

Prediction of Solubility of Racemic (R/S) (\pm)-Ibuprofen in n-Heptane, Toluene, Benzene and Ethanol

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Abstract

The solubility of racemic (R/S) (\pm)-ibuprofen in pure solvents: n-heptane, toluene, benzene and ethanol at range 15°C to 60°C using the regular-solution theory, the UNIFAC model and the UNIQUAC model is predicted and compared with the corresponding experimental values reported in previous study. The results of the ideal solubility show that is negligible in comparison to the molar enthalpy of fusion. There is a good agreement between the experimental solubility data of racemic (R/S) (\pm)-ibuprofen and the results of UNIQUAC model.

Keywords: Racemic (R/S) (\pm)-ibuprofen; Solubility; Activity coefficient; UNIQUAC; UNIFAC; Regular-solution theory

Introduction

A racemic compound of species is indicated as a mixture of two enantiomers by 50:50 ratio, and can exist as a racemic conglomerate, a racemic compound, or a solid solution (pseudoracemate) [1]. The definition in enantiomers, if a plane of polarized light is passed through any enantiomer and the light to the counterclockwise as levorotatory or (-)-enantiomer or R-form; on the contrary, the light to the clockwise as dextrorotatory or (+)-enantiomer or S-form [2]. Opposite enantiomers have identical physical and chemical properties such as molecular weight, solubility, melting point, and they only difference is their three-dimensional spatial arrangement. Racemic compound of ibuprofen, (R/S) (\pm)-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 [3], and it is water insoluble compound. The chemical formula of racemic ibuprofen is C₃H₁₈O₂ and the structure of racemic (R/S) (\pm)-ibuprofen is shown in FIG. 1.

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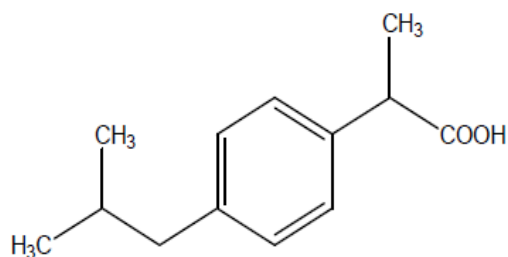


FIG. 1. Structure of racemic (R/S) (±)-ibuprofen [1].

Solubility is the most basic information in a crystallization process. Crystallization process is a key unit operation in the production of pharmaceutical solids and fine chemicals, which has a major effect on drug quality in terms of crystal size distribution. It is evident that the solubility prediction is necessary in solvent selection and control of crystallization processes where the experimental data are scarce. One of the popular methods to predict solubility is based on the activity coefficient evaluation.

In the present study, four assumption applied for the ideal solubility of racemic ibuprofen are investigated; the solubility of racemic (R/S) (±)-ibuprofen in n-heptane, toluene, benzene and ethanol is predicted using the different models (regular-solution theory, the UNIFAC and the UNIQUAC model) and then compared with the corresponding experimental data reported in thesis [1].

Experimental Theory

At equilibrium [4]:

$$f_2^s = f_2^{sat} \quad (1)$$

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 temperature T and p^{sat} as the standard state for activity coefficient (γ_2) and assuming no solubility of solvent in solid

f_2^{sat} can be written:

$$f_2^{sat} = x_2 \gamma_2 f_2^l \quad (2)$$

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. Thus,

$$\frac{f_2^l}{f_2^s} = \frac{1}{x_2 \gamma_2} \quad (3)$$

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

$$\Delta g = RT \ln \frac{f_2^l}{f_2^s} = -RT \ln a_2 \quad (4)$$

The ratio of $\frac{f_2^s}{f_2^l}$ is called activity (a_2) and the molar Gibbs energy changes can also be related to the molar enthalpy (Δh) and entropy (Δs) changes.

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

$$\ln \frac{1}{x_2 \gamma_2} = \frac{\Delta h}{RT} - \frac{\Delta s}{R} \quad (5)$$

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 et al. [4] applied a thermodynamic cycle to evaluate the enthalpy and entropy changes [5].

$$\Delta h = \Delta h_t^{fus} + \int_{T_t}^T \Delta c_p dT$$

$$\Delta s = \Delta s_t^{fus} + \int_{T_t}^T \frac{\Delta c_p}{T} dT$$

$$\Delta c_p = c_p^l - c_p^s \quad (6)$$

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 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,

$$\ln \frac{1}{x_2 \gamma_2} = \frac{\Delta h_m^{fus}}{RT} - \frac{\Delta s_m^{fus}}{R} + \frac{1}{RT} \int_{T_m}^T \Delta c_p dT - \frac{1}{R} \int_{T_m}^T \frac{\Delta c_p}{T} dT \quad (7)$$

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

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

thus:

$$\ln x_2^{ideal} = \frac{\Delta h_m^{fus}}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) - \frac{1}{RT} \int_{T_m}^T \Delta c_p dT + \frac{1}{R} \int_{T_m}^T \frac{\Delta c_p}{T} dT \quad (8)$$

The measured solubility is often in terms of g of solute per 100 g of solvent (shown by S). To convert the solubility in terms of mole fraction (x_2) to this unit, we have to use the following equations:

$$S = \frac{x M_w^{solute}}{M_w^{solvent}} \times 100 \quad x_2 = \frac{x}{x+1} \quad (9)$$

M_w is the molecular weight, g/mole. The ideal and experimental mole fractions are related by:

$$x_2 = \frac{x_2^{ideal}}{\gamma_2} \quad (10)$$

Prediction of the actual solubility requires the actual activity coefficient of the solute in the solution, γ_2 , which should be calculated from the thermodynamic models.

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 [5]:

$$\ln x_2^{ideal} = \frac{\Delta H_m^{fus}}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) - \frac{1}{RT} \int_{T_m}^T \Delta C_p dT + \frac{1}{R} \int_{T_m}^T \frac{\Delta C_p}{T} dT \quad (11)$$

Eqn. (11) 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 eqn. (11) to estimate the ideal solubility.

Case A: In most chemical engineering applications, the first term of the right-hand side of eqn. (11) is the dominant one, and the next two terms with two opposite signs tend to cancel each other.

$$\ln x_2^{ideal} = \frac{\Delta H_m^{fus}}{RT_m} \left(1 - \frac{1}{T_r} \right) \quad (12)$$

Where T_r is the ratio of melting temperature to solution temperature $\left(\frac{T_m}{T} \right)$.

Case B: Assumption $\Delta C_p = 0$ is a good approximation to solve eqn. (11).

$$\ln x_2^{ideal} = \frac{-\Delta H_m^{fus}}{RT_m} \ln T_r \quad (13)$$

Eqn. (13) has been applied to pharmaceuticals [5] and has resulted in better approximations.

Case C: To estimate the ideal solubility more accurately, eqn. (11) can be simplified if the differential molar heat capacity is assumed to be constant and estimated at the melting point.

$$\ln x_2^{ideal} = \frac{\Delta H_m^{fus}}{RT_m} (1 - T_r) + \frac{\Delta C_p}{R} \Big|_{T_m} (T_r - 1 - \ln T_r) \quad (14)$$

Case D: If ΔC_p is not constant, eqn. (11) has to be integrated with respect to differential molar heat capacity changes. In case of linear changes ΔC_p in temperature for ibuprofen, eqn. (11) can be rewritten as:

$$\Delta C_p = b + mT$$

$$\ln x_2^{ideal} = \frac{\Delta H_m^{fus}}{RT_m} (1 - T_r) + \frac{b}{R} (T_r - 1 - \ln T_r) + \frac{mT_m}{2R} \left(\frac{1}{T_r} + T_r - 2 \right) \quad (15)$$

Results and Discussion

Thermodynamic models (Hildebrand, the UNIFAC and the UNIQUAC models) were used to predict the activity coefficient and solubility of racemic ibuprofen in different pure solvents: n-heptane, toluene, benzene and ethanol. 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) or group contribution of the solute and solvent (UNIFAC), and the semi-empirical models (UNIQUAC) need experimental data to estimate adjustable parameters to predict the activity coefficient.

The optimization procedure was based on the minimization of the error between the calculated and experimental values of the activity coefficients:

$$\text{Min Error} = \sum (\gamma_{2Exp.} - \gamma_{2Calc.})^2 \quad (16)$$

Where $\gamma_{2Exp.}$ and $\gamma_{2Calc.}$ are the experimental and calculated activity coefficients of racemic (R/S) (\pm)-ibuprofen, respectively. To predict the mole fraction of solute in the solvent, an iterative procedure was performed:

1. Calculate the ideal mole fractions from eqns. (12-15) at temperatures that the solubility of solids is available.
2. Calculate the experimental activity coefficient from eqn. (10).
3. Calculate the corresponding activity coefficient from the thermodynamic models (Hildebrand, the UNIFAC and the UNIQUAC models).
4. Write a regression program in Excel that program changes the adjustable parameters of the UNIQUAC model to minimize the error in eqn. (16).

In order to predict of activity coefficient, the thermal properties of racemic (R/S) (\pm)-ibuprofen are needed. A scanning calorimeter method was used to measure the heat of fusion and melting temperature [1]. So, the values heat of fusion and melting temperature of racemic ibuprofen are 25.5 kJ/mol and 77°C, respectively [6]. FIG. 2 shows liquid and solid molar heat capacities of racemic compound of ibuprofen [7]; according to the data, the differential molar heat capacity is calculated:

$$\Delta c_p = 45.2916 + 0.0712T \quad (17)$$

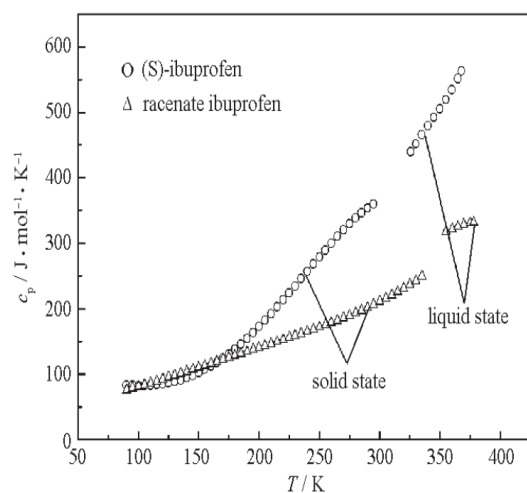
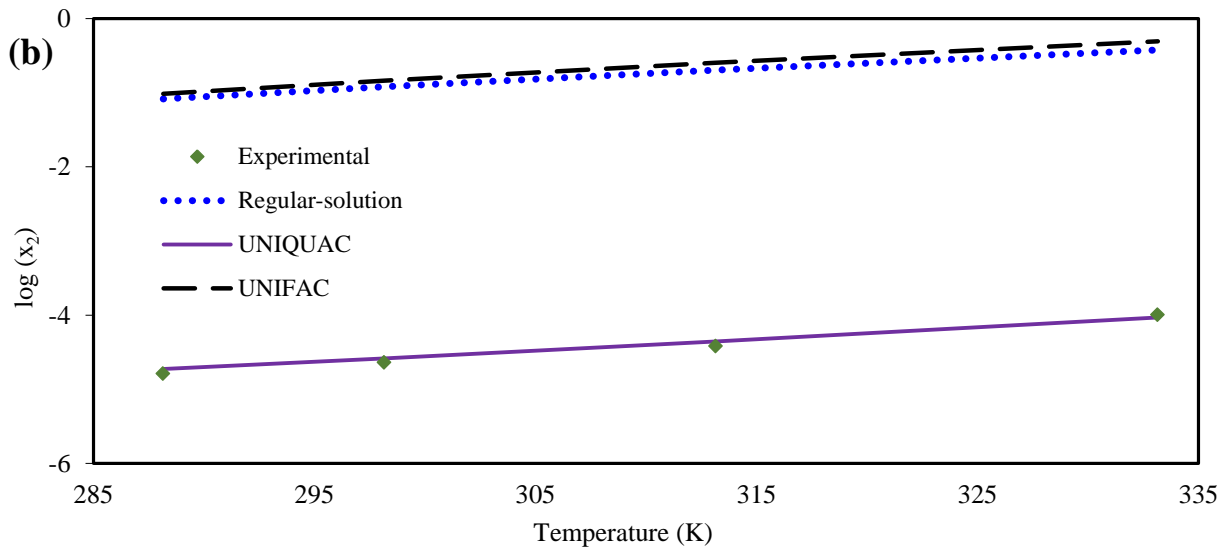
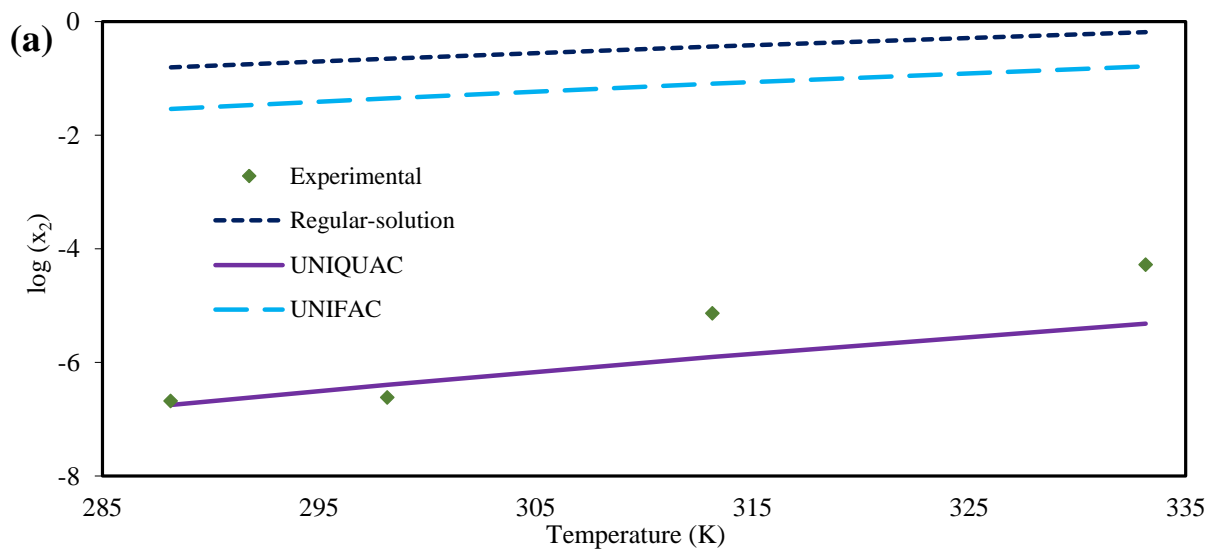


FIG. 2. The heat capacities of racemic ibuprofen [7].



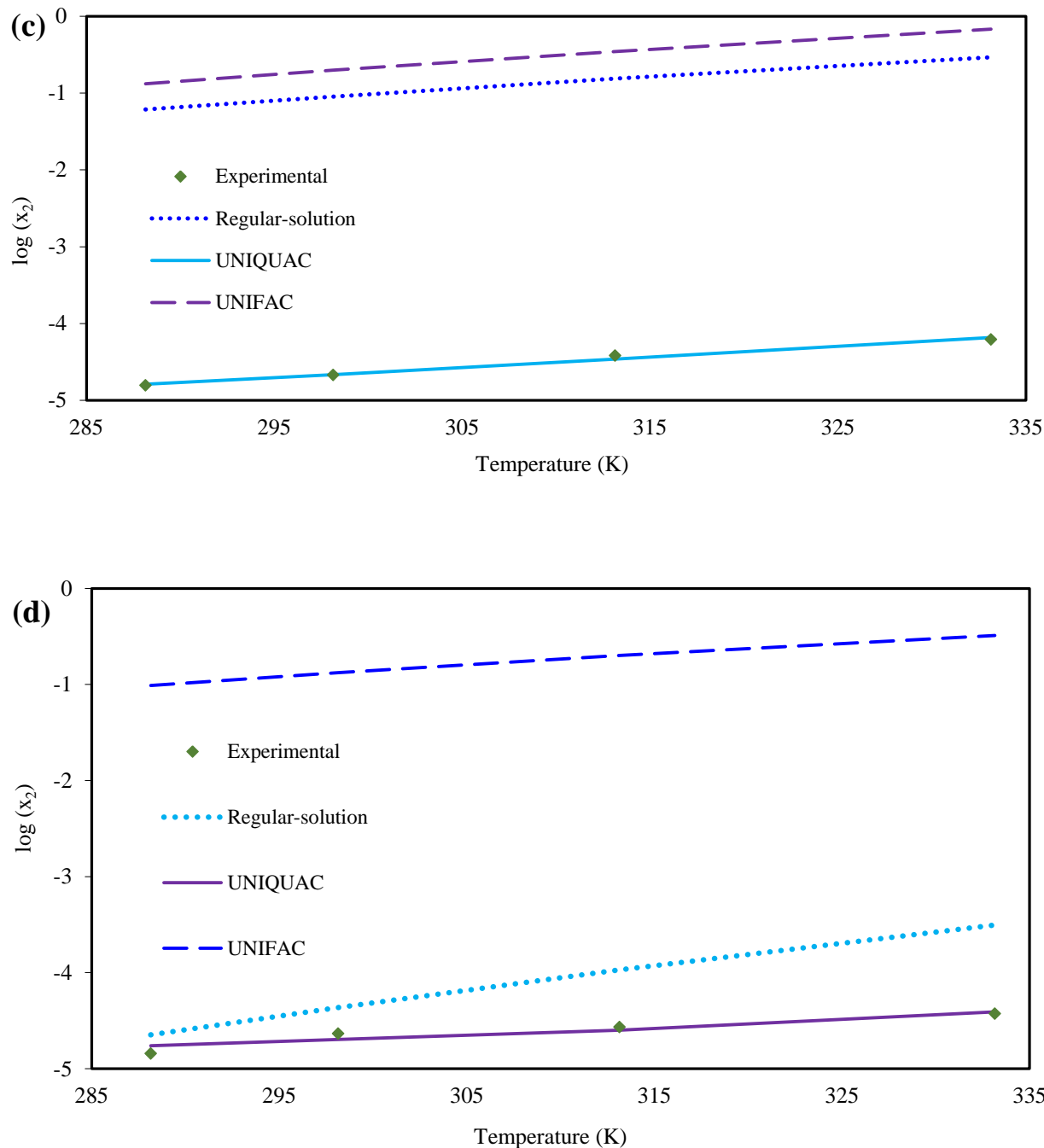


FIG. 3. The comparison between experimental solubility of racemic (R/S) (±)-ibuprofen and theoretical solubility by using the regular-solution theory, UNIQUAC and UNIFAC models in (a) n-heptane (b) toluene (c) benzene (d) ethanol.

Experimental data of solubility of racemic (R/S) (±)-ibuprofen in different solvents at the range of 15°C to 60°C are illustrated in TABLE 1 [1].

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

Solvent	Temperature ($^{\circ}\text{C}$)			
	15	25	40	60
n-Heptane	2.95	3.41	103	745
Toluene	316	448	742	1970
Benzene	361	496	884	1430
Ethanol	500	808	943	1300

Ideal solubility of racemic (R/S) (\pm)-ibuprofen

Using thermal properties of racemic (R/S) (\pm)-ibuprofen and eqns. (12-15), the ideal solubility of racemic (R/S) (\pm)-ibuprofen at temperature range are obtained in TABLE 2.

TABLE 2. **Ideal solubility of racemic (R/S) (\pm)-ibuprofen.**

T ($^{\circ}\text{C}$)	x_2^{ideal} from cases			
	A	B	C	D
15	0.1563	0.1857	0.1844	0.1837
25	0.2234	0.2506	0.2494	0.2489
40	0.3656	0.3857	0.3849	0.3847
60	0.6583	0.6647	0.6644	0.6644

Prediction of real solubility of racemic (R/S) (\pm)-ibuprofen

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 $\gamma_i \geq 1$; i.e., a regular solution can exhibit only positive deviations from Raoult's law. Regular-solution theory shows that for a binary solution of nonpolar molecules, the solute activity coefficient can be expressed by:

$$\ln \gamma_2 = \frac{v_2^l}{RT} (\delta_2 - \delta_1)^2 \phi_1^{*2} \quad (18)$$

Where ϕ_1^* is a volume fraction of solvent, defined by:

$$\phi_1^* = \frac{x_1 v_1^l}{x_1 v_1^l + x_2 v_2^l} \quad (19)$$

V_i^l and δ_i are the molar volume and solubility parameter of components, respectively. Solubility parameter δ_i are function of temperature, but the difference between these solubility parameters, $\delta_2 - \delta_1$, is often nearly independent of temperature [4]. The molar volume of racemic (R/S) (\pm) -ibuprofen is $185.8378 \text{ cm}^3 \text{ mol}^{-1}$, which is calculated from $V_2^l = \frac{MW_{solute}}{\rho_2}$ using $M_{wsolute} = 206.28 \text{ g/mol}$ and $\rho_2 = 1.11 \frac{\text{g}}{\text{cm}^3}$ [1]. The solubility parameter of racemic ibuprofen, $16.44 (\text{J cm}^{-3})^{0.5}$ [8].

The UNIQUAC activity coefficient model is semi-empirical model based on two adjustable parameters [4]:

$$\ln \gamma_2 = \ln \frac{\varphi_2}{x_2} + \frac{zq_2}{2} \ln \frac{\theta_2}{\varphi_2} + \varphi_1 \left(l_2 - \frac{r_2}{r_1} l_1 \right) - q_2' \ln(\theta_2' + \theta_1' \tau_{12}) + \theta_1' q_2' \left(\frac{\tau_{12}}{\theta_2' + \theta_1' \tau_{12}} - \frac{\tau_{21}}{\theta_1' + \theta_2' \tau_{21}} \right) \quad (20)$$

where

$$l_1 = \frac{z}{2} (r_1 - q_1) - (r_1 - 1) \quad , \quad l_2 = \frac{z}{2} (r_2 - q_2) - (r_2 - 1) \quad (21)$$

$$\tau_{12} = \exp\left(\frac{-a_{12}}{T}\right) \quad , \quad \tau_{21} = \exp\left(\frac{-a_{21}}{T}\right) \quad (22)$$

where the coordination number Z is set to equal 10. Segment fraction, φ , and area fractions, θ , and θ^l , are given by

$$\varphi_1 = \frac{r_1 x_1}{r_1 x_1 + r_2 x_2} \quad , \quad \varphi_2 = \frac{r_2 x_2}{r_1 x_1 + r_2 x_2} \quad (23)$$

$$\theta_1 = \frac{q_1 x_1}{q_1 x_1 + q_2 x_2} \quad , \quad \theta_2 = \frac{q_2 x_2}{q_1 x_1 + q_2 x_2} \quad (24)$$

$$\theta_1^l = \frac{q_1^l x_1}{q_1^l x_1 + q_2^l x_2} \quad , \quad \theta_2^l = \frac{q_2^l x_2}{q_1^l x_1 + q_2^l x_2} \quad (25)$$

Parameter r , q and q^l are pure-component molecular-structure constants depending on molecular size and external surface areas. Basically, q^l is equal to q , but for alcohols it differs. 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 provides the contribution due to molecular interactions (residual part) [9]:

$$\ln \gamma_i = \ln \gamma_i^c + \ln \gamma_i^R \quad (26)$$

where

$$\ln \gamma_i^c = \ln \frac{\varphi_i}{x_i} + \frac{z}{2} q_i \ln \frac{\theta_i}{\varphi_i} + l_i - \frac{\varphi_i}{x_i} \sum_j x_j l_j \quad (27)$$

$$\ln \gamma_i^R = q_i \left[1 - \ln \left(\sum_j \theta_j \tau_{ji} \right) - \sum_j \frac{\theta_j \tau_{ij}}{\sum_k \theta_k \tau_{kj}} \right] \quad (28)$$

For cases that the van der Waals area and volume are not available, the functional group approach is used.

$$r_i = \sum_k v_k^{(i)} R_k \quad , \quad q = \sum_k v_k^{(i)} Q_k \quad (29)$$

Where k is the number of functional groups in the molecule, which is 6 for racemic ibuprofen and $v_k^{(i)}$ is the repeating number of each functional group in the solute or solvent molecule. R_k and Q_k are group volume and area [9]. The functional groups and group volume and area of racemic ibuprofen are given in TABLE 3.

TABLE 3. Functional groups and the group volume and area parameter of racemic ibuprofen.

	R	Q	Number of groups in the molecular (v)
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

Using this table and eqn. (26), the numerical values of r and q for racemic (R/S) (\pm)-ibuprofen were calculated equal to 8.429 and 6.604, respectively.

n-heptane has two functional groups, CH₃ and CH₂; toluene has three main functional groups, CH₃, ACH and AC; benzene has only one functional group, ACH; finally, main functional groups of ethanol are CH₃, CH₂ and OH. 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 literatures [9].

The residual part of the activity coefficient, eqn. (28), is replaced by the solution-of-groups concept.

$$\ln \gamma_i^R = \sum_k v_k^{(i)} \left(\ln \Gamma_k - \ln \Gamma_k^{(i)} \right) \quad (30)$$

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 .

$$\ln \Gamma_k = Q_i \left[1 - \ln \left(\sum_m \theta_m \psi_{mk} \right) - \sum_m \frac{\sum_n \theta_n \psi_{kn}}{\sum_n \theta_n \psi_{mm}} \right] \quad (31)$$

θ_m is the area fraction of group m , and the sums are over all different groups. θ_m is calculated in a manner similar to that for θ_i :

$$\theta_m = \frac{Q_m X_m}{\sum_n Q_n X_n} \quad (32)$$

Where X_m is the mole fraction of group m in the mixture. The group-interaction parameter ψ_{mn} is given by:

$$\psi_{mn} = \exp\left(\frac{-a_{mn}}{T}\right) \quad (33)$$

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

In order to choose the best predictive model for ideal solubility of racemic (R/S) (\pm)-ibuprofen in different solvents, all models are compared by the summation of absolute errors between the experimental and the calculated solubility using regular-solution theory, UNIFAC and UNIQUAC models (in mole fraction) defined by:

$$|error| = \sum |x_{2,exp} - x_{2,cal}| \quad (34)$$

TABLE 4 is obtained absolute errors for all activity models (Regular-solution theory, UNIFAC and UNIQUAC models) in different pure solvents: n-heptane, toluene, benzene and ethanol at temperature range 15°C to 60°C.

TABLE 4. Comparison of errors due to solubility prediction of regular-solution theory, UNIQUAC and UNIFAC.

Solvent	Regular-solution				UNIQUAC				UNIFAC			
	Case A	Case B	Case C	Case D	Case A $\times 10^5$	Case B $\times 10^5$	Case C $\times 10^5$	Case D $\times 10^5$	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	0.31×10^{-3}	0.32×10^{-3}	0.32×10^{-3}	0.32×10^{-3}	8.119	8.781	8.756	8.746	0.754	0.803	0.801	0.800

It is apparent that in all activity coefficient models, case A is better than other cases for racemic ibuprofen. So, ideal solubility of racemic ibuprofen is calculated by case A.

TABLE 5 shows adjustable parameters of UNIQUAC for case A that were calculated from minimization the error in eqn. 16. The reported errors in this table are the absolute deviation between the calculated solubility using UNIQUAC and the experimental data:

$$\%error = average \sum \left(\frac{|x_{2,exp} - x_{2,cal}|}{x_{2,exp}} \right) \times 100 \quad (35)$$

TABLE 5. Adjustable parameters of UNIQUAC; subscript 1 refer to solvents and 2 refer to racemic (R/S) (\pm)-ibuprofen.

Solvent	T range (°C)	<i>r</i>	<i>q</i>	<i>q'</i>	<i>a</i> ₁₂	<i>a</i> ₂₁	%error
n-Heptane	15-60	5.17	4.40	4.40	604.96	-6.60	63.82
Toluene	15-60	3.92	2.97	2.97	1016.36	-323.81	13.15
Benzene	15-60	3.19	2.40	2.40	1158.08	-363.27	5.22
Ethanol	15-60	2.11	1.97	0.92	1382.84	-415.90	11.28

FIG. 3 depicts the comparison between experimental and calculated solubility of racemic (R/S) (\pm)-ibuprofen in different pure solvents: n-heptane, toluene, benzene and ethanol, respectively.

UNIQUAC model have best prediction compared with the regular-solution theory and UNIFAC model, in all solvents. Regular-solution theory cannot be considered as a suitable predictive model; in all solvents this model has a large error except Ethanol solution. It is apparent that for non-polar binary mixtures, regular-solution theory is good model. However, regular-solution theory usually provides an easy way for approximation of solubility and activity coefficient by using the bulk properties of solute. It was found that as the polarity of solvent increases the solubility of racemic compound of ibuprofen also increases:

Solubility: n-heptane<toluene<benzene<ethanol

Polarity: n-heptane<toluene<benzene<ethanol

Conclusion

Ideal solubility of the racemic ibuprofen was calculated using four cases. The results show that the $\Delta c_p = 0$ assumption in case A is best assumption for estimation racemic ibuprofen solubility and activity coefficient. Assuming linear changes Δc_p with temperature (case D) in better estimation that cases B and C, because working temperature range are near the melting point. The UNIQUAC activity coefficient model with adjustable parameters is a better predictive model than the other models (regular-solution theory, UNIFAC).

Symbols	
a_{ij}	Binary adjustable parameters of UNIQUAC model (k) [-----]
a_{mn}	Group interaction parameters of UNIFAC model (k) [-----]
a	Activity [-----]
c_p	Molar heat capacity [$\text{J mol}^{-1} \text{K}^{-1}$]
f	Fugacity [bar]
g	Molar gibbs energy [J mol^{-1}]
h	Molar enthalpy [J mol^{-1}]
M_w	Molecular weight [g mol^{-1}]
P	Pressure [bar]
R	Universal gas constant [$\text{J mol}^{-1} \text{K}^{-1}$]
S	Solubility [g solute/100 g solvent]
s	Molar entropy [$\text{J mol}^{-1} \text{K}^{-1}$]
T	Temperature [K]
T_r	Ratio of melting temperature to solution temperature [-----]
V	Molar volume [$\text{cm}^3 \text{mol}^{-1}$]
x	Mole fraction [-----]
z	Coordination number [-----]

Greek Letters	
φ	Segment fraction [-----]
φ^*	Volume fraction [-----]
δ	Solubility parameter [J cm^{-3}] ^{0.5}
Δ	Property changes [-----]
γ	Activity coefficient [-----]
Γ_k	Group residual activity coefficient [-----]
θ	Area fraction [-----]
θ'	Area fraction [-----]
v	Repeating number of functional group [-----]
ρ	Density [g cm^{-3}]
ψ	Group interaction parameters of UNIFAC model [-----]

Subscripts	
1	Solute
2	Solvent
cal	Calculated
exp	Experimental
m	Melting point
t	Triple point

Superscripts	
C	Combinational
fus	Fusion
ideal	Ideal state
l	Liquid
R	Residual
s	Solid
sat	Saturation

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