

Measurement and Prediction of Solubility of Paracetamol in Water–Isopropanol Solution. Part 2. Prediction

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Abstract:

The solubility of paracetamol in water–isopropanol mixtures at 30 °C using the *regular-solution* theory, the UNIFAC model, and the UNIQUAC model is predicted and compared with the corresponding experimental values reported in part A of this study. The results of the ideal solubility show that Δc_p should be integrated with respect to differential molar heat capacity changes with temperature, if sub-cooled liquid heat capacity is approximated by liquid heat capacity. The modified *regular-solution* theory underestimates the solubility, whereas the UNIFAC model overestimates it. The UNIQUAC model results in the best predictions. However, various vapor–liquid equilibrium data sets to calculate the UNIQUAC solvent–solvent adjustable parameters result in different accuracies.

Introduction

The experimental determination of solubility of pharmaceuticals in various organic solvents requires a large amount of the solute and is usually a time-consuming procedure. In many pharmaceutical applications there are only a few milligrams of a solid available; therefore, solubility prediction using thermodynamic models is the preferred choice.

The thermodynamic properties of liquid–vapor, liquid–liquid, and solid–liquid chemical systems found by using various methods (for example group-contribution methods or *regular-solution* theory) are reported in the literature. However, the solubility prediction of pharmaceutical solids in various solvents has received less attention. Solubility prediction needs an estimation of the ideal solubility and activity coefficient of the solute in a particular solvent. In their pharmaceutical crystallization studies, Neau, Bhandarhar, and Hellmuth¹ used paracetamol as a model compound and compared its ideal solubility at 25 °C using measurement of liquid and solid heat capacity. Using the measured heat capacities and solubility of paracetamol in 26 different solvents, Granberg and Rasmuson² reported the activity coefficient of paracetamol at 30 °C. Their experimental results were later used to compare the predicted paracetamol solubility at 25 °C using the UNIFAC model, assuming constant differential heat capacity.³

In the present study, four assumptions applied for the ideal solubility of paracetamol are investigated; the solubility of paracetamol in isopropanol–water mixtures is then predicted using the binary adjustable parameters and three different models (*regular-solution* theory, the UNIFAC model, and the UNIQUAC model) and compared with the corresponding experimental data reported in part A of this study.

Theory

At equilibrium:⁴

$$f_1^s = f_1^{\text{sat}} \quad (1)$$

where f_1^s and f_1^{sat} are the fugacities of pure solid and of solute in the solution, respectively. Using the sub-cooled liquid at temperature T and P^{sat} as the standard state for activity coefficient (γ_1) and assuming no solubility of solvent in solid, f_1^{sat} can be written:

$$f_1^{\text{sat}} = x_1 \gamma_1 f_1^1 \quad (2)$$

where x_1 is the solubility of solid in liquid in mole fraction and f_1^1 is the fugacity of the pure sub-cooled liquid state of the solid. Thus,

$$\frac{f_1^1}{f_1^s} = \frac{1}{x_1 \gamma_1} \quad (3)$$

The fugacity ratio is independent of the solvent properties and can be related to the molar Gibbs energy changes (Δg) of the solid.

$$\Delta g = RT \ln \frac{f_1^1}{f_1^s} = -RT \ln a_1 \quad (4)$$

The ratio of f_1^s/f_1^1 is called activity (a_1) and the molar Gibbs energy changes can also be related to the molar enthalpy (Δh) and entropy (Δs) changes.

$$\Delta g = \Delta h - T\Delta s$$

$$\ln \frac{1}{x_1 \gamma_1} = \frac{\Delta h}{RT} - \frac{\Delta s}{R} \quad (5)$$

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(3) Gracin, S.; Brinck, T.; Rasmuson, A. C. Prediction of Solubility of Solid Organic Compounds in Solvents by UNIFAC. *Ind. Eng. Chem. Res.* **2002**, *41*, 5114–5124.

(4) Prausnitz, J. M.; Lichtenthaler, R. N.; de Azevedo, E. G. *Molecular Thermodynamics of Fluid-Phase Equilibria*, 3rd ed.; Prentice Hall: New Jersey, 1999.

where R is the universal gas constant. Since both enthalpy and entropy are state functions (not path functions), they can be evaluated from any thermodynamic path. Using triple point of the solid, Prausnitz, Lichtenthaler, and Azevedo⁴ applied a thermodynamic cycle to evaluate the enthalpy and entropy changes.

$$\begin{aligned}\Delta h &= \Delta h_t^{\text{fus}} + \int_{T_t}^T \Delta c_p \, dT \\ \Delta s &= \Delta s_t^{\text{fus}} + \int_{T_t}^T \frac{\Delta c_p}{T} \, dT \\ \Delta c_p &= c_p^l - c_p^s\end{aligned}\quad (6)$$

where Δh_t^{fus} is the molar enthalpy of fusion at triple point, Δs_t^{fus} is the molar entropy of fusion at triple point, T_t is the absolute temperature of triple point, c_p^l is the heat capacity of liquid, and c_p^s is the heat capacity of solid. The triple point can also be substituted by the melting point. Thus,

$$\ln \frac{1}{x_1 \gamma_1} = \frac{\Delta h_m^{\text{fus}}}{RT} - \frac{\Delta s_m^{\text{fus}}}{R} + \frac{1}{RT} \int_{T_m}^T \Delta c_p \, dT - \frac{1}{R} \int_{T_m}^T \frac{\Delta c_p}{T} \, dT \quad (7)$$

where the index m shows all properties at melting point. The enthalpy of fusion is also related to entropy of fusion.

$$\Delta h_m^{\text{fus}} = T_m \Delta s_m^{\text{fus}}$$

thus:

$$\ln \frac{1}{x_1 \gamma_1} = \frac{\Delta h_m^{\text{fus}}}{R} \left(\frac{1}{T} - \frac{1}{T_m} \right) + \frac{1}{RT} \int_{T_m}^T \Delta c_p \, dT - \frac{1}{R} \int_{T_m}^T \frac{\Delta c_p}{T} \, dT \quad (8)$$

Ideal Solubility. Assuming ideal solution, the activity coefficient of solute in the solution is equal to unity, and the general equation of ideal solubility can be written as:

$$\ln x_1^{\text{ideal}} = \frac{\Delta h_m^{\text{fus}}}{R} \left(\frac{1}{T} - \frac{1}{T_m} \right) - \frac{1}{RT} \int_{T_m}^T \Delta c_p \, dT + \frac{1}{R} \int_{T_m}^T \frac{\Delta c_p}{T} \, dT \quad (9)$$

It can be shown easily that:

$$x_1 = \frac{x_1^{\text{ideal}}}{\gamma_1} \quad (10)$$

Equation 9 calculates the saturation mole fraction of solute in an ideal solution using the thermal properties of the solid phase. Because limited data are available in the literature to calculate Δc_p , some assumptions are applied to eq 9 to estimate the ideal solubility.

Case A. In most chemical engineering applications, the first term of the right-hand side of eq 9 has the largest effect, and the next two terms with two opposite signs tend to compensate each other. Thus, Δc_p is negligible in comparison to the molar enthalpy of fusion and can be considered zero.

$$\ln x_1^{\text{ideal}} = \frac{\Delta h_m^{\text{fus}}}{RT_m} (1 - T_r) \quad (11)$$

where T_r is the ratio of melting temperature to solution temperature (T_m/T).

Case B. It is shown⁵ that there is a linear relationship between $\ln x_1$ and $\ln T$ assuming $\Delta c_p \cong \Delta s_m^{\text{fus}}$

$$\ln x_1^{\text{ideal}} = - \frac{\Delta h_m^{\text{fus}}}{RT_m} \ln T_r \quad (12)$$

Using an infinite series of $\ln T_r$ for $T_r > 0.5$, Grant and Higuchi⁶ showed that eqs 11 and 12 are identical. They claimed that this is at least as good an approximation as the assumption $\Delta c_p = 0$. Equation 12 has been applied to pharmaceuticals¹ and has resulted in better approximations.

Case C. To estimate the ideal solubility more accurately, eq 9 can be simplified if the differential molar heat capacity is assumed to be constant and estimated at the melting point.

$$\ln x_1^{\text{ideal}} = \frac{\Delta h_m^{\text{fus}}}{RT_m} (1 - T_r) + \frac{\Delta c_p}{R} \Big|_{T_m} (T_r - 1 - \ln T_r) \quad (13)$$

Case D. In general, if Δc_p is not constant, eq 9 has to be integrated with respect to differential molar heat capacity changes. In case of linear changes in Δc_p , eq 9 can be rewritten as:

$$\Delta c_p = b + mT$$

$$\begin{aligned}\ln x_1^{\text{ideal}} &= \frac{\Delta h_m^{\text{fus}}}{RT_m} (1 - T_r) + \frac{b}{R} (T_r - 1 - \ln T_r) + \\ &\quad \frac{mT_m}{2R} \left(\frac{1}{T_r} + T_r - 2 \right)\end{aligned}\quad (14)$$

Prediction of Ideal Solubility of Paracetamol

Referring to the eqs 11 and 12–14, one can find that the ideal solubility is a function of temperature and thermal properties of the solid. The molar enthalpy of fusion, the melting temperature, and the differential molar heat capacity of the solid can be measured using a differential scanning calorimeter (DSC) device.

Thermal Properties at Melting Point. A differential scanning calorimeter (DSC822, Mettler Toledo) was used to measure the heat of fusion and melting temperature of paracetamol. An accurate balance (AX205, Mettler Toledo) was used to weigh five samples. These samples, weighing between 5 and 7 mg, were used to measure the thermal properties of paracetamol. The temperature was varied from 5 to 190 °C, and the heating rate was 1 °C/min. The mean values of Δh_m^{fus} and T_m are $28.1 \pm 0.3 \text{ kJ mol}^{-1}$ and $442.2 \pm 0.3 \text{ °C}$, respectively, which are in good agreement with reported data in the literature.^{1,2,7} The thermal properties of paracetamol vary according to its purity.

Liquid and solid molar heat capacities of paracetamol reported by Neau, Bhandarhar, and Hellmuth¹ were used in

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 (6) Grant, D. J. W.; Higuchi, T. *Solubility Behavior of Organic Compounds*; John Wiley & Sons: New York, 1990.
 (7) Szelagiewicz, M.; Marcolli, C.; Cianferani, S.; Hard, A. P.; Vit, A.; Burkhard, A.; von Raumer, M.; Hofmeier, U. C.; Zilian, A.; Francotte, E.; Schenker, R. In-situ Characterization of Polymorphic Forms, the Potential of Raman Techniques. *J. Therm. Anal.* **1999**, *57*, 23–43.

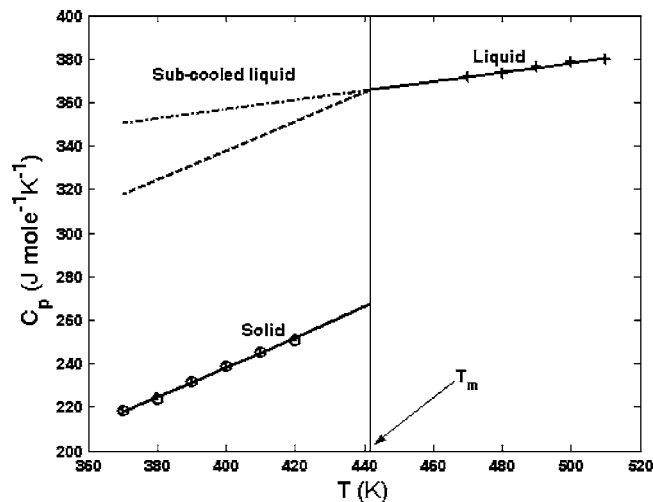


Figure 1. Molar heat capacity of paracetamol (Neau et al., 1997).

Table 1. Ideal solubility of paracetamol

T (K)	x_1^{ideal} from eqs				% error for eqs		
	11	12	13	14	11	12	13
278.2	0.0111	0.0290	0.0503	0.0758	85.4	61.7	33.6
283.2	0.0137	0.0333	0.0551	0.0793	82.7	58.0	30.5
288.2	0.0169	0.0380	0.0604	0.0834	79.8	54.4	27.6
293.2	0.0206	0.0434	0.0662	0.0881	76.6	50.8	24.8
298.2	0.0250	0.0493	0.0727	0.0934	73.2	47.2	22.2
303.2	0.0302	0.0560	0.0797	0.0994	69.7	43.6	19.8
308.2	0.0361	0.0635	0.0875	0.1062	66.0	40.2	17.6
313.2	0.0430	0.0718	0.0961	0.1137	62.2	36.9	15.5

this study. Figure 1 shows the linear behavior of both heat capacities with temperature. If sub-cooled liquid heat capacity is extrapolated and estimated by liquid heat capacity, the data shows that differential molar heat capacity is not constant and varies linearly with temperature.

$$\Delta c_p = 302.54 - 0.4589T \quad (15)$$

where T and Δc_p are in K and $\text{J mol}^{-1} \text{K}^{-1}$, respectively.

Ideal Solubility of Paracetamol. Using thermal properties of paracetamol and eqs 11 and 12–14, the ideal solubility of paracetamol at different temperatures (between 5 and 40 °C) along with the absolute relative errors of eqs 11, 14, and 15 with respect to eq 16 are calculated and presented in Table 1.

$$\% \text{ error} = \left| \frac{(x_1^{\text{ideal}})_{\text{eq}(i)} - (x_1^{\text{ideal}})_{\text{eq}(16)}}{(x_1^{\text{ideal}})_{\text{eq}(16)}} \right| \times 100$$

Although the Δc_p term can be ignored in comparison with the Δh_m^{fus} term (or estimated by $\Delta c_p \cong \Delta s_m^{\text{fus}}$ in some cases), the importance of the Δc_p term in the ideal solubility equation for many pharmaceutical compounds has been previously reported in the literature.^{1,3,4,6} Assuming that, at working temperatures far from the melting point $\Delta c_p \cong \Delta s_m^{\text{fus}}$ gives better estimation than $\Delta c_p = 0$, both assumptions fail and cause large errors in estimating the ideal solubility. For paracetamol, there are still significant errors in the predicted

ideal solubility, assuming no differential heat capacity changes with temperature. At 30 °C (303.2 K), for instance, the difference in the predicted ideal solubility of eqs 13 and 16 is almost 20%; however in general, the difference increases when the temperature difference between working and melting temperatures increases. Thus, assuming $\Delta c_p = 0$, $\Delta c_p \cong \Delta s_m^{\text{fus}}$, or $\Delta c_p = \text{const}$ can affect prediction of ideal solubility significantly. In this study the ideal solubility of paracetamol was calculated using eqs 14 and 15 for Δc_p changes.

Prediction of Real Solubility

The real solubility can be predicted using eq 10 and ideal solubility together with an appropriate thermodynamic model to estimate the activity coefficient. The activity coefficient is a function of many factors including molecular size, polarity, and interaction forces between solute and solvent. These depend on the physical bulk properties of the pure compound that are functions of intermolecular forces (Van der Waals forces, hydrogen bonding, and dipole–dipole forces), molar volume, and degree of polarity.

There are many thermodynamic models to predict the activity coefficient, which can be categorized in predictive (theoretical) and semi-empirical models. The predictive models have no adjustable parameters and use the thermodynamic bulk properties (*regular-solution* theory) or group-contribution (UNIFAC) of the solute and solvent, whereas the semi-empirical models (Wilson, NRTL, UNIQUAC) need experimental data to estimate one, two, or more adjustable parameters to predict the activity coefficient.

The UNIFAC and *regular-solution* theory have been proposed⁴ to predict the activity coefficient of a solute in a cosolvent. In this study, both models as well as the UNIQUAC model were used to predict the activity coefficient of paracetamol in isopropanol–water mixtures.

Regular-Solution Theory. Assuming $s^E = 0$ and $V^E = 0$ at constant temperature and pressure along with the geometric mean assumption, Scatchard–Hildebrand theory shows that for a binary solution of nonpolar molecules, the solute activity coefficient can be expressed by:

$$\ln \gamma_1 = \frac{V_1^L}{RT} (\delta_1 - \delta_2)^2 \Phi_2^2 \quad (16)$$

where the solvent molar volume fraction (Φ_2) is defined as:

$$\Phi_2 = \frac{x_2 V_2^L}{x_1 V_1^L + x_2 V_2^L}$$

Equation 16 is known as the Scatchard–Hildebrand equation and can estimate the activity coefficient of nonpolar molecules using the bulk properties of the solute and solvent. This theoretical equation has no adjustable parameter, but it is shown that the geometric mean assumption of the theory can cause serious defects in the prediction of the activity coefficient.^{4,6} For example, *regular-solution* theory is not able to predict the negative deviations from Raoult's law ($\gamma_i < 1$) because the right-hand side of eq 16 is always greater than or equal to zero. The modified Scatchard–Hildebrand

has been proposed to overcome the deviation problem. According to this modification, the activity coefficient of a solid in a solvent and in a cosolvent is given by, respectively:

$$\ln \gamma_1 = \frac{V_1^L}{RT} [(\Delta_1 - \delta_2)^2 + 2L_{12}\delta_1\delta_2]\Phi_2^2 \quad (17)$$

$$\ln(\gamma_1) = \frac{V_1}{RT} [A_{1,2}\Phi_2^2 + A_{1,3}\Phi_3^2 + (A_{1,2} + A_{1,3} - A_{2,3})\Phi_2\Phi_3] \quad (18)$$

where

$$A_{i,j} = (\delta_i - \delta_j)^2 + 2L_{i,j}\delta_i\delta_j \quad \text{and} \quad \Phi_i = \frac{x_i V_i}{\sum_k x_k V_k}$$

$L_{i,j}$ is an adjustable binary parameter (positive or negative) that represents deviations from the geometric mean assumption and is a function of temperature. Although it has not been recommended for the polar solutions and the nonpolar solutions that are close to ideal solution, the *regular-solution* theory can predict solubility behavior of a solid in cosolvent mixtures. According to this theory, the solubility curve of a solid in a cosolvent shows a maximum at a specific solvent, if the solubility parameter of solute is between the solubility parameters of both solvents.

Estimation of Parameters. To model the solubility of paracetamol in an isopropanol–water mixture with the *regular-solution* theory, the adjustable parameters, L_{ij} , should be obtained using experimental binary data. As mentioned, L_{ij} is a function of temperature and should be estimated using binary data at the same temperature. The solubility parameter, δ_i , is also a function of temperature and is usually reported at 25 °C. The temperature dependence of δ_i can be ignored because the difference between two solubility parameters, $\delta_1 - \delta_2$, in eq 17 can be considered independent of temperature.⁴ The molar volume of paracetamol is also unknown and has to be determined. Various estimation methods were tested; however, the results showed a wide range for the paracetamol molar volume. Thus, it was assessed by measuring the molar volume of paracetamol solutions with known concentration in two different solvents and at 30 °C. Dimethyl sulfoxide and *N,N*-dimethylformamide were selected because paracetamol solubility was great enough in both solvents and both solvents have relatively high boiling points to minimize evaporation during the experiments. The solutions were prepared by adding an appropriate mass of paracetamol and solvent and mixing until all paracetamol was dissolved at the given temperature. Assuming ideal solution and using the measured molar volume of solutions resulted in a value of 128.82 cm³ mol⁻¹ for the molar volume of paracetamol. The solubility parameter of paracetamol, 27.8 (J cm⁻³)^{0.5}, reported by Barra, Lescure, Doelker, and Bustamate⁸ was used in this study. The values of δ_i and molar volume for isopropanol and water

Table 2. L_{12} and L_{13} parameters for different ideal solubility at 30 °C

ideal solubility equation	paracetamol in isopropanol		paracetamol in water	
	γ_1	L_{12}	γ_1	L_{13}
11	0.5888	-0.0230	14.5997	-0.1303
12	1.0942	-0.0120	27.1306	-0.1256
13	1.5574	-0.0058	38.6155	-0.1230
14	1.9420	-0.0018	48.1507	-0.1213

can be found in the literature. Using eq 17 as well as experimental activity coefficients of paracetamol in pure isopropanol and pure water at 30 °C, L_{12} and L_{13} were calculated and are given in Table 2. $L_{2,3}$ can be estimated using binary vapor–liquid equilibrium (VLE) data⁹ for isopropanol and water. At low pressures, the modified Raoult's equation can be used to calculate the activity coefficient of isopropanol in the liquid phase.

$$\gamma_2 = \frac{y_2 P_T}{x_2 P_2^{\text{sat}}} \quad (19)$$

where P_T is the total pressure and P_2^{sat} is the vapor pressure of isopropanol that can be calculated from the Antoine equation.⁹

$$\log P_2^{\text{sat}} (\text{mmHg}) = 8.87829 - \frac{2010.33}{t(^{\circ}\text{C}) + 252.636}$$

The activity coefficients of isopropanol (γ_2) along with square of volume fractions of water (Φ_3^2) are given in Table 3. A nonlinear regression method was applied to estimate $L_{2,3}$. The optimization procedure was based on the minimization of the error between the calculated and experimental values of the activity coefficient.

$$\min \text{Error} = \sum (\gamma_{2,\text{exp}} - \gamma_{2,\text{cal}})^2$$

where $\gamma_{2,\text{exp}}$ and $\gamma_{2,\text{cal}}$ are the experimental and calculated activity coefficients of isopropanol, respectively. At 95% confidence level, Figure 2 shows the prediction results of the activity coefficient along with experimental data and error bars for each data point. The calculated value of $L_{2,3}$ is:

$$L_{2,3} = 0.2163 \pm 7.6525 \times 10^{-4} \quad R^2 = 0.9903$$

Prediction of the Solubility. Using data obtained from the previous section and eq 18, the solubility of paracetamol in isopropanol–water mixtures can be predicted. Figure 3 shows the predicted and experimental solubility using four ideal solubility values. It is apparent that the *regular-solution* theory does not offer a good prediction for the solubility of polar solutions, but the solubility curve obeys the expected trend. There is a maximum solubility between 0.2 and 0.3 water mass fraction (solute free), confirming that the solubility parameter of paracetamol is between the solubility parameters of isopropanol and of water, much closer to the

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Table 3. VLE data of isopropanol and water mixture at 25 °C

x_2	γ_2	P_T (mmHg)	γ_2	Φ_3^2	x_2	γ_2	P_T (mmHg)	γ_2	Φ_3^2
0.0188	0.3313	34.89	14.1696	0.8551	0.3361	0.5469	48.84	1.8315	0.1007
0.0227	0.3409	36.23	12.5390	0.8284	0.3577	0.5531	49.02	1.7468	0.0882
0.0347	0.4210	39.25	10.9745	0.7525	0.3892	0.5595	49.28	1.6326	0.0727
0.0379	0.4329	39.85	10.4899	0.7338	0.4440	0.5740	49.68	1.4801	0.0518
0.0590	0.4762	42.63	7.9295	0.6235	0.4540	0.5806	49.75	1.4662	0.0487
0.0598	0.4709	42.71	7.7508	0.6197	0.4843	0.5857	49.94	1.3919	0.0401
0.0865	0.5009	44.55	5.9453	0.5085	0.5153	0.5993	50.11	1.3431	0.0328
0.1287	0.5109	46.07	4.2147	0.3774	0.5453	0.6098	50.25	1.2950	0.0269
0.1772	0.5197	47.05	3.1801	0.2726	0.5857	0.6277	50.39	1.2446	0.0204
0.1907	0.5271	47.25	3.0098	0.2497	0.6240	0.6462	50.46	1.2043	0.0154
0.2452	0.5331	47.94	2.4020	0.1765	0.6635	0.6674	50.46	1.1697	0.0114
0.2962	0.5407	48.47	2.0391	0.1286	0.6956	0.6853	50.40	1.1443	0.0087
0.3040	0.5453	48.55	2.0070	0.1226	0.7296	0.7081	50.25	1.1239	0.0064
0.3248	0.5438	48.74	1.8806	0.1079	0.7588	0.7231	50.05	1.0992	0.0048

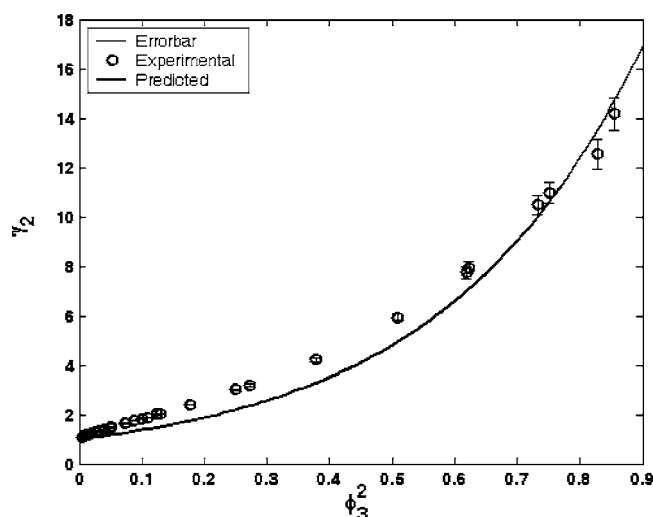


Figure 2. Activity coefficient of isopropanol using VLE data at 25 °C ($R^2 = 0.9903$).

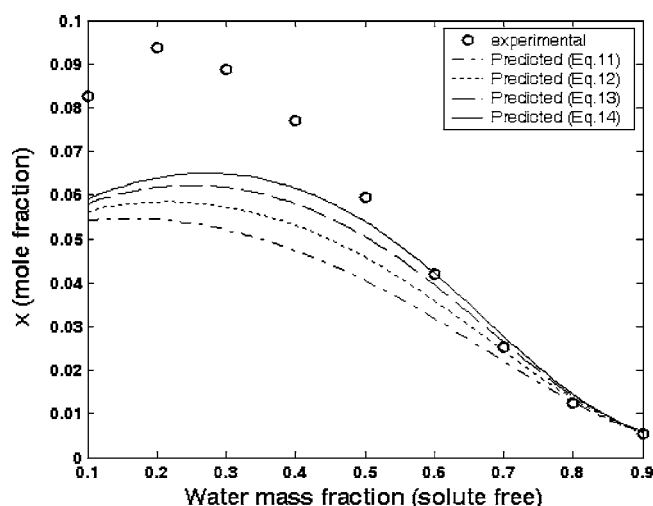


Figure 3. Prediction of paracetamol solubility in isopropanol–water mixture using regular-solution theory.

solubility parameter of isopropanol. Also, the results show that the effective solubility of the cosolvents is a function of solvent composition. The theory, however, is useful for the selection of solvents in a crystallization process.

Group-Contribution Methods. Using functional group concepts and quasi-chemical theory of liquid mixtures,

Abrams and Prausnitz¹⁰ presented the UNIQUAC model to predict the activity coefficient of each component in a liquid mixture. The model is a semi-empirical equation based on two adjustable parameters that can be estimated from experimental binary data. Later on, based on the extension of the UNIQUAC model, a theoretical approach, the UNIFAC, was proposed by Fredenslund, Jones, and Prausnitz¹¹ to calculate the activity coefficients of non-electrolyte solutions. Both models consist of two different parts, a combinatorial part ($\ln \gamma_i^C$) and a residual part ($\ln \gamma_i^R$).

$$\ln(\gamma_i) = \ln(\gamma_i^C) + \ln(\gamma_i^R) \quad (20)$$

The combinatorial part represents the entropic contribution and is defined similarly in both models, whereas the residual part of the activity coefficient describes the intermolecular forces and is defined differently in each model. The details of the models can be found in the literature.^{4,11,12}

Prediction of Solubility Using the UNIFAC Model. In this section the solubility of paracetamol in isopropanol–water mixtures is predicted at 30 °C using eq 10 and the UNIFAC model. Paracetamol is identified by four functional groups, *ACH*, *ACOH*, *ACNH*, and *CH₃CO*. The functional group properties of *ACNH* are not found in the literature and are estimated by *ACNH₂* functional group properties. Isopropanol has three functional groups, *CH₃*, *CH*, and *OH*, whereas, water has only one main functional group, *H₂O*. The main group and sub-group numbers along with the properties of specified functional groups, together with the values of group interaction parameters (a_{mn}) were adapted from Poling, Prausnitz, and O’Connell.¹² These data were used to calculate both combinatorial and residual parts of the UNIFAC activity coefficient equation.

At 30 °C, the activity coefficient of paracetamol in isopropanol–water mixtures was predicted using the UNIFAC model and four different ideal solubility values of

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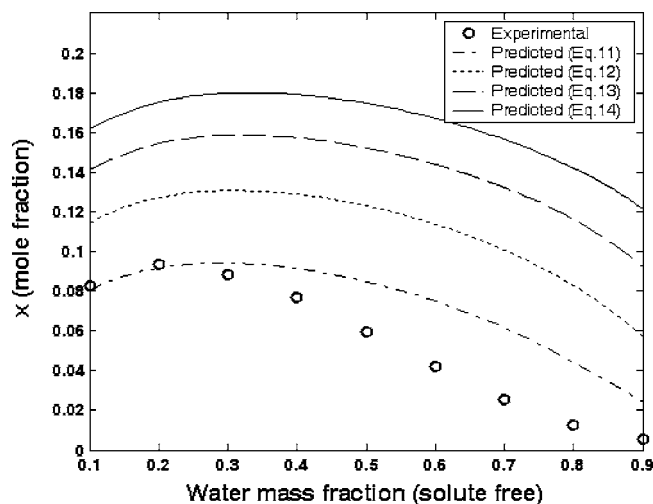


Figure 4. Prediction of paracetamol solubility in isopropanol–water mixture using the UNIFAC model.

paracetamol. Then the mole fractions were calculated and plotted in Figure 4. In all cases, the UNIFAC model overestimated the solubility. Using the UNIFAC model as well as eqs 12 and 13 for calculating ideal solubility, Gracin, Brinck, and Rasmuson³ predicted the solubility of paracetamol in different pure organic solvents at 25 °C. Their solubility predictions in water and isopropanol were also higher than the experimental results. They showed that the properties of a functional group depend on the rest of the molecule, and this is a violation of the major assumption of the UNIFAC model. Although the high accuracy prediction of the model is not expected due to the estimation of functional group properties of *ACNH* and the error contribution of functional group dependency, as with the *regular-solution* theory, the UNIFAC predicts the right trend for the solubility of paracetamol in isopropanol–water mixture including a maximum solubility between 0.2 and 0.3 water mass fractions (solute free).

Prediction of Solubility Using the UNIQUAC Model. The combinatorial part of activity coefficient of the UNIQUAC model can be calculated using functional group properties adopted from Poling, Prausnitz, and O’Connell.¹² The only difference between the UNIFAC and UNIQUAC model is the residual part of the activity coefficient. This part consists of adjustable parameters that have to be estimated by binary solubility data.

The interaction adjustable parameters between the two solvents can be found from the liquid–liquid or vapor–liquid equilibrium data. Two sets of the adjustable parameters between isopropanol and water obtained from vapor–liquid equilibrium data⁹ were used in this study. For different ideal solubility equations, the binary adjustable parameters of paracetamol in pure isopropanol and pure water were calculated using the experimental solubility data and the nonlinear regression methods.

MATLAB software was used for all regression and related statistical analyses (at the 95% confidence level). Figure 5a,b, for example, shows the regression results of paracetamol solubility in water using eq 12 and in isopropanol using eq 13, respectively. All predicted values of binary adjustable

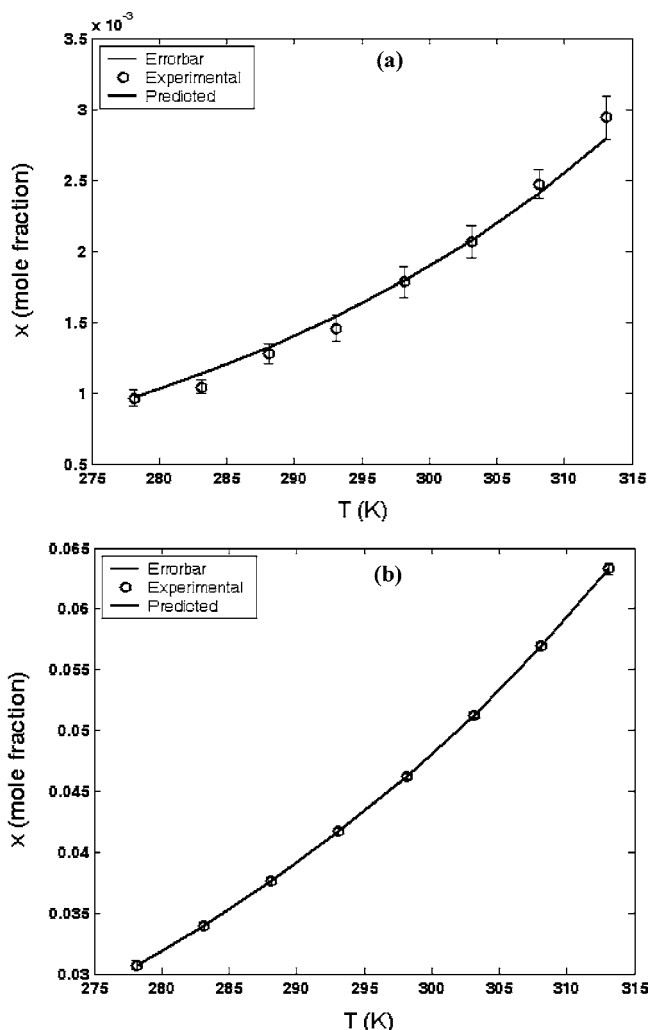


Figure 5. Solubility prediction of paracetamol: (a) in pure water using the UNIQUAC model and eq 12 for ideal solubility and (b) in pure isopropanol using the UNIQUAC model and eq 13 for ideal solubility.

Table 4. Binary adjustable parameters of the UNIQUAC model for the mixture of paracetamol (1), isopropanol (2), and water (3)

eq	paracetamol			isopropanol			water		
	a_{12}	a_{21}	R^2	a_{13}	a_{31}	R^2	a_{23}	a_{32}	R^2
11	-300.7	477.8	0.9988	-225.2	335.4	0.9973	316.3	-46.45	N/A ^a
14	329.7	-212.8	0.9997	-4.319	47.69	0.9960	316.3	-46.45	N/A
15	6.310	10.71	0.9996	-36.98	71.98	0.9940	316.3	-46.45	N/A
16	-15.70	52.19	0.9988	-62.77	150.2	0.9950	316.3	-46.45	N/A

^a N/A: not available

parameters along with their statistical values of R^2 are listed in Table 4. The confidence intervals for the parameters are not reported in this section because they show very wide ranges. This statistical value is related inversely to the degree of freedom and directly to t distribution if the numbers of data are large enough. The degree of freedom is defined as the difference between the numbers of data (n) and the numbers of parameters (p). In these cases, n and p values were 9 and 2, respectively. The degree of freedom and n are not large enough to use this statistical parameter for

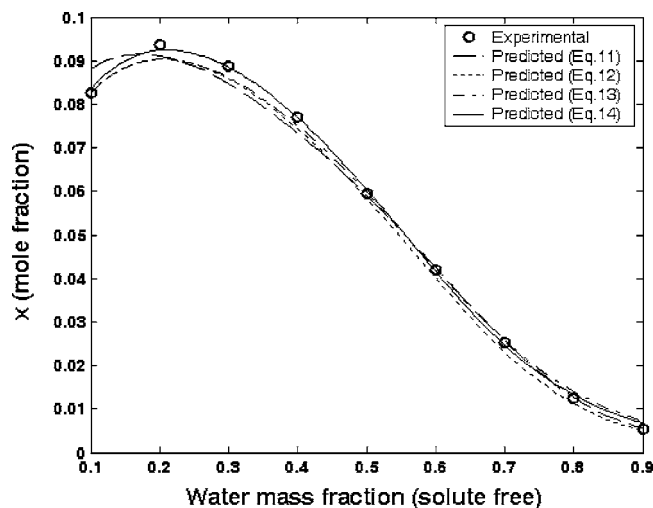


Figure 6. Prediction of paracetamol solubility in isopropanol–water mixtures using the UNIQUAC model at 30 °C.

analyzing the regression results, but other statistical results show that the UNIQUAC model offers a good prediction for the solubility of paracetamol in pure isopropanol and water.

The data listed in Table 4 were used to predict the solubility of paracetamol in isopropanol–water mixtures. Applying an iterative procedure, at 30 °C the mole fractions of paracetamol for different ideal solubility values were predicted and plotted in Figure 6. The results show good agreement between the experimental and the predicted solubility indicating the advantages of the UNIQUAC model. There are six adjustable parameters incorporating the interactions between solute and each solvent as well as the interactions between the solvents. In all cases the maximum solubility is predicted approximately at 0.2 water mass fraction (solute free) as shown by the experimental data.

The solubility prediction using the UNIQUAC model results in excellent prediction with almost the same precision for all ideal solubility equations. In fact using binary solubility data to predict the solubility in ternary solution may compensate the errors due to different assumptions applied for the ideal solubility equation. Figure 7 shows the predictions of three models for the solubility of paracetamol in isopropanol–water mixtures at 30 °C using eq 14. The results indicate that the estimated solubility using the UNIQUAC model offers a better prediction compared with other predictive models, *regular-solution* theory, and UNIFAC.

It is worth mentioning that the binary adjustable parameters between two solvents chosen for this study (set 1) offer the best fit for the UNIQUAC prediction. There are different vapor–liquid equilibrium data sets in the literature to estimate the UNIQUAC binary adjustable parameters between isopropanol and water. Using the recommended values (set 2) of Gmehling and Onken⁹ for the UNIQUAC adjustable parameters of isopropanol and water ($a_{23} = 165.2$ and $a_{32} = 32.43$ K) presents a poor prediction at 30 °C in comparison with the data chosen in the present study. Although the recommended data set results in better predictions at 10 °C in comparison to 20 °C, both sets predict the

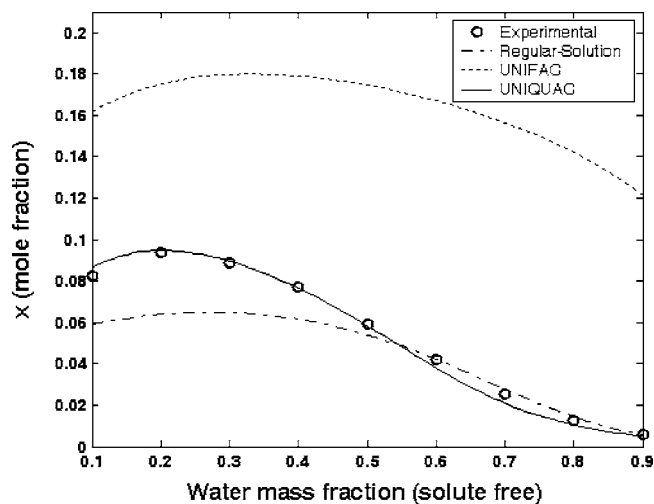


Figure 7. Prediction of paracetamol solubility in isopropanol–water mixtures using three different models at 30 °C and eq 14 for ideal solubility.

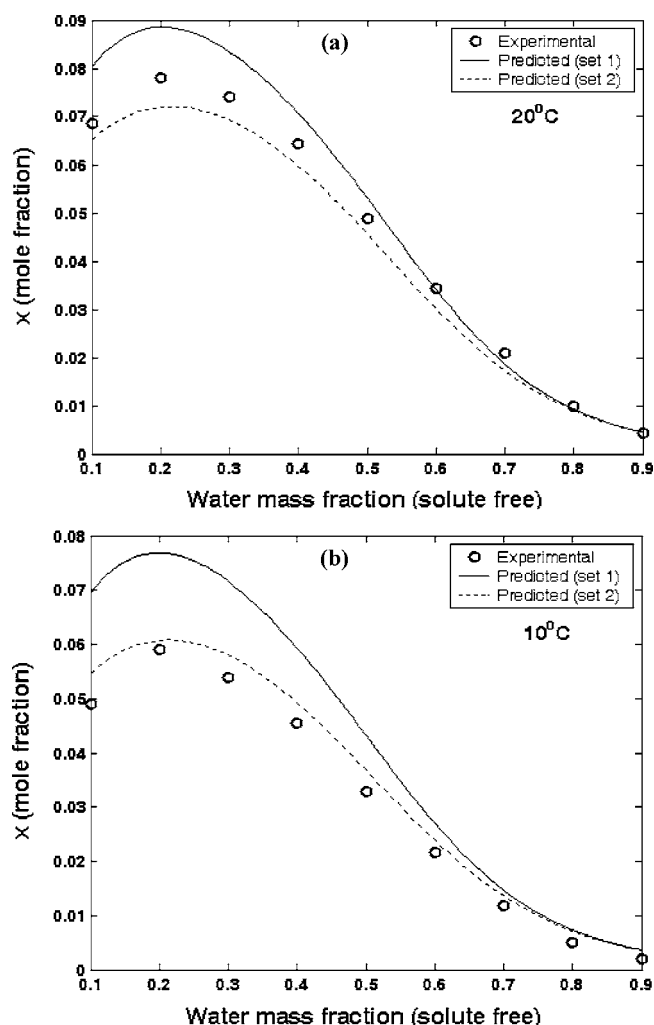


Figure 8. Prediction of paracetamol solubility in isopropanol–water mixtures using the UNIQUAC model at (a) 20 °C and (b) 10 °C.

solubility with almost the same accuracy at 20 °C (see Figure 8a,b). Thus, choosing a reliable data set from the data banks for the adjustable parameters is a difficult task.

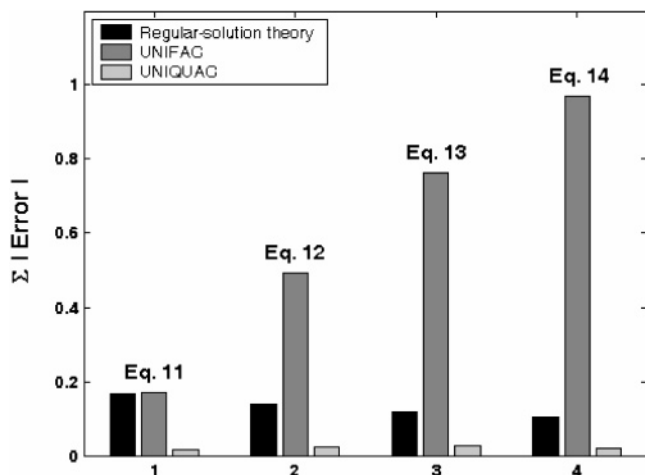


Figure 9. Summation of errors due to solubility prediction of *regular-solution* theory, the UNIFAC and UNIQUAC models for different ideal solubility equations.

In order to assess the validity of the different assumptions employed for the ideal solubility, for all models the summation of absolute errors between the experimental and the calculated solubility (in mole fraction) defined by:

$$|\text{error}| = \sum |x_{\text{exp}} - x_{\text{cal}}| \quad (21)$$

was used and plotted in Figure 9. The errors represent the effect of assumptions on the solubility prediction. Regardless of the validity and accuracy of the *regular-solution* theory and the UNIFAC model, the results show significant differences in the prediction of paracetamol solubility using different assumptions applied for ideal solubility. Although the *regular-solution* predictions for the real solubility tend to be underestimated for all equations of ideal solubility, eq 14 gives better estimation for the solubility of paracetamol in isopropanol–water mixture showing neither of three simplifications have enough accuracy to apply for paracetamol case. Unlike *regular-solution* theory, eq 14 indicates highest error level among the ideal solubility equations for the UNIFAC model. Thus, due to the overestimation of the UNIFAC model, the highest error for eq 14 would be expected. Although the summations of absolute errors of eqs 11 and 14 for the UNIQUAC model show the lowest errors among the ideal solubility equations, the results of eqs 12 and 13 are comparable with those of eqs 11 and 12. In fact, the solubility prediction using the UNIQUAC model results in good prediction with almost the same precision for all ideal solubility equations. Thus, assessing different ideal solubility assumptions with this point of view cannot be useful.

Conclusions

The paracetamol ideal solubility was calculated using four different assumptions. The results show that the order of magnitude of the Δc_p term in the ideal solubility equation is almost as high as that of the Δh_m^{fus} term and Δc_p term should be included in the equation for an accurate estimation of paracetamol ideal solubility. Assuming $\Delta c_p \cong \Delta s_m^{\text{fus}}$ results in better estimation than $\Delta c_p = 0$, whereas both assumptions

fail at a working temperature if Δc_p is assumed to be constant at the melting point. At working temperatures that are far from the melting point, it is shown that all assumptions fail if the differential molar heat capacity varies with temperature. However the validity of assumptions cannot be confirmed using the results obtained from the predictive models.

The modified *regular-solution* theory, the UNIFAC, and the UNIQUAC models were applied to predict the activity coefficients and solubility of paracetamol in a cosolvent (water–isopropanol) using available binary datum. All models predict well the solubility trend of paracetamol in the solvent mixture including detection of a maximum between 0.2 and 0.3 water mass fractions. The modified *regular-solution* theory assumes solutions of nonpolar molecules and has one binary adjustable parameter that depends on temperature. In our case, the solutions of paracetamol in isopropanol, water, as well as isopropanol–water mixtures are polar, and only one solubility data point is available at any temperature. Thus, the theory underestimates the solubility. The UNIFAC model can calculate the activity coefficients of paracetamol in the mixture of solvents using the interactions and properties of functional groups of the molecules. The major assumption behind this model is the independence of each functional group from the rest of the molecule. It has been shown that the properties of a functional group depend on the rest of molecule.³ Also the interactions and properties of some functional groups for complex molecules such as pharmaceutical compounds are not available and should be estimated. Hence, the model overestimates the solubility. The semi-empirical UNIQUAC activity coefficient model with adjustable parameters that can be estimated from the binary equilibrium data offers a better predictive capability than the other two models. At any constant temperature, the solubility of paracetamol in isopropanol–water mixture shows a maximum at almost 0.2 mole fraction of water if the solubility is plotted versus the water mole fractions (solute free). However, there are a lot of vapor–liquid equilibrium data sets by which to calculate the UNIQUAC solvent–solvent adjustable parameters, which result in different accuracies for the solubility prediction at a certain temperature that can be related to uncertainties of the data.

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Notation

a_{ij}	binary adjustable parameters of UNIQUAC model (K)
a_{mn}	group interaction parameters of UNIFAC model (K)
a	activity
b	adjustable parameter of Δc_p equation ($\text{J mol}^{-1} \text{K}^{-1}$)
c_p	molar heat capacity ($\text{J mol}^{-1} \text{K}^{-1}$)
f	fugacity
g	molar Gibbs energy (J mol^{-1})

h	molar enthalpy (J mol^{-1})
L_{ij}	adjustable binary parameters for <i>regular-solution</i> theory
m	adjustable parameter of Δc_p equation ($\text{J mol}^{-1} \text{K}^{-2}$)
n	number of data
P	pressure (mmHg)
p	number of parameters
R	universal gas constant ($\text{J mol}^{-1} \text{K}^{-1}$)
R^2	squared correlation coefficient
s	molar entropy ($\text{J mol}^{-1} \text{K}^{-1}$)
T	temperature (K or °C)
T_r	ratio of melting temperature to solution temperature
V	molar volume ($\text{cm}^3 \text{mol}^{-1}$)
x	mole fraction

Greek letters

Φ	volume fraction
δ	solubility parameter (J cm^{-3}) ^{0.5}
Δ	property changes
γ	activity coefficient

Subscripts

1	paracetamol
2	isopropanol
3	water
cal	calculated

exp	experimental
m	melting point
t	triple point
T	total

Superscripts

C	combinational
fus	fusion
ideal	ideal state
l	liquid
R	residual
s	solid
sat	saturation
E	excess property

Abbreviations

DSC	differential scanning calorimetry
UNIQUAC	UNIversal QUAsi-Chemical theory
UNIFAC	UNIversal Functional Activity Coefficient theory
VLE	vapor–liquid equilibrium

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