  is the mass fraction of water (3) in the binary acetone (2) + water (3) mixture.

**Solubility Data.** After validating the heating rate, the mole fraction solubility of MOD in neat solvents and binary solvent mixtures (acetone + water and methanol + water) was determined by employing a heating rate of 0.3 K/min. The experimentally measured mole fraction solubility ( $x_i$ ) data of MOD (1) with corresponding temperatures and the RD between  $x_{1,i}^{\text{exp}}$  and  $x_{1,i}^{\text{cal}}$  are summarized in Tables 2–4. Specifically,  $x_1$  values in the ten neat solvents (acetone, acetonitrile, DMF, ethanol, ethyl acetate, methanol, MEK, 1-propanol, 2-propanol, and water) are shown in Table 2. The data for the binary solvent mixtures [acetone (2) + water (3) and methanol (2) + water (3)] are given in Tables 3 and 4, respectively.

To our knowledge, among all neat solvents employed in this study, the solubility of MOD was only determined in water at 298.15 and 310.15 K using the isothermal method.<sup>23</sup> Thimmasetty et al.<sup>23</sup> measured the MOD concentration in water offline using a UV–vis spectrophotometer by diluting its saturated solution obtained at the two temperatures. Unfortunately, the solubility of MOD was only reported in the unit mg/mL,<sup>23</sup> which is an unusual unit to report solubility data, which is typically reported in mole fraction solubility.<sup>26,28–30,39</sup> No further information regarding the weight of the solute and solvent was provided that would permit extracting the mole fraction solubility from the literature values.<sup>23</sup> Therefore, it was decided to compare the MOD solubility in water documented in the literature at 298.15 and

310.15 K with the solubility determined in this study in the unit mg/mL using the polythermal method (Table S4 in the Supporting Information). The solubility of MOD in water in mg/mL for 298.15 and 310.15 K was interpolated from the experimental data determined in this study by utilizing a mathematical expression with the best possible fit. The MOD concentrations reported in the literature at 298.15 and 310.15 K are 0.014 and 0.050 mg/mL, respectively,<sup>23</sup> which are underestimated compared to the values 1.199 and 2.115 mg/mL obtained in this work. To further evaluate this discrepancy, the MOD solubility in water was determined using the isothermal method at 298.15 and 310.15 K, resulting in average values of  $1.186 \pm 0.01$  and  $2.217 \pm 0.02$  mg/mL, respectively. Interestingly, these solubility data agree well with the values of 1.199 and 2.115 mg/mL determined by employing the polythermal method. Thus, the results demonstrate the reliability of the polythermal method and the data provided in this work. It also supports the statement that the literature data reported by Thimmasetty et al.<sup>23</sup> are likely underestimated (Table S4 in the Supporting Information).

All experimentally measured solubility data within this study were correlated by employing the modified Apelblat and  $\lambda h$  equations. The correlation parameters along with the ARD % for both model equations in neat and binary solvent mixtures are summarized in Table 5. The low ARD % values of  $\leq 1.0275$  for the modified Apelblat equation demonstrate a good

**Table 4. Experimental and Correlated Mole Fraction Solubility of MOD  $x_1$  in Binary Solvent Mixture of Methanol (2) + Water (3) at Different Temperatures  $T$  and at Pressure  $p = 101.3$  kPa<sup>a</sup>**

$T/K$	$10^3 x_1^{\text{exp}}$	Apelblat		$\lambda h$		$T/K$	$10^3 x_1^{\text{exp}}$	Apelblat		$\lambda h$	
		$10^3 x_1^{\text{cal}}$	$10^2$ RD	$10^3 x_1^{\text{cal}}$	$10^2$ RD			$10^3 x_1^{\text{cal}}$	$10^2$ RD	$10^3 x_1^{\text{cal}}$	$10^2$ RD
$w_3 = 0.12$											
281.5	1.755	1.754	2.557	1.440	19.985	276.2	1.014	1.018	-1.844	0.714	28.643
286.3	2.039	2.101	-5.033	1.861	6.962	281.7	1.299	1.265	2.720	0.999	23.168
290.9	2.526	2.514	-0.555	2.360	5.591	287.2	1.600	1.587	0.818	1.380	13.726
295.3	3.086	3.002	3.161	2.943	5.057	292.9	2.036	2.028	-1.406	1.906	4.693
305.2	4.468	4.558	-1.285	4.730	-5.118	303.0	3.206	3.203	-0.091	3.280	-2.494
313.7	6.736	6.640	0.895	6.952	-3.762	312.8	5.136	5.109	-0.171	5.377	-5.428
322.5	9.882	9.949	-0.489	10.158	-2.614	322.3	8.197	8.183	0.200	8.451	-3.058
329.4	13.811	13.784	0.115	13.510	2.099	330.9	12.706	12.705	-0.044	12.468	1.827
$w_3 = 0.34$											
281.3	0.819	0.799	0.069	0.638	20.276	277.9	0.413	0.414	-0.943	0.249	39.174
286.5	1.007	1.011	-1.082	0.880	12.025	285.0	0.547	0.560	-1.790	0.410	25.420
291.2	1.255	1.258	3.266	1.165	10.375	290.1	0.688	0.705	-2.226	0.578	16.270
295.5	1.536	1.543	-2.878	1.495	0.328	294.2	0.889	0.856	3.825	0.754	15.235
303.6	2.341	2.295	0.213	2.347	-2.045	306.1	1.542	1.554	-0.938	1.573	-2.112
312.4	3.588	3.585	0.411	3.734	-3.727	315.2	2.551	2.529	0.808	2.659	-4.260
320.3	5.437	5.411	-0.208	5.550	-2.778	324.5	4.238	4.258	-0.413	4.416	-4.155
328.1	8.216	8.197	0.030	8.067	1.621	333.1	7.018	7.015	0.069	6.896	1.766
$w_3 = 0.54$											
290.3	0.429	0.430	0.100	0.360	16.198						
295.9	0.543	0.562	-4.058	0.515	4.694						
298.1	0.661	0.626	5.081	0.590	10.625						
303.0	0.799	0.803	-0.383	0.794	0.778						
309.8	1.135	1.148	-0.728	1.181	-3.552						
316.7	1.659	1.674	-0.827	1.737	-4.616						
323.1	2.419	2.401	0.802	2.450	-1.241						
329.3	3.429	3.436	-0.174	3.380	1.468						

<sup>a</sup>Standard uncertainties  $u$  are  $u(T) = 2$  K. Relative standard uncertainties  $u_r$  are  $u_r(p) = 0.1$ ,  $u_r(x_1) = 0.02$ , and  $u_r(w_3) = 0.0001$ .  $x_1^{\text{exp}}$  refers to the experimental mole fraction solubility.  $x_1^{\text{cal}}$  refers to the calculated solubility data using the modified Apelblat and  $\lambda h$  equations. RD represents the corresponding relative deviation.  $w_3$  is the mass fraction of water (3) in the binary methanol (2) + water (3) mixture.

correlation between the experimental and correlated solubility data of MOD in all neat and binary solvent mixtures. On the other hand, the  $\lambda h$  model reveals larger ARD % values, especially for 2-propanol ( $\leq 6.2011$ ) and the binary solvent mixture methanol + water at  $w_3 = 0.24$  ( $\leq 7.6345$ ) and  $w_3 = 0.45$  ( $\leq 10.9174$ ), indicating the superior solubility correlation of the modified Apelblat equation compared to the  $\lambda h$  model. This assessment is in line with the reported solubility studies for other solutes.<sup>28,29,39,47,51</sup>

The experimental and correlated mole fraction solubility values of MOD using the modified Apelblat equation are shown in Figures 2 and 3 for neat and binary solvent mixtures, respectively. The results using the  $\lambda h$  equation are shown in Figures S3b, S4b, and S5 in the Supporting Information. In all figures, the mole fraction solubility of MOD increases with increasing temperature in neat solvents and at constant solvent composition in the binary solvent mixtures.

Moreover, the mole fraction solubility of MOD in neat solvents (Figure 2) decreases in the following orders: DMF > methanol > acetone > MEK > 1-propanol > ethanol > acetonitrile > 2-propanol > ethyl acetate > water up to 312 K. From 312 to 320 K, DMF > methanol > acetone > 1-propanol > MEK > acetonitrile > ethanol > 2-propanol > ethyl acetate > water. Above 320 K, DMF > methanol > acetone > acetonitrile > 1-propanol > MEK > 2-propanol > ethanol > ethyl acetate > water. The latter presents a relatively low solubility of MOD at  $\leq 1$  mg/mL below 290.65 K (Figure 2). Therefore, water was

further studied as a potential antisolvent in the determination of the solubility of MOD in binary solvent mixtures with methanol and acetone (Figure 3). Both methanol and acetone have been chosen because they (i) are reported to lead to MOD form I,<sup>11,31</sup> (ii) are employed in crystallization processes,<sup>33,34</sup> (iii) possess low boiling points ( $< 373.15$  K),<sup>45</sup> and (iv) possess favorable solubility characteristics of  $\geq 25$  mg/mL in the temperature range measured.<sup>55</sup> Acetonitrile would also meet these criteria but was excluded because it has also been reported to form an undesired solvate with MOD.<sup>20</sup> Surface plots showing the experimental and correlated mole fraction solubility employing the  $\lambda h$  equation can be found in Figure S5 in the Supporting Information.

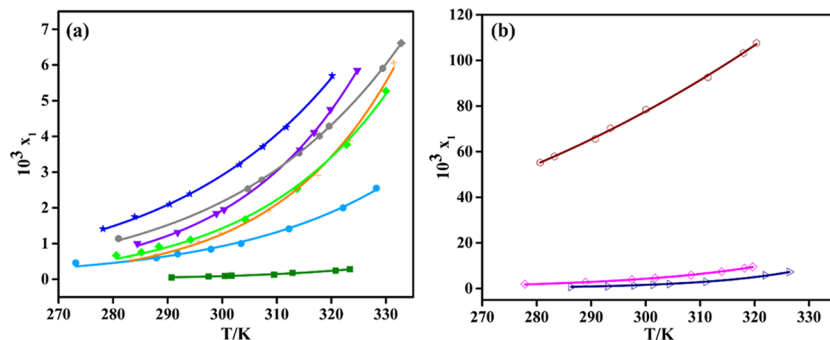
Figure 3a depicts that  $x_1$  in the binary methanol (2) + water (3) mixture increases with increasing temperature but decreases with increasing weight fraction of water, indicating the suitability of water as an antisolvent in this solvent mixture. On the other hand, the binary acetone (2) + water (3) mixture depicts a different effect of the solvent composition on  $x_1$  (Figure 3b). Specifically, the solubility of MOD exceeds its solubility in either of the two neat solvents, indicating a partial cosolvent effect of water in this binary solvent mixture reaching a maximum at a mass fraction ( $w_3$ ) of  $\sim 20$  wt %. Similar observations have been reported in the literature for other solutes.<sup>39,56,57</sup>

**PXRD Analysis.** Since MOD has seven known polymorphic forms (I–VII), two solvates (acetonitrile, chloroform), and

**Table 5. Optimized Values for the Correlation Parameters in the Modified Apelblat and  $\lambda h$  Equations Used for the Correlation of the Mole Fraction Solubility of MOD (1) in All Neat and Binary Solvent Mixtures along with the Respective ARD %**

solvent	model						
	Apelblat			ARD % <sup>a</sup>	$\lambda h$		
	A	B	C		$\lambda$	H	ARD % <sup>a</sup>
acetone	-171.8318	4900.6862	26.2370	0.0292	0.0578	49933.0124	0.5967
acetonitrile	-152.2246	1651.5829	24.5813	0.8924	0.7487	7942.7787	0.6984
DMF	-11.1258	-894.1520	2.0251	0.0074	0.1843	6024.4609	0.0287
ethanol	-293.9270	9705.9966	44.7088	0.0635	0.1072	38494.9352	3.6154
ethyl acetate	-342.8101	12550.0794	51.5392	0.0156	0.0264	121934.8920	2.9717
methanol	-282.0413	9408.2139	42.9928	0.0469	0.1900	19054.2098	1.3790
MEK	-166.8508	4664.7088	25.4532	0.4657	0.0595	53735.3926	0.8673
1-propanol	-123.7879	1748.7657	19.5848	0.5570	0.1637	25927.3703	1.1793
2-propanol	-502.5799	19013.6494	75.8360	0.6805	0.1962	24574.2545	6.2011
water	-97.3582	53.9610	15.4016	0.0189	0.0118	397420.4700	0.2405
			Acetone (2) + Water (3) <sup>b</sup>				
$w_3 = 0.12$	-152.8236	4001.0418	23.6219	0.0053	0.2169	14227.5624	1.2655
$w_3 = 0.23$	-116.0763	1967.3923	18.3618	0.0074	0.3434	10340.8392	0.6792
$w_3 = 0.36$	-202.3318	5661.2810	31.2811	0.0029	0.3402	11090.9230	0.9668
$w_3 = 0.47$	-176.9064	4068.5038	27.7964	1.0275	0.4123	10707.3339	1.9861
$w_3 = 0.57$	-377.5679	13152.6463	57.4351	0.2903	0.2426	18444.2345	3.4929
			Methanol (2) + Water (3) <sup>c</sup>				
$w_3 = 0.12$	-310.5977	10421.0301	47.3808	0.0791	0.3281	13060.7627	3.5251
$w_3 = 0.24$	-328.7805	10942.7156	50.2167	0.0230	0.4057	11707.7652	7.6345
$w_3 = 0.34$	-317.6819	10175.1923	48.6540	0.0223	0.3539	14061.2381	4.5094
$w_3 = 0.45$	-403.2043	13901.1795	61.3787	0.2010	0.3634	15260.7084	10.9174
$w_3 = 0.54$	-404.0057	13885.8117	61.4403	0.0235	0.2015	27078.7657	3.0442

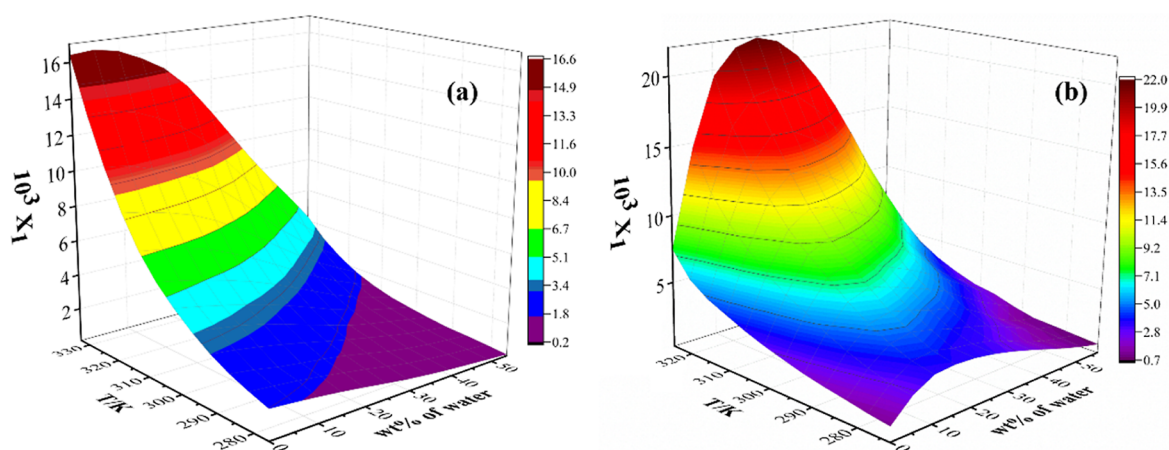
<sup>a</sup>ARD % represents the corresponding percentage ARD. <sup>b</sup> $w_3$  is the mass fraction of water (3) in the binary acetone (2) + water (3) mixture. <sup>c</sup> $w_3$  is the mass fraction of water (3) in the binary methanol (2) + water (3) mixture.



**Figure 2.** Experimental and correlated mole fraction solubility of MOD (1) in neat solvents, (a) class 3 and universal class solvents and (b) class 2 solvents. From top to bottom in (a), blue closed star, acetone; gray closed hexagonal, MEK; purple closed triangle, 1-propanol; light green closed tetragonal, ethanol; orange plus sign, 2-propanol; light blue closed circle, ethyl acetate; and green closed square, water and in (b), brown open hexagon, DMF; pink open tetragon, methanol; and navy open triangle, acetonitrile. The solid lines were calculated by using the modified Apelblat equation.  $x_1$  represents the mole fraction solubility of MOD, and  $T$  is the temperature in K.

two hydrates (monohydrate, dihydrate),<sup>20–22</sup> the commercial MOD (“as-received”) was characterized by PXRD before solubility measurements.<sup>26</sup> The solid form was confirmed as that of the known form I of MOD.<sup>11,58</sup> Additionally, all solids recovered from the resulting suspensions after completing the solubility experiments (polythermal and isothermal) in neat and binary solvent mixtures were filtered and characterized by PXRD (Figures S6 and S11 in the Supporting Information). The PXRD analysis confirmed that all recrystallized material resulted in the known commercial form I of MOD, except for 2-propanol. These results confirm the reported data, with the exception of ethanol and 2-propanol.<sup>11,31</sup> Ethanol should lead to form II upon crystallization,<sup>31</sup> but the recrystallized material (in triplicate) in this study was identified as form I (Figure S6

in the Supporting Information). The use of 2-propanol should also result in MOD form II. However, the authors are unable to validate form II because no crystallographic information file has been documented for form II in the Cambridge Structural Database.<sup>20,21,56–58</sup> Only the simulated PXRD diffractograms for form I, III, and IV could be retrieved.<sup>20,21,58,59</sup> The crystal structures of MOD forms V, VI, and VII are not reported in the Cambridge Structural Database.<sup>60</sup> Interestingly, the experimental PXRD diffractogram for MOD form II extracted from the literature<sup>31</sup> matches the characteristic peaks of the simulated form III (Figure S7 in the Supporting Information).<sup>20,21,59</sup> MOD form II was first discovered by Lafon in 1978<sup>9,61,62</sup> but is recognized as a highly metastable polymorph.<sup>61</sup> On this account, the authors are only able to



**Figure 3.** Surface plots of the mole fraction solubility of MOD ( $x_1$ ) in binary solvent systems (a) methanol (2) + water (3) and (b) acetone (2) + water (3) correlated with the modified Apelblat equation.  $T$  represents the temperature in K.

conclude that the PXRD diffractogram of the crystalline material recovered from 2-propanol reveals the presence of concomitant polymorphs (mainly forms I and III)<sup>54</sup> shown in Figures S6 and S7 in the Supporting Information.<sup>20,21,58,59</sup> Moreover, the simulated diffractograms of form IV, hydrates (monohydrate, dihydrate), and solvates (acetonitrile, chloroform) significantly differ from the experimental PXRD diffractogram of the crystalline material obtained from 2-propanol in this study (Figure S12 in the Supporting Information).<sup>60</sup>

## CONCLUSIONS

The solubility of MOD in ten neat solvents and two binary solvent mixtures was experimentally determined between 278.15 and 333.15 K by utilizing the polythermal method. The modified Apelblat and  $\lambda h$  equations were employed to correlate the experimental data and provide a general quantification and understanding of the solubility of MOD. The low ARD % values obtained for the modified Apelblat equation ( $\leq 1.0275$ ) prove that the experimental data agree well with the solubility data calculated using this model compared to the  $\lambda h$  equation, revealing larger values of  $\leq 10.9174$ . Here, the modified Apelblat equation is superior compared to the  $\lambda h$  equation. Moreover, this study demonstrates that the commercial form I of MOD can be recrystallized from neat solvents and binary solvent mixtures thereof, except for 2-propanol. Consequently, the solubility data presented in this study provide pathways for the development of advanced pharmaceutical crystallization processes for MOD.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.jced.3c00738>.

Detailed experimental procedure for the solubility curves of MOD in neat solvents and binary solvent mixtures, calculated scatter and surface plots of MOD using the  $\lambda h$  equation, DSC and TGA thermographs with detailed analysis, and powder X-ray diffractograms (PDF)

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## Notes

The authors declare no competing financial interest.

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## NOMENCLATURE

$A, B, C$	empirical model parameters for Apelblat equation
ARD %	percentage average relative deviation
DSC	differential scanning calorimetry
$h$	model parameter for $\lambda h$ equation representing excess
$m$	mass (g)
$M$	molecular mass (g/mol)
PXRD	powder X-ray diffraction
RD	relative deviation
$T$	absolute temperature (K)
TGA	thermogravimetric analysis
$T_m$	melting temperature (K)
$T_{m,onset}$	onset melting temperature (K)
$u$	standard uncertainty
$u_r$	relative standard uncertainty
$w_i$	mass fraction of solvent mixture compositions
$x_i$	mole fraction solubility
$x_i^{cal}$	calculated mole fraction solubility
$x_i^{exp}$	experimental mole fraction solubility

## GREEK SYMBOLS

$\lambda$	model parameter for $\lambda h$ equation representing nonideal properties of the system
$\Delta H_{fus}$	molar enthalpy of fusion (kJ/mol)

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