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SOLUBILITY OF IBUPROFEN IN CONVENTIONAL SOLVENTS AND SUPERCRITICAL CO_2: EVALUATION OF IDEAL AND NON-IDEAL MODELS

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Abstract. In this study solubility of racemic (R/S)(±)-ibuprofen in pure conventional solvents (*n*-heptane, toluene, benzene and ethanol) and supercritical carbon dioxide is predicted and the results are compared with experimental data. The results of the ideal solubility show great deviation from experimental points. However, it seems that liquid phase non-ideality is the main problem in the modeling of this system. To capture the non-ideality of the system UNIQUAC, UNIFAC, NRTL, Wilson, and regular-solution theory are used. The results prove that UNIQUAC is more appropriate than regular-solution theory and UNIFAC for calculation of racemic (R/S)(±)-ibuprofen solubility data. Also, the solubility of (R/S)(±)-ibuprofen in supercritical CO_2 (SC-CO_2) was investigated by using Peng-Robinson equation of state (PR EoS). The results of modeling are in good agreement with experimental data.

Keywords: ibuprofen, solubility, supercritical CO_2, solution theory.

1. Introduction

A racemic compound of species is indicated as a mixture of two enantiomers with 50:50 ratio, and can exist as a racemic conglomerate, a racemic compound, or a solid solution (pseudoracemate) [1]. Racemic compound of ibuprofen, (R/S)(±)-ibuprofen 2-[4-isobutylphenyl] propionic acid, is a non-steroidal anti-inflammatory drug. It is most often prescribed to treat menstrual symptoms, pain, arthritis, and fever. Racemic ibuprofen is a relatively weak acid compound and it is a water insoluble compound [2, 3]. The chemical formula of racemic ibuprofen is $C_3H_{18}O_2$ and the structure of racemic (R/S)(±)-ibuprofen is shown in Fig. 1.

Solubility data in different solvents are an important issue for separation and crystallization processes involving complex molecules such as natural products and pharmaceutical drugs. Nevertheless, solubility data are in general difficult to obtain, and so models are important tools to generate the necessary estimates. It is evident that the solubility prediction is also necessary in solvent selection and control of crystallization processes. One of the popular methods to predict solubility is based on the activity coefficient evaluation.

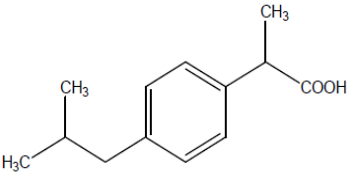

Fig. 1. Structure of racemic (R/S)(±)-ibuprofen [1]

Different correlative, statistical and thermodynamic models have been proposed to evaluate solubility. From these, more theoretically sound thermodynamic models allow to generate estimates at broader temperature, pressure and composition conditions while using a smaller amount of experimental information. Among them some are described below.

Wang *et al.* [4] measured solubility of ibuprofen in alcohols in the temperature range of 283–318 K. Solubility data were also correlated with a semi-empirical equation. The calculated results show a fine representation of experimental data. Rashid *et al.* [5] measured solubility of ibuprofen in pure ethanol and water–ethanol mixtures at the temperatures of 283–303 K, the expected range relevant to its industrial crystallization. Dun *et al.* [6] measured the solubility of ibuprofen in acetone-water mixture and correlated them by the modified Apelblat equation, the Buchowski equation and van't Hoff model. The modified Apelblat equation was the best model for correlating the solubility of ibuprofen. A study was presented by Spyriouni *et al.* [7] for predicting the solubility of pharmaceutical molecules by perturbed chain statistical associating fluid theory (PC-SAFT) EoS. They studied solubility of ibuprofen, paracetamol, naproxen, flurbiprofen, ketoprofen, and lovastatin in three different solvents: a hydrophilic solvent (water), a polar solvent,

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and a hydrophobic solvent. The results indicated that PC-SAFT EoS predictions were in good agreement with experimental data without using adjustable parameter (k_{ij}). However, the SAFT-based equations are complex and very computer time consuming as well as require at least three adjustable parameters.

In this study, four assumptions are applied for calculation of the ideal solubility of racemic ibuprofen in *n*-heptane, toluene, benzene, and ethanol as well as five models for calculation of activity coefficient (*i.e.*, regular-solution theory, UNIFAC, UNIQUAC, NRTL, and Wilson model). However, the aim is the accurate calculation of experimental data [1] in the range of 288–333 K and evaluation of models. Also, the two-parameter EoS, *i.e.* PR EoS was used to predict the solubility of ibuprofen in SC-CO_2 at three temperatures and wide range of pressure.

2. Theoretical

Let us see the equilibrium [8]:

$$f_2^s = f_2^{sat} \tag{1}$$

where f_2^s and f_2^{sat} are the fugacities of pure solid and of solute in the solution, respectively. Using the sub-cooled liquid at the temperature T and P^{sat} (saturated pressure) as the standard state for activity coefficient (g_2) and assuming no solubility of solvent in solid, f_2^{sat} can be written:

$$f_2^{sat} = x_2 g_2 f_2^l \tag{2}$$

where x_2 is the solubility of solid in liquid in mole fraction and f_2^l is the fugacity of the pure sub-cooled liquid state of the solid:

$$\frac{f_2^l}{f_2^s} = \frac{1}{x_2 g_2} \tag{3}$$

The fugacity ratio is independent of the solvent properties and can be related to the molar Gibbs function changes (ΔG) of the solid. Consequently, using molar Gibbs function changes definition, actual solubility is (see Appendix A):

$$\ln\frac{1}{x_2 g_2} = \frac{\Delta H_m^{fus}}{RT} - \frac{\Delta S_m^{fus}}{R} + \\ + \frac{1}{RT}\int_{T_m}^{T}\Delta C_p dT - \frac{1}{R}\int_{T_m}^{T}\frac{\Delta C_p}{T}dT \tag{4}$$

where R, ΔH_m^{fus}, ΔS_m^{fus}, ΔC_p and T_m are the universal gas constant, the molar enthalpy of fusion at melting point, the molar entropy of fusion at melting point, the molar heat capacity changes, and the melting point, respectively. The ideal and real mole fractions are related by:

$$x_2 = \frac{x_2^{ideal}}{g_2} \tag{5}$$

Prediction of the actual solubility requires the actual activity coefficient of the solute in the solution, g_2, which should be calculated from the thermodynamic models. The measured solubility is often in terms of g of solute per 100 g of solvent. To convert the solubility (S) in terms of mole fraction (x_2), we have to use the following equations:

$$S = \frac{xM_{w_{solute}}}{M_{w_{solvent}}}\cdot 100 \quad \text{then} \quad x_2 = \frac{x}{x+1} \tag{6}$$

where M_w is the molecular weight, g/mol.

2.1. Ideal Solubility

Assuming ideal solution (g_2 = 1), the activity coefficient of solute in the solution is equal to unity, and the general equation of ideal solubility can be written as [9]:

$$\ln x_2^{ideal} = \frac{\Delta H_m^{fus}}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) - \\ - \frac{1}{RT}\int_{T_m}^{T}\Delta C_p dT + \frac{1}{R}\int_{T_m}^{T}\frac{\Delta C_p}{T}dT \tag{7}$$

Eq. (7) calculates the ideal 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. (7) to estimate the ideal solubility. The details of assumptions are given in Appendix B.

2.2. Solid-Supercritical CO_2 Equilibrium

A supercritical fluid (SCF) is defined as a state of a compound or mixture above its critical pressure (P_c) and critical temperature (T_c) but below the pressure required to condense it into a solid. A SCF has high diffusivity (like gas) and density (like liquid) and, consequently, it is a promising solvent for many industrials.

For phase equilibrium calculations, the equality of the fugacity of pure solute (ibuprofen) to its fugacity in supercritical fluid (CO_2) has been assumed as follows [2]:

$$f_i^{\,pure\ solid} = f_i^{\,supercritical} \tag{8}$$

where f refers to the fugacity and i stands for solute in the mixture. Eq. (8) is rewritten as the following equation [8]:

$$y_i j_i^{SCF} P = P_i^{sat}\, exp\left[\frac{u_i^s (P - P_i^{sat}}{RT}\right] \tag{9}$$

where P is the pressure, u_i^s is the solid molar volume, R is the universal gas constant, T refers to temperature, superscripts s and sat stand for solid and saturation conditions, respectively; y_i and φ_i are the mole fraction and fugacity coefficient of the solute in supercritical phase, respectively. The details of fugacity coefficient based on PR EoS are given in Appendix D. The thermodynamic properties of ibuprofen and CO_2 are included in Table 1.

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Table 1

Thermodynamic properties of CO_2 and ibuprofen [2]

Compound	T_c, K	P_c, kPa	ω	v^s, cm^3/mol
Carbon dioxide	304	7382	0.228	–
Ibuprofen	749	2315	0.820	182.14

3. Results and Discussion

There are many successful activity coefficient models in the literature. However, it could be reasonably argued that the most well-known and widely used ones are Wilson, NRTL, UNIFAC, UNIQUAC, and regular solution theory. The Wilson and UNIQUAC models typically have two binary interaction parameters (which can be temperature dependent), while the NRTL equation has three parameters. The activity coefficient is a function of many factors such as molecular size, polarity and interaction forces between solute and solvent. Thermodynamic models to predict the activity coefficient can be categorized in theoretical and semi-empirical models. The theoretical models have no adjustable parameters and use the thermodynamic bulk properties (regular-solution theory) while UNIFAC makes use of group contribution of the solute and solvent. The semi-empirical models (UNIQUAC, NRTL, Wilson) need experimental data to estimate adjustable parameters to predict the activity coefficient.

The optimization procedure was used for calculation of parameters and it is based on the minimization of the objective function defined as:

$$OF = \sum \left[\left(x_{2Exp} - x_{2Calc} \right) / x_{2Exp} \right]^2 \qquad (10)$$

where x_{2Exp} and x_{2Calc} are the experimental and calculated activity coefficients of ibuprofen, respectively.

To predict the mole fraction of solute in the solvent, the following procedure was performed:

1. To calculate the ideal mole fractions from Eqs. (B.1)–(B.4) at the temperatures at which the solubility of solids is available.

2. To calculate the corresponding activity coefficient from the thermodynamic models (regular solution, UNIFAC, UNIQUAC, NRTL, and Wilson).

3. To write a regression program that changes the adjustable parameters to minimize the error in Eq. (10).

4. To calculate the solubility according to Eq. (5).

In order to predict the activity coefficient, the thermal properties of racemic (R/S)(±)-ibuprofen are needed. A scanning calorimeter method was used to measure the heat of fusion and melting temperature of ibuprofen in [10] and the following values were reported, respectively: 25.5 kJ/mol and 350 K. Fig. 2 shows liquid and solid molar heat capacities of racemic compound of ibuprofen [11]; according to the data, the differential molar heat capacity is calculated as:

$$\Delta C_p = 45.2916 + 0.0712T \qquad (11)$$

Experimental data of solubility of racemic (R/S)(±)-ibuprofen in different solvents at the range of 288–333 K are given in Table 2 [1].

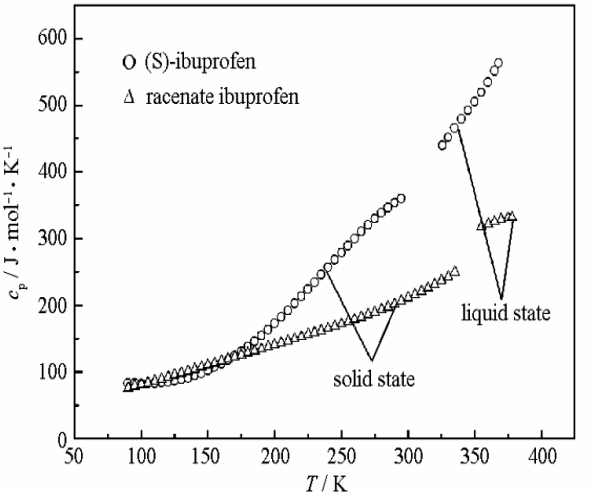

Fig. 2. Heat capacities of racemic (R/S)(±)-ibuprofen [12]

Table 2

Experimental data [1] of solubility (mg/ml) of racemic (R/S)(±)-ibuprofen in different solvents: *n*-heptane, toluene, benzene, and ethanol

Solvent	Temperature, K			
	288	298	313	333
n-Heptane	2.95	3.41	103	745
Toluene	316	448	742	1970
Benzene	361	496	884	1430
Ethanol	500	808	943	1300

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Table 3

Ideal solubility of racemic (R/S)(±)-ibuprofen

T, K	x_2^{ideal} calculated by four different cases			
	A	B	C	D
288	0.1563	0.1857	0.1844	0.1837
298	0.2234	0.2506	0.2494	0.2489
313	0.3656	0.3857	0.3849	0.3847
333	0.6583	0.6647	0.6644	0.6644

3.1. Ideal Solubility of Racemic (R/S)(±)-Ibuprofen

Using thermal properties of racemic (R/S)(±)-ibuprofen and Eqs. (B.1)–(B.4), the ideal solubility of racemic (R/S)(±)-ibuprofen at the temperature range of 288–333 K are calculated and presented in Table 3.

3.2. Correlation of Real Solubility of Racemic (R/S)(±)-Ibuprofen

In spite of extreme importance of ibuprofen crystallization, accurate reproduction methods of solubility data of this drug are scarce. Thermodynamic models can be used to estimate these solubilities, and activity coefficient models have been applied for this purpose in this paper. The NRTL and UNIFAC and some other models offer a practical thermodynamic framework to predict drug solubility in a wide range of solvents, based on a small initial set of measured solubility data.

Details of activity coefficient models are given in Appendix C and here a brief of them is presented. UNIQUAC has two contributions to the excess Gibbs function and the activity coefficient: a combinatorial term accounting for differences in size and shape between the components; and a residual (energetic) term accounting for energy differences between the molecules. The r and q parameters are measures of the molecular volume and area. The only fitted parameters to experimental phase equilibrium data are, in most cases, the energy interactions. The UNIFAC activity coefficient model is separated into two parts: one part provides the contribution due to differences in molecular size and shape (combinational part) and the other one provides the contribution due to molecular interactions (residual part) [8]:

$$\ln g_i = \ln g_i^C + \ln g_i^R \tag{12}$$

n-Heptane has two functional groups, CH_3 and CH_2; toluene has three main functional groups, CH_3, ACH and AC; benzene has only one functional group, ACH and the main functional groups of ethanol are CH_3, CH_2 and OH (A in ACH and AC refer to aromatic carbon, *e.g.*, benzene consists of six ACH groups). 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 literature [12].

Wilson postulated that the ratio of local compositions is related to the overall mole fractions through a Boltzmann type expression [8]:

$$\frac{x_{ij}}{x_{ii}} = \frac{x_j \exp\left(-\frac{l_{ij}}{RT}\right)}{x_i \exp\left(-\frac{l_{ii}}{RT}\right)} \tag{13}$$

Using this relationship, he arrived at expressions for the local 'volume' fractions, which he combined with the Flory-Huggins equation for polymer solutions to develop an expression for the excess Gibbs function.

Renon and Prausnitz modified Wilson's equation for the local mole fractions by introducing the parameter α to account for the non-randomness of liquid solutions [8]:

$$\frac{x_{ij}}{x_{ii}} = \frac{x_j}{x_i} \exp\left(\frac{-a_{ij}(G_{ij} - G_{ii})}{RT}\right) \tag{14}$$

where G_{ij} – residual Gibbs function and a_{ij} – non-randomness parameter. Regular-solution theory **(**Scatchard-Hildebrand theory) assumes that the excess entropy and volume changes are zero during the mixing of components. The regular-solution equations always predict $g_i \geq 1$, *i.e.*, a regular solution can exhibit only positive deviations from Raoult's law.

In order to choose the most appropriate correlative model for solubility of racemic (R/S)(±)-ibuprofen in different solvents, all models are compared by the summation of absolute errors between the experimental and the calculated values.

Tables 4-5 shows absolute errors for all activity models (Regular-solution theory, UNIFAC, UNIQUAC, NRTL, and Wilson models) in different solvents: *n*-heptane, toluene, benzene, and ethanol within the temperature range of 288–333 K.

It is apparent that in all activity coefficient models, case A is better than other cases for racemic ibuprofen. The reported errors in the Tables 4-5 are the absolute deviation between the calculated solubility using calculated and the experimental data:

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$$\% \, error = \sum \left(\left| \frac{x_{2Exp} - x_{2Calc}}{x_{2Exp}} \right| \right) \cdot 100$$

Table 6 shows adjustable parameters of UNIQUAC for case A that were calculated from minimization of the error.

Fig. 3 depicts the comparison between experimental and calculated solubility of racemic (R/S)(±)-ibuprofen in different solvents. UNIQUAC model predictions show the most agreement compared to the other models, in all solvents. Regular-solution theory and Wilson model cannot be considered as a suitable predictive model because in all solvents these models have a large deviation from experimental data. It was found that as the polarity of solvent increases the solubility of racemic compound is also increased:
Solubility: *n*-heptane < toluene < benzene < ethanol
Polarity: *n*-heptane < toluene < benzene < ethanol

In all cases UNIQUAC and NRTL have good agreement with experimental data because of strong theoretical basis. However, Wilson and regular solution cannot describe with accuracy, in broad temperature ranges, the behavior of these molecules. It is apparent that for non-polar components, regular-solution theory is a good candidate. However, regular-solution theory usually provides an easy way for approximation of solubility and activity coefficient by using the bulk properties of solute.

The results of ibuprofen-CO_2 are given in Table 7 and Fig. 4. According to this figure, the experimental solubility increases as the pressure increasing and this trend is also followed by PR EoS. Fig. 4 tells us that PR EoS can predict the solubility of solid using binary interaction parameter, k_{ij}, with good accuracy. The value of k_{ij} is small and positive.

Table 4

Errors of solubility prediction by regular-solution theory, UNIQUAC and UNIFAC

Solvent	Regular-solution				UNIQUAC				UNIFAC			
	Case A	Case B	Case C	Case D	Case A·10^5	Case B·10^5	Case C·10^5	Case D·10^5	Case A	Case B	Case C	Case D
n-Heptane	1.399	1.481	1.478	1.477	5.436	5.508	5.505	5.504	0.319	0.336	0.335	0.335
Benzene	0.597	0.631	0.630	0.630	0.867	1.461	1.433	1.418	1.356	1.430	1.427	1.426
Toluene	0.782	0.826	0.824	0.824	2.043	1.356	1.364	1.370	0.990	1.045	1.043	1.042
Ethanol	$0.31 \cdot 10^{-3}$	$0.32 \cdot 10^{-3}$	$0.32 \cdot 10^{-3}$	$0.32 \cdot 10^{-3}$	8.119	8.781	8.756	8.746	0.754	0.803	0.801	0.800

Table 5

Errors of solubility prediction by Wilson and NRTL models

Solvent	Wilson				NRTL			
	Case A	Case B	Case C	Case D	Case A·10^5	Case B·10^5	Case C·10^5	Case D·10^5
n-Heptane	1.212	1.403	1.429	1.434	7.672	7.780	7.528	7.448
Benzene	0.418	0.514	0.510	0.508	1.048	2.287	2.024	1.918
Toluene	0.510	0.601	0.595	0.589	2.984	2.148	2.309	1.863
Ethanol	0.449	0.604	0.612	0.598	9.572	9.974	9.906	9.648

Table 6

Adjustable parameters of UNIQUAC within the temperature range of 288–333 K

Solvent	r	q	q'	a_{12}	a_{21}
n-Heptane	5.17	4.40	4.40	604.96	-6.60
Benzene	3.92	2.97	2.97	1016.36	-323.81
Toluene	3.19	2.40	2.40	1158.08	-363.27
Ethanol	2.11	1.97	0.92	1382.84	-415.90

Notes: subscript 1 refer to solvents and 2 refer to racemic (R/S)(±)-ibuprofen

Table 7

AAPD of binary ibuprofen-CO_2 system calculated by PR EoS

T, K	AAPD	Pressure range,kPa	Number of data
308	6.12	$(8–22) \cdot 10^3$	15
313	8.04	$(9.5–22) \cdot 10^3$	6
318	4.51	$(8.5–17) \cdot 10^3$	8
Average AAPD	6.23	–	–
Total number of data[1]	–	–	29

Note: [1] experimental data from [2].

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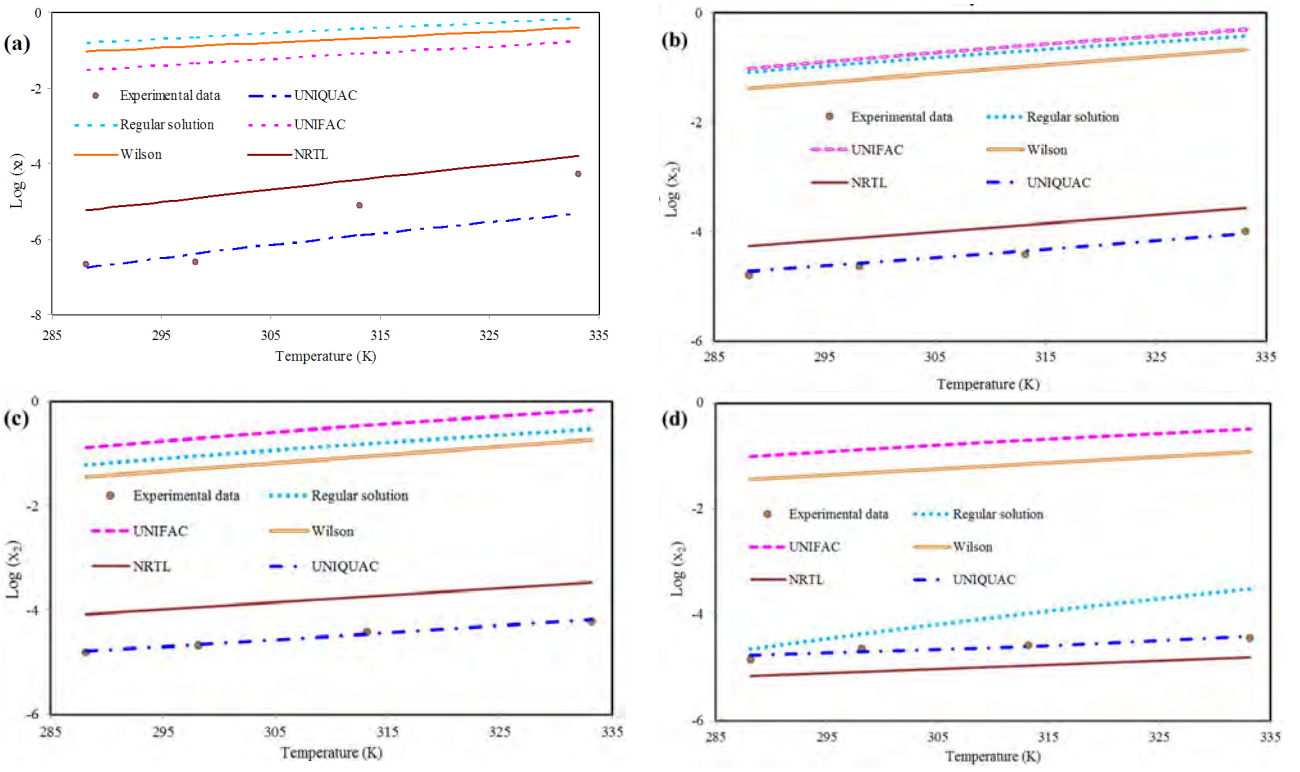

Fig. 3. The comparison between experimental solubility of racemic (R/S)(±)-ibuprofen and theoretical solubility by regular-solution theory, UNIQUAC, UNIFAC, NRTL and Wilson models in *n*-heptane (a); toluene (b); benzene (c) and ethanol (d)

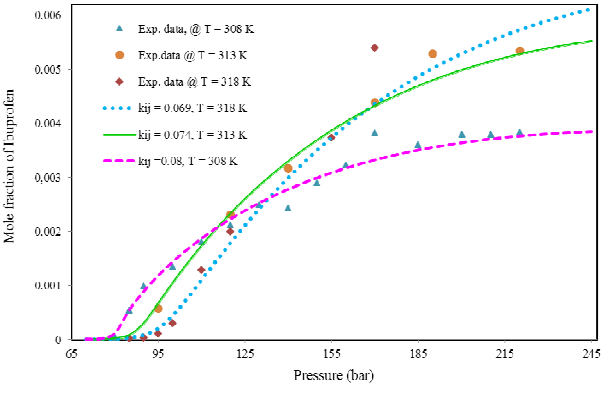

Fig. 4. Solubility of ibuprofen in supercritical carbon dioxide at different temperatures. The results are based on PR EoS. The experimental data are taken from [2]

4. Conclusions

Here, we investigated the applicability of some valuable models for predicting drug solubility in pure solvents. The model yields satisfactory results in first correlating drug solubility in a few representative pure solvents. Ideal solubility of the racemic ibuprofen was calculated by four assumptions in cases A to D. The results show that the $\Delta C_p = 0$ assumption in case A is the most appropriate assumption for the purpose of ibuprofen solubility calculation. Assumption regarding the linear change of ΔC_p with temperature (case D) is better than cases B and C, because prevailing temperature ranges are near the melting point. The UNIQUAC and NRTL activity coefficient models with adjustable parameters are better predictive models than the other models and UNIQUAC had minimum deviation from experimental data. Thus, the model is a useful tool in support of the early stages of crystallization process development and other areas of drug process design. Moreover, PR EoS with van der Waals as mixing rules was used to predict the solubility of ibuprofen-CO_2 binary system in the range of 308–318 K and (8–22)·10^3 kPa. To obtain much better agreement with experimental data, the binary interaction

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parameter was used. The interaction parameter reduced the inaccuracy.

Appendix A

The fugacity ratio is independent of the solvent properties and can be related to the molar Gibbs function changes (ΔG) of the solid. Consequently:

$$\Delta G = RT \ln \frac{f_2^l}{f_2^s} = -RT \ln a_2 \qquad (A.1)$$

The ratio of $\frac{f_2^l}{f_2^s}$ is called activity (a_2) and the molar Gibbs function changes can also be related to the molar enthalpy (ΔH) and entropy (ΔS) changes:

$$\Delta G = \Delta H - T\Delta S, \qquad ln\frac{1}{x_2 g_2} = \frac{\Delta H}{RT} - \frac{\Delta S}{R} \qquad (A.2)$$

where R is the universal gas constant. Since both enthalpy and entropy are state functions (no path functions) they can be evaluated from any thermodynamic path. Using triple point of solid, Prausnitz, Lichtenthalar and Azevedo [8] applied a thermodynamic cycle to evaluate the enthalpy and entropy changes [9].

$$\Delta H = \Delta H_t^{fus} + \int_{T_t}^{T} \Delta C_p dT, \quad \Delta S = \Delta S_t^{fus} + \int_{T_t}^{T} \frac{\Delta C_p}{T} dT,$$

$$\Delta C_p = C_p^l - C_p^s \qquad (A.3)$$

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 triple point temperature, which can be considered as the melting point; C_p^l and C_p^s are the heat capacities of solute in liquid and solid states. Thus:

$$ln\frac{1}{x_2 g_2} = \frac{\Delta H_m^{fus}}{RT} - \frac{\Delta S_m^{fus}}{R} + \\ + \frac{1}{RT}\int_{T_m}^{T} \Delta C_p dT - \frac{1}{R}\int_{T_m}^{T} \frac{\Delta C_p}{T} dT \qquad (A.4)$$

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

$$\Delta H_m^{fus} = T_m \Delta S_m^{fus}$$

and the ideal solubility is:

$$\ln x_2^{ideal} = \frac{\Delta H_m^{fus}}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) - \\ - \frac{1}{RT}\int_{T_m}^{T} \Delta C_p dT + \frac{1}{R}\int_{T_m}^{T} \frac{\Delta C_p}{T} dT \qquad (A.5)$$

Appendix B

Case A. In most chemical engineering applications, the first term of Eq. (A.5) is the dominant one, and the next two terms with two opposite signs tend to cancel each other.

$$\ln x_2^{ideal} = \frac{\Delta H_m^{fus}}{RT_m}(1 - T_r) \qquad (B.1)$$

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

Case B. It is shown in [9] that there is a linear relationship between $\ln x_2$ and $\ln T$ assuming $\Delta C_p \cong \Delta S_m^{fus}$

$$\ln x_2^{ideal} = \frac{-\Delta H_m^{fus}}{RT_m} \ln T_r \qquad (B.2)$$

Using an infinite series of $\ln T_r$ Eqs. (B.1) and (B.2) are identical.

Case C. To estimate the ideal solubility more accurately, Eq. (A.5) can be simplified if the molar heat capacity is assumed to be constant and estimated at the melting point.

$$\ln x_2^{ideal} = \frac{\Delta H_m^{fus}}{RT_m}(1 - T_r) + \frac{\Delta C_p}{R}\bigg|_{T_m} (T_r - 1 - \ln T_r) \qquad (B.3)$$

Case D. If ΔC_p is not constant, Eq. (A.5) has to be integrated with respect to molar heat capacity changes with temperature. In case of linear changes of ΔC_p in temperature for ibuprofen, Eq. (A.5) can be rewritten as:

$$\Delta C_p = b + mT$$

$$\ln x_2^{ideal} = \frac{\Delta H_m^{fus}}{RT_m}(1 - T_r) + \frac{b}{R}(T_r - 1 - \ln T_r) + \\ + \frac{mT_m}{2R}\left(\frac{1}{T_r} + T_r - 2\right) \qquad (B.4)$$

Appendix C

Regular-solution theory shows that for a binary solution of nonpolar molecules, the solute activity coefficient can be expressed by [8]:

$$\ln g_2 = \frac{V_2^l}{RT}(d_2 - d_1)^2 j_1^{*2} \qquad (C.1)$$

where j_1^* is the volume fraction of solvent, defined as:

$$j_1^* = \frac{x_1 V_1^l}{x_1 V_1^l + x_2 V_2^l} \qquad (C.2)$$

where V_i^l and d_i are the molar volume and solubility parameter of components, respectively. Solubility parameters d_i are the function of temperature, but the difference between these solubility parameters ($d_2 - d_1$) is often nearly independent of temperature [8].

The UNIQUAC activity coefficient model is semi-empirical model based on two adjustable parameters [8]:

$$lng_2 = ln\frac{j_2}{x_2} + \frac{Zq_2}{2} ln\frac{q_2}{j_2} + j_1(l_2 - \frac{r_2}{r_1} l_1) - q_2' ln(q_2' +$$

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$$+q_1't_{12})+q_1'q_2'\left(\frac{t_{12}}{q_2'+q_1't_{12}}-\frac{t_{21}}{q_1'+q_2't_{21}}\right) \quad (C.3)$$

$$l_1=\frac{Z}{2}(r_1-q_1)-(r_1-1),\ l_2=\frac{Z}{2}(r_2-q_2)-(r_2-1) \quad (C.4)$$

$$t_{12}=\exp\left(\frac{-a_{12}}{T}\right),\qquad t_{21}=\exp\left(\frac{-a_{21}}{T}\right) \quad (C.5)$$

where the coordination number Z is equal to 10. Segment fraction j, and area fractions, q and $q¢$, are given by:

$$j_1=\frac{r_1x_1}{r_1x_1+r_2x_2},\qquad j_2=\frac{r_2x_2}{r_1x_1+r_2x_2} \quad (C.6)$$

$$q_1=\frac{q_1x_1}{q_1x_1+q_2x_2},\qquad q_1=\frac{q_2x_2}{q_1x_1+q_2x_2} \quad (C.7)$$

$$q_1'=\frac{q_1'x_1}{q_1'x_1+q_2'x_2},\quad q_2'=\frac{q_2'x_2}{q_1'x_1+q_2'x_2} \quad (C.8)$$

Parameters r, q and q' are pure-component molecular-structure constants depending on molecular size and external surface areas. Basically, q' is equal to q, but for alcohols it differs. The values a_{12} and a_{21} are the adjustable parameters of UNIQUAC activity coefficient model. The adjustable parameters can be used in simulation software for predicting other properties of the employed chemicals or for predicting the equilibrium in multi-component systems.

The UNIFAC activity coefficient model is separated into two parts: one part provides the contribution due to differences in molecular size and shape (combinational part), and the other one provides the contribution due to molecular interactions (residual part) [12]:

$$\ln g_i=\ln g_i^C+\ln g_i^R \quad (C.9)$$

$$\ln g_i^C=\ln\frac{j_i}{x_i}+\frac{Z}{2}q_i\ln\frac{q_i}{j_i}+l_i-\frac{j_i}{x_i}\sum_j x_jl_j \quad (C.10)$$

$$\ln g_i^R=q_i\left[1-\ln\left(\sum_j q_jt_{ji}\right)-\sum_j\frac{q_jt_{ij}}{\sum_k q_kt_{kj}}\right] \quad (C.11)$$

For cases that the van der Waals area and volume are not available, the functional group approaches are used:

$$r_i=\sum_k u_k^{(i)}R_k,\qquad q=\sum_k u_k^{(i)}Q_k \quad (C.12)$$

where k is the number of functional groups in the molecule, which is 6 for racemic ibuprofen and $u_k^{(i)}$ is the repeating number of each functional group in the solute or solvent molecule. R_k and Q_k are group volume and area, respectively [12]. The functional groups and group volume and area of racemic ibuprofen are given in Table C.1.

Using this Table and Eq. (C.9), the numerical values of r and q for racemic (R/S)(±)-ibuprofen were calculated equal to 8.43 and 6.60, respectively (A in ACH and AC refer to aromatic carbon).

Table C.1

Functional groups and the group volume and area parameter of racemic ibuprofen

Subgroup	R	Q	Number of groups in the molecular, u
CH_3	0.9011	0.848	3
CH_2	0.6744	0.54	1
CH	0.4469	0.228	2
ACH	0.5313	0.4	4
AC	0.3652	0.12	2
COOH	1.3013	1.224	1

The residual part of the activity coefficient, Eq. (C.11), is replaced by the solution-of-groups concept.

$$\ln g_i^R=\sum_k u_k^{(i)}\left(\ln\Gamma_k-\ln\Gamma_k^{(i)}\right) \quad (C.13)$$

where Γ_k is the group residual activity coefficient and $\Gamma_k^{(i)}$ is the residual activity coefficient of group k in a reference solution containing only molecules of type i.

$$\ln\Gamma_k=Q_i\left[1-\ln\left(\sum_m q_my_{mk}\right)-\sum_m\frac{\sum_n q_my_{km}}{\sum_n q_ny_{nm}}\right] \quad (C.14)$$

where q_m is the area fraction of group m, and the sums are over all different groups. The value q_m is calculated in a manner similar to that for q_i:

$$q_m=\frac{Q_mx_m}{\sum_n Q_nx_n} \quad (C.15)$$

where x_m is the mole fraction of group m in the mixture. The group-interaction parameter y_{mn} is given by:

$$y_{mn}=\exp\left(\frac{-a_{mn}}{T}\right) \quad (C.16)$$

The group interaction parameters a_{mn} must be evaluated from experimental phase equilibrium data. Note that a_{mn} has units of kelvins and $a_{mn}\neq a_{nm}$.

Based on molecular consideration, Wilson obtained the following Eq. for the activity coefficient

$$\ln g_k=1-\ln\left(\sum_i x_il_{ki}\right)-\sum_j\left(\frac{x_jl_{jk}}{\sum_i x_il_{ji}}\right) \quad (C.17)$$

Renon and Prausnitz developed the "Non-Random Two-Liquid" (NRTL) expression for the excess Gibbs function, from which the following equation is obtained for the activity coefficient of component 2 in a binary mixture:

$$\ln g_2=x_1^2\left(t_{12}\left(\frac{G_{12}}{x_3+x_1G_{12}}\right)^2+\frac{G_{21}t_{21}}{(x_1+x_2G_{21})^2}\right) \quad (C.18)$$

$$G_{ij}=\exp(-a_{ij}t_{ij}) \quad (C.19)$$

$$t_{ij}=\frac{G_{ii}-G_{jj}}{RT} \quad (C.20)$$

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Appendix D

In the study, the fugacity coefficient is found using the pressure-explicit PR EoS [13]:

$$P = \frac{RT}{u-b} - \frac{a(T)}{u(u+b)+b(u-b)} \quad (D.1)$$

where u is the molar volume and R is the universal gas constant. The pure component parameters a_i and b_i are given by the following equations [14]:

$$a_i = \left(0.457235\frac{R^2T_{ci}^2}{P_{ci}}\right)\cdot\left[1+m_i\left(1-\sqrt{\frac{T}{T_{ci}}}\right)\right]^2 \quad (D.2)$$

$$b_i = 0.077796\frac{RT_{ci}}{P_{ci}} \quad (D.3)$$

where T_{ci} and P_{ci} are the critical temperature and pressure of component i, respectively; m_i is calaulated in accordance to [15]:

$$m_i = 0.37464 + 1.5422w_i - 0.26992w_i^2 \quad (D.4)$$

where w_i is the acentric factor of component i.

The fugacity coefficient of the solute in supercritical phase is obtained by [14]:

$$\ln\hat{f}_1 = \frac{b_i}{b}(Z-1) - \ln(Z-B) + \\ + \frac{A}{2\sqrt{2}B}\left(\frac{2\sum_{j=1}^{N} y_j\sqrt{a_ia_j}(1-k_{ij})}{a} - \frac{b_i}{b}\right)\ln\left(\frac{Z+(1-\sqrt{2})B}{Z+(1+\sqrt{2})B}\right) \quad (D.5)$$

$$Z^3 + (B-1)Z^2 + (A-2B-3B^2)Z + (B^3+B^2-AB) = 0 \quad (D.6)$$

$$A = \frac{aP}{(RT)^2} \quad (D.7)$$

$$B = \frac{bP}{RT} \quad (D.8)$$

The coefficients a and b for mixtures, are obtained from the following mixing rules [13]:

$$a = \sum_i\sum_j y_iy_j\sqrt{a_ia_j}(1-k_{ij}) \quad (D.9)$$

$$b = \sum_i y_ib_i \quad (D.10)$$

Nomenclature

a_{ij}	binary adjustable parameters of UNIQUAC, K
a_{mn}	group interaction parameters of UNIFAC, K
a	activity
a	attractive term parameter of PR equation of state, Pa·(m^3·mol^{-1})^2
b	repulsive term(co-volume) parameter of PR equation of state, m^3 mol^{-1}
c_p	molar heat capacity, J·mol^{-1}·K^{-1}
f	fugacity, Pa
G	molar Gibbs function, J·mol^{-1}
H	molar enthalpy, J·mol^{-1}
k_{ij}	binary interaction parameter
M_w	molecular weight, g·mol^{-1}
P	pressure, Pa
R	universal gas constant, J·mol^{-1}·K^{-1}
S	solubility, g solute/100 g solvent
T	temperature, K
T_r	ratio of melting temperature to solution temperature
V	molar volume, cm^3·mol^{-1}
x	mole fraction
Z	compressibility factor
z	coordination number

Greek letter

j	segment fraction
j^*	volume fraction of solvent
d	solubility parameter, (J·cm^{-3})$^{0.5}$
Δ	property changes
g	activity coefficient
Γ_k	group residual activity coefficient
q	area fraction
$q¢$	area fraction
u	repeating number of functional group
r	density, g·cm^{-3}
ψ	group interaction parameters of UNIFAC model
φ	fugacity coefficient
ω	acentric factor

Subscript

1	solute
2	solvent
Cal	calculated
Exp	experimental
m	melting point
t	triple point

Superscript

C	combinational
fus	fusion
ideal	ideal state
l	liquid
r	residual
s	solid
sat	saturation

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РОЗЧИННІСТЬ ІБУПРОФЕНУ В ЗВИЧАЙНИХ РОЗЧИННИКАХ І НАДКРИТИЧНОМУ CO_2: ОЦІНКА ІДЕАЛЬНИХ ТА НЕІДЕАЛЬНИХ МОДЕЛЕЙ

Анотація. *Показана можливість розчинення рацемічного (R/S)(±)-ібупрофена у чистих звичайних розчинниках (н-гептані, толуені, бензені та етанолі) і надкритичному діоксиді карбону. Проведено порівняння одержаних результатів із експериментальними даними. Результати ідеальної розчинності показали значне відхилення від експериментальних точок. Показано, що основною проблемою моделювання такої системи є неідеальність рідкої фази. Для вирішення проблеми запропоновано використовувати UNIQUAC, UNIFAC, NRTL, Wilson і теорію регулярних розчинів. Доведено, що UNIQUAC є більш придатною для розрахунку розчинності рацемічного (R/S)(±)-ібупрофена, ніж теорія регулярного розчину та UNIFAC. З використанням рівняння Peng-Robinson (PR EoS) досліджено розчинність (R/S)(±)-ібупрофена у надкритичному CO_2 (SC-CO_2). Встановлено, що результати моделювання добре узгоджуються з експериментальними даними.*

Ключові слова: *ібупрофен, розчинність, надкритичний CO_2, теорія розчину.*

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