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Ternary diagram: alpha-(3-benzoylphenyl)-propionic acid (ketoprofen) in acetone–water mixtures at different temperatures. Experimental data and predicted results

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Abstract

Experimental data are determined for a ternary system, ketoprofen–acetone–water, at various temperatures and atmospheric pressure. Specific procedures are applied. The diagram exhibits five regions: one homogeneous, three two-phase (two liquid–solid and one liquid–liquid equilibria) and one three-phase zones.

The variation of the solubility of ketoprofen in acetone–water mixtures is interpreted by analysing the molecular forces induced in the solution according to the acetone mass ratio in the mixture.

The validity of semi-empirical models is tested for liquid–solid and liquid–liquid equilibria by comparing the calculated values with the experimental ones. The agreement depends on the precision of the estimated parameters used for calculations.

Keywords: Multicomponent; Phase equilibria; Experimental data; Polar interactions; UNIQUAC model

1. Introduction

Liquid–solid equilibria (LSE) and liquid–liquid equilibria (LLE) data are needed in design of crystallization processes. For specific industrial problems, these data are rarely found in literature and must be most of time determined experimentally.

This study deals with a crystallization process in which a pharmaceutical drug, ketoprofen called "Ke" in this work, dissolved in acetone is precipitated out by adding water, acting as an anti solvent, to the solution. The aims of this article are to present experimental equilibria data for the system acetone–water–drug and to examine the validity of the semi-empirical models UNIQUAC for predictions of LLE and LSE, at several temperatures.

2. Experimental

2.1. Materials

The pharmaceutical drug is a well-known antiinflammatory agent under generic name of ketoprofen. It is racemic α -(3-benzoylphenyl)-propionic acid (\pm). It is made up of three groups: a phenyl group ($-\text{C}_6\text{H}_5$), a benzoyl group ($-\text{C}_6\text{H}_4-\text{CO}$) and an acetic chain ($-\text{CH}-\text{COOH}$). It is provided by Rhône-Poulenc Rorer Company.

Bidistilled water is used and synthesis grade acetone, with a minimum purity of 99.7%, is purchased from Société de Distribution de Service et de Recherche.

2.2. Procedure and techniques

Preliminary experiments were carried out, with binary systems (ketoprofen–acetone on the one hand and ketoprofen–water on the other hand), and with the ternary system (ketoprofen–acetone–water), in order to roughly position the different zones of the ternary diagram. These preliminary experiments allowed to set up the experimental techniques. Then, more precise measurements were achieved.

The solubility of ketoprofen in acetone was determined according to an usual procedure (Mullin, 1972) consisting in dissolving periodically small amounts of ketoprofen in acetone contained in a 25 ml stirred vessel maintained at a constant temperature ($T \pm 0.1$ °C). When ketoprofen does not seem to dissolve any more, the suspension is still stirred for a few days more, during which the evolution of the concentration of ketoprofen in acetone is measured. The equilibrium is considered reached when the concentration remains constant. As the experiments proceed, loss of acetone due to evaporation is avoided by condensing the vapor. Sampling of the solution for the measurement of the concentration of ketoprofen in acetone requires stopping the stirring of the suspension for one hour and taking 1–3 ml from the solution with a syringe. The sample is then filtered through a $0.45 \mu\text{m}$ porosity membrane and weighed at room temperature. The concentration of ketoprofen is obtained by weighing the dry solid after complete evaporation of the solvent.

The solubility of ketoprofen in water is determined according to the same experimental procedure as that described above. The concentrations of ketoprofen in water are measured by using a high performance liquid chromatograph (HPLC). The maximum relative deviation between all the data has been evaluated to 12% at 30 °C. This maximum can be explained by the difference between the solution temperature (30 °C) and the room temperature (about 20–25 °C) which can induce crystallization of the drug during sampling. However it can be noted that absolute deviations are only a few hundreds of ppm concentrations.

According to the number of the existing phases of the ternary system ketoprofen–acetone–water, three experimental procedures have been used. The first one is the dissolution procedure previously described for liquid–solid equilibria. The second one is a settling procedure for liquid–liquid equilibria. An acetone–water–ketoprofen mixture of about 100 ml, is stirred continuously for one hour in a reactor at a constant temperature controlled by less than ± 0.1 °C. After one hour agitation, this mixture is poured into a thermostated settling flask. After twenty four hours settling, the liquid aqueous and organic phases are separated and stored. The concentrations of ketoprofen and water are determined respectively by weighing the dry extract and by measuring out with a Karl Fisher titrator.

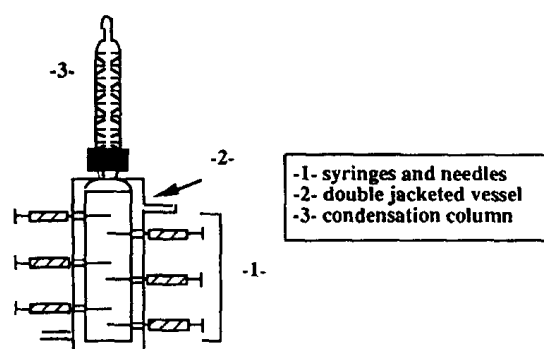


Fig. 1. Schematical representation of the reactor used to establish liquid-liquid-solid equilibrium.

The third procedure used is a specific procedure for liquid-liquid-solid equilibria. An acetone-water-ketoprofen mixture, of about 100 ml is also continuously stirred for one hour in a particular reactor at constant temperature. The system is allowed to separate and settle in this reactor whose a schematical representation is shown in Fig. 1. The reactor is a small double jacketed glass vessel with facilities for sampling a few ml of the solution with syringes at various levels. So, syringes permit to take simultaneously samples of the two liquid phases without disturbing the equilibrium.

3. Results

The nature of the observed phases depends on the mass ratio of acetone in acetone-water mixtures (R_a).

For weight fractions of acetone in the acetone-water mixtures, R_a , ranging approximately between 0 and 0.35, and between 0.70 and 1, a liquid-solid equilibrium is found. A liquid-liquid equilibrium is reached for values of R_a between 0.35 and 0.70 and a liquid-liquid-solid equilibria are obtained in the same range of R_a ($0.35 < R_a < 0.70$).

3.1. Binary systems

Solubilities of ketoprofen in acetone and in pure water, at atmospheric pressure, are presented in Table 1. The range of temperatures corresponds to that used in the crystallization process studied. The upper limit is fixed by the boiling point of acetone (56 °C). Deviations on the concentration of the

Table 1
Solubility of ketoprofen in pure acetone and in pure water solutions

Temperature (°C)	Solvent: acetone W_{ke}^* (kg ketoprofen/kg solution)	Solvent: water $W_{ke}^* \cdot 10^6$ (kg ketoprofen/kg solution)
9.8	0.360 ± 0.003	86 ± 3
19.8	0.431 ± 0.007	
20.1		124 ± 1
29.9	0.513 ± 0.005	
30.0		225 ± 27
41.1	0.613 ± 0.005	
49.3	0.677 ± 0.006	

Table 2
Solubility of ketoprofen in acetone–water mixture at 20.2 °C

(a) Experimental liquid–solid equilibrium at 20.15 ± 0.15 °C				
W_{Ke}^* (kg ketoprofen/ kg solution)	R_a (kg acetone/ kg acetone– water mixture)			
$151.5 \times 10^{-6} \pm 1.5 \times 10^{-6}$	0.016			
$177 \times 10^{-6} \pm 8 \times 10^{-6}$	0.024			
$337 \times 10^{-6} \pm 12 \times 10^{-6}$	0.072			
$1\ 410.5 \times 10^{-6} \pm 72 \times 10^{-6}$	0.163			
0.498	0.755			
0.517	0.786			
0.529	0.868			
0.502	0.910			
0.510	0.941			
0.487	0.961			
(b) Experimental liquid–liquid–solid equilibrium at 20.0 ± 0.1 °C				
W_{Ke}^{*aq} (kg ketoprofen/ kg solution)	R_a^{aq} (kg acetone/ kg acetone– water mixture)	W_{Ke}^{*org} (kg ketoprofen/ kg solution)	R_a^{org} (kg acetone/ kg acetone– water mixture)	
0.021	0.243	0.482	0.672	
(c) Binodal compositions of the experimental liquid–liquid equilibrium at 20.6 ± 0.3 °C				
T (°C)	W_{Ke}^{*aq} (kg ketoprofen/ kg solution)	R_a^{aq} (kg acetone/ kg acetone– water mixture)	W_{Ke}^{*org} (kg ketoprofen/ kg solution)	R_a^{org} (kg acetone/ kg acetone– water mixture)
20.0	0.058 ± 0.0004	0.399	0.358 ± 0.002	0.649
20.9	0.087 ± 0.001	0.438	0.305 ± 0.004	0.626
20.7	0.098 ± 0.001	0.458	0.287 ± 0.004	0.600
20.6	0.118 ± 0.0003	0.475	0.276 ± 0.0008	0.610

solid in solution are also given in Table 1. The results show a high solubility of ketoprofen in acetone, and a very low solubility (a few hundreds of ppm) of ketoprofen in pure water. In both cases, the solubilities obtained increase with increasing temperature.

3.2. Ternary system

Tables 2–5 report all the experimental data with their absolute deviation, in ternary mixtures at several temperatures (10.1 ± 0.1 °C, 20.2 ± 0.2 °C, 30.2 ± 0.2 °C and 48.9 ± 0.1 °C).

Table 3
Solubility of ketoprofen in acetone–water mixture at 10.1 °C

(a)			
Experimental liquid–solid equilibrium at 10.15 ± 0.15 °C			
W_{Ke}^* (kg ketoprofen/ kg solution)	R_a (kg acetone/ kg acetone– water mixture)		
$105 \times 10^{-6} \pm 3 \times 10^{-6}$	0.023		
$199 \times 10^{-6} \pm 6 \times 10^{-6}$	0.072		
$623 \times 10^{-6} \pm 31 \times 10^{-6}$	0.151		
$2\,182 \times 10^{-6}$	0.219		
0.410	0.727		
0.427	0.773		
0.444	0.811		
0.447	0.888		
0.423	0.906		
0.447	0.960		
0.416	0.967		
(b)			
Experimental liquid–liquid–solid equilibrium at 10.1 ± 0.1 °C			
W_{Ke}^{*aq} (kg ketoprofen/ kg solution)	R_a^{aq} (kg acetone/ kg acetone– water mixture)	W_{Ke}^{*org} (kg ketoprofen/ kg solution)	R_a^{org} (kg acetone/ kg acetone– water mixture)
0.073	0.462	0.269	0.606
(c)			
Binodal compositions of the experimental liquid–liquid equilibrium at 10.0 ± 0.1 °C			
W_{Ke}^{*aq} (kg ketoprofen/ kg solution)	R_a^{aq} (kg acetone/ kg acetone– water mixture)	W_{Ke}^{*org} (kg ketoprofen/ kg solution)	R_a^{org} (kg acetone/ kg acetone– water mixture)
0.089 ± 0.00001	0.474	0.304 ± 0.00006	0.657

Table 2 shows that the solubility of the drug at 20.2 °C slightly increases with the weight fraction of acetone for $R_a < 0.24$. The increase becomes more abrupt as R_a increases, up to a liquid–liquid phase splitting ($R_a = 0.24$). The solubility reaches a maximum for a value of R_a in the interval contained between 0.90 and 0.95 kg acetone kg⁻¹ acetone–water mixture. All these results are plotted in the ternary diagram illustrated in Fig. 2 at 20.2 °C. So, in acetone–water mixtures, depending on the acetone mass ratio, two phases (liquid–liquid or liquid–solid phases) are in equilibrium. These liquid–liquid and liquid–solid zones surround a three-phase area (liquid–liquid–solid). The different one-phase, two-phase and three-phase regions are indicated in Fig. 2 by the regions I, II, III.

The same trends have been observed for the other temperatures (Tables 3–5). The curves corresponding to 10.1, 20.2, 30.2 and 48.9 °C have been gathered on the same ternary diagram in Fig. 3.

Table 4
Solubility of ketoprofen in acetone–water mixture at 30.2 °C

(a) Experimental liquid–solid equilibrium at 30.15 ± 0.15 °C			
W_{Ke}^* (kg ketoprofen/ kg solution)	R_a (kg acetone/ kg acetone– water mixture)		
$261 \times 10^{-6} \pm 27 \times 10^{-6}$	0.017		
$261 \times 10^{-6} \pm 17.10^{-6}$	0.026		
0.550	0.669		
0.577	0.730		
0.596	0.747		
0.589	0.796		
0.576	0.896		
0.602	0.902		
0.589	0.934		
(b) Experimental liquid–liquid–solid equilibrium at 30.0 ± 0.1 °C			
W_{Ke}^{*aq} (kg ketoprofen/ kg solution)	R_a^{aq} (kg acetone/ kg acetone– water mixture)	W_{Ke}^{org} (kg ketoprofen/ kg solution)	R_a^{org} (kg acetone/ kg acetone– water mixture)
0.038	0.342	0.452	0.646
(c) Binodal compositions of the experimental liquid–liquid equilibrium at 30.4 ± 0.1 °C			
W_{Ke}^{aq} (kg ketoprofen/ kg solution)	R_a^{aq} (kg acetone/ kg acetone– water mixture)	W_{Ke}^{*org} (kg ketoprofen/ kg solution)	R_a^{org} (kg acetone/ kg acetone– water mixture)
0.058 ± 0.0007	0.367	0.359 ± 0.004	0.624

Table 5
Solubility of ketoprofen in acetone–water mixture at 48.9 °C: experimental liquid–solid equilibrium

W_{Ke}^* (kg ketoprofen/kg solution)	R_a (kg acetone/ kg acetone–water mixture)
0.703	0.852
0.710	0.924
0.701	0.950
0.695	0.967

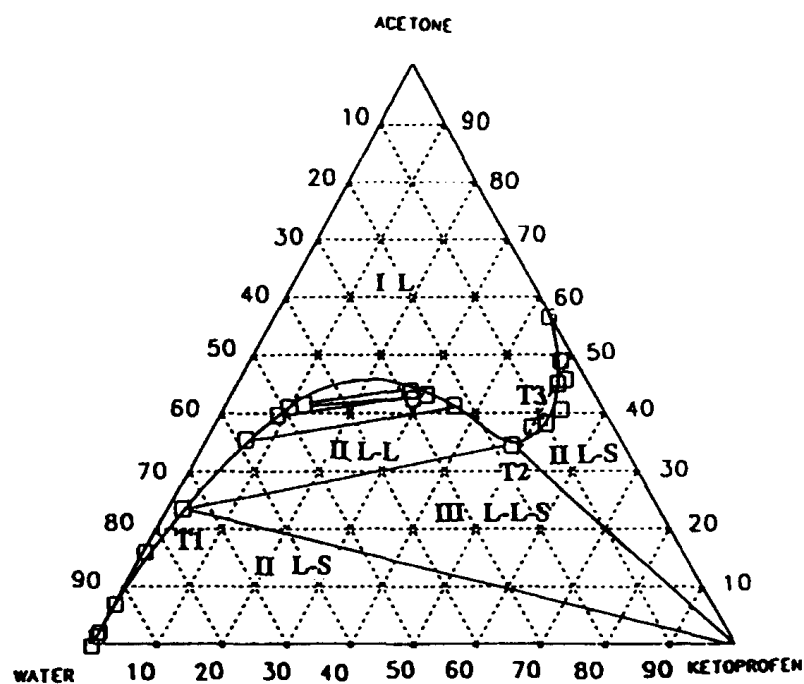


Fig. 2. Five different zones in the ternary diagram studied: one L area, two LSE area, one LLE area and one LLSE area. Experimental data at 20.2 °C.

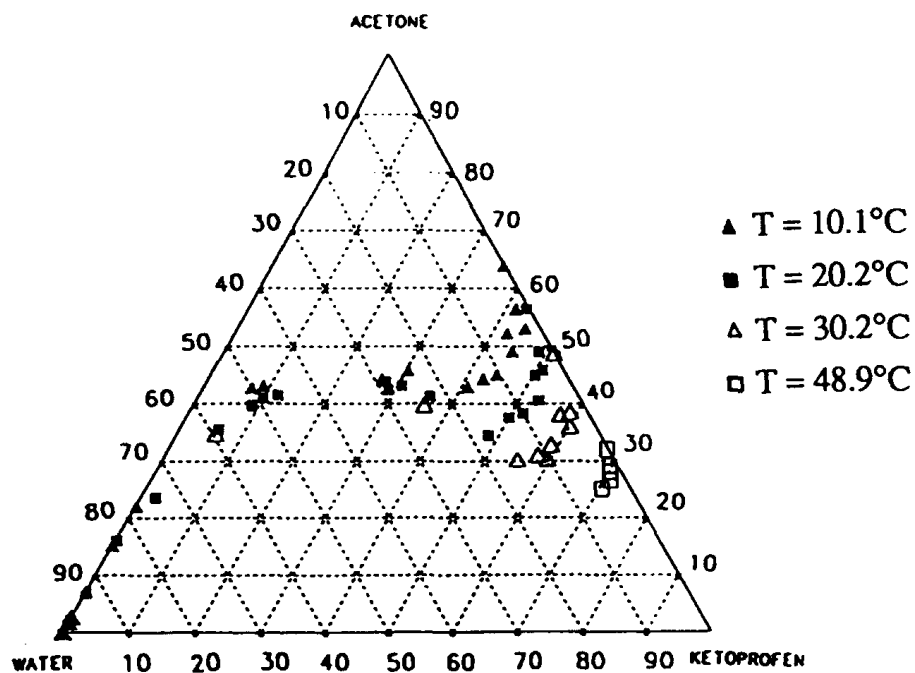


Fig. 3. Experimental data at 10.1, 20.2, 30.2 and 48.9 °C.

In the liquid–solid regions, the solubility of ketoprofen increases with temperature. However the influence of the temperature in these solid–liquid regions is much more important for high values of R_a on the right side of the phase diagram than for small ones on the left side.

A comparison between the liquid–liquid regions obtained respectively at 10.1 °C and 20.1 °C shows that this region is reduced as the temperature decreases. But this tendency is reversed when comparing the experimental points at 20.2 °C and 30.2 °C. This last observation is probably due to the increase of experimental errors at 30.2 °C.

4. Discussion

Several observations can be drawn from the experimental data with binary and ternary systems.

First, let us deal with the difference of the solubility of ketoprofen according to the nature of the pure solvent used in the case of binary solutions.

The structure of the crystals has been modeled by using a molecular simulation software (Cavalier-Frontin et al., 1992). It has enabled us to build an elementary lattice of a crystal and a combination of elementary lattices. The atomic coordinates of ketoprofen crystal used have been given by Briard and Rossi (1990), from a crystallographic study. This representation shows that the crystal exhibits more numerous hydrophobic faces ($-\text{C}_6\text{H}_5$) than hydrophilic ones ($-\text{COOH}$). So water keeps its maximally hydrogen-bonded and voluminous structure in front of the hydrophobic faces and the drug is weakly soluble in water. On the contrary, acetone exhibits charges all along its

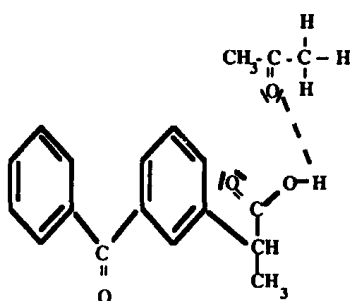


Fig. 4. Schematic representation of molecular interactions between the two components: ketoprofen–acetone.

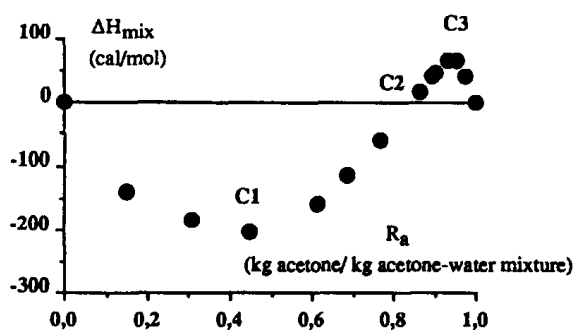


Fig. 5. Enthalpy of mixing data of acetone–water mixtures vs. acetone mass ratio, R_a at 20 °C (Timmermans, 1960).

structure so that hydrogen bonds are created with the ketoprofen molecules. Fig. 4 gives a schematic representation of the interactions occurring.

We have calculated the solubility of ketoprofen in acetone versus temperature, in the case of an ideal solution. The experimental solubility is 40% higher than the calculated one. This difference may be explained by the strong polar solvent–drug interactions which cannot be neglected when calculating activities of the components of the system (Bustamante and Selles, 1983).

In the case of the ternary system, it can also be referred to interactions between acetone and water. Mixtures of both species exhibit changes of structure with acetone mass ratio, R_a . For example, these changes of structure affect the enthalpy of mixtures. Indeed, the study of the enthalpy of acetone–water mixture, ΔH_{mix} , presents a particular behaviour versus acetone mass ratio as given in Fig. 5 (Timmermans, 1960). It shows that ΔH_{mix} is negative for $R_a \leq 0.85$ and becomes positive for $R_a \geq 0.85$. It can be assumed that the enthalpy of mixing, ΔH_{mix} , is the result of two additional thermal effects (Franks and Ives, 1966): the endothermic destruction of water–water hydrogen bonds and the exothermic formation of rather strong and well-organized acetone–water hydrogen bonds. It may be inferred that intercomponent attractions are dominant factors in the formation of acetone–water mixtures and in the formation of ketoprofen–acetone water mixtures.

Fig. 5 brings to the fore three particular points marked C1, C2, C3. Point C2 corresponds to $R_a^{C2} = 0.85$ for which the enthalpy is equal to zero. Points C1 and C3 are respectively the minimum for $R_a^{C1} = 0.45$ and the maximum for $R_a^{C3} = 0.92$ of the enthalpy curve. These particular ratios, R_a^{C1} , R_a^{C2} , R_a^{C3} , can be compared to particular ratios, R_a^{T1} , R_a^{T2} , R_a^{T3} , appearing in the ternary diagram of Fig. 2.

In the acetone–water mixture, for an acetone mass ratio less than R_a^{C1} , the enthalpy of the mixture is negative and its absolute value increases as the acetone mass ratio increases: the number of hydrogen bonds between water molecules and acetone molecules increases. In the presence of ketoprofen, whose molecule has a ketone functional group in the acetic chain, the number of hydrogen bonds between water molecules, acetone molecules and ketoprofen molecules also increases. Thus, the solubility of ketoprofen in the mixture increases. In fact, the ternary diagram shows that the maximum solubility of ketoprofen is observed with an acetone mass ratio, R_a^{T1} , equal to approximately 0.24.

For R_a between R_a^{C1} and R_a^{C2} , i.e. between C1 and C2, the number of hydrogen bonds between water molecules and acetone molecules is important but decreases as the absolute value of ΔH_{mix} decreases. In fact, in the ternary system, two liquid phases are in equilibrium for R_a between 0.24 and 0.67. Moreover liquid–liquid phase splitting occurs for $R_a^{T1} = 0.24$, at 20.0 °C.

For an acetone mass ratio equal to R_a^{C2} (point C2 in the Fig. 5), ΔH_{mix} is equal to zero. In the ternary mixture, the ratio corresponding to the change of two liquid phases in one liquid phase is 0.67. It can be compared with the point where ΔH_{mix} is equal to zero.

As the acetone mass ratio increases between R_a^{C2} and R_a^{C3} , the positive enthalpy of binary mixture increases: the number of hydrogen-bonded water molecules decreases; thus in the ternary mixture, the solubility of ketoprofen increases. On the ternary diagram the maximum solubility is obtained for R_a^{T3} equal to 0.90–0.95.

For an acetone mass ratio above 0.92, the number of hydrogen-bonded water molecules increases, and this increase explains the observed decrease of the solubility of ketoprofen in the ternary mixture.

The previous comparisons between the particular ratios appearing in the enthalpy diagram and those obtained in phase diagram, have shown the influence of ketoprofen. Indeed, the presence of

ketoprofen in the mixture moves back the positions of the particular ratios obtained in the enthalpy diagram.

All this development has been made for a temperature of 20 °C. The behaviour of the ternary system at 10.1 or at 30.2 °C is similar to the one at 20.2 °C as shown in Fig. 3. But the particular ratios, R_a^{T1} , R_a^{T2} , R_a^{T3} are function of temperature.

5. Representation model for LSE

In the case of solute solid, the condition of equality of partial fugacities at equilibrium leads to the reduced relation (Walas, 1985):

$$x_S^L \gamma_S^L = \exp \left(\frac{\Delta H_m}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) \right) \quad (1)$$

with x_S^L : mol fraction of the solute, S, in the solution

γ_S^L : activity coefficient of the solute, S, in the solution

ΔH_m : melting enthalpy of the pure solid (J mol⁻¹)

T_m : melting temperature of the solid (K)

The required input data on ketoprofen are the melting enthalpy, ΔH_m , the melting temperature, T_m , and the activity coefficient, γ_{Ke}^{cal} .

ΔH_m and T_m have been obtained for pure solid component by differential scanning calorimetry (DSC). They are respectively equal to $28,226 \pm 254$ J mol⁻¹ and 94.21 ± 0.5 °C.

The LSE is calculated to find the optimal value of parameters by minimizing the difference between computed and experimental activity coefficients, $\gamma_S^{calc} - \gamma_S^{exp}$.

Using the same model for liquid phase activity coefficients, calculated either from measurements of vapor–liquid equilibria (VLE) or liquid–liquid equilibria (LLE), or liquid–solid equilibria (Walas, 1985), we have considered reasonable to choose the UNIQUAC model (Abrams and Prausnitz, 1975) to estimate γ_S^{calc} in the liquid phase.

The UNIQUAC model has a combinatorial contribution to the activity coefficients, essentially due to the differences in size and shape of the molecules, and a residual contribution essentially due to energetic interactions:

$$\ln \gamma_i = \ln \gamma_i^C + \ln \gamma_i^R \quad (2)$$

The combinatorial term can be written as follows:

$$\ln \gamma_i^C = \ln \frac{\phi_i}{x_i} + \frac{z}{2} * q_i * \ln \frac{\theta_i}{\phi_i} + l_i - \frac{\phi_i}{x_i} * \sum_j x_j l_j \quad (3)$$

where z is the coordination number, equal to 10;

$$l_i = \frac{z}{2} * (r_i - q_i) - (r_i - 1) \quad (4)$$

θ_i and ϕ_i are the molecular surface area and molecular volume of each component i with

$$\phi_i = \frac{r_i x_i}{\sum_j x_j r_j} \quad (5)$$

$$\theta_i = \frac{q_i x_i}{\sum_j x_j q_j} \quad (6)$$

x_i is the mol fraction of the component i .

Pure components parameters r_i and q_i are, respectively, determined from measurements of molecular van der Waals volumes and molecular surface areas. They are calculated as the sum of the group-volume and group-area parameters, R_k and Q_k :

$$r_i = \sum \nu_k^{(i)} R_k \text{ and } q_i = \sum \nu_k^{(i)} Q_k \quad (7)$$

where $\nu_k^{(i)}$, always an integer, is the number of groups of type k in the molecule i . Group parameters R_k and Q_k are obtained from van der Waals group volumes V_k and surface areas A_k (Bondi, 1964). The expression of R_k and Q_k can be given as follows:

$$R_k = \frac{V_k}{15.17} \quad (8)$$

$$Q_k = \frac{A_k}{2.5 \times 10^9} \quad (9)$$

The normalization factors appearing in Eqs. (8) and (9), 15.17 and 2.5×10^9 are those derived by Abrams and Prausnitz (1975).

However, since data for the benzoyl group are not available, this group has been decomposed into two independent groups, C_6H_4 and $C=O$. The van der Waals group volumes, V_k , and surface areas, A_k of $>C=O$ group are given by Bondi (1964). The other volume and surface factors of others groups have been found in Walas (1985).

The expression of the residual term, in UNIQUAC equation, is:

$$\ln \gamma_i^R = q_i * \left(1 - \ln \left(\sum_j \theta_j \tau_{ji} \right) - \sum_j \frac{\theta_j \tau_{ij}}{\theta_k \tau_{kj}} \right) \quad (10)$$

with

$$\tau_{ij} = \exp \left(- \frac{u_{ij} - u_{ii}}{RT} \right) \quad (11)$$

Table 6
Volume and surface factors, r_i and q_i , calculated from data given by Walas, 1985

System	Volume factor	Surface factor
Ketoprofen	9.2979	6.900
Acetone	2.5735	2.336
Water	0.9200	1.400

Table 7

Parameters of the UNIQUAC model for the system studied, LSE

System	i-j	u_{ij} (J mol ⁻¹)
Ketoprofen(1)- Acetone(2)	1-2	-746.25
Ketoprofen(1)- Water(3)	2-1	747.13
Acetone(2)- Water(3)	1-3	2 931.03
	3-1	-103.68
	2-3	3 744.90
	3-2	-866.76

The u_{ij} are the interaction parameters between the two components i and j. They can be found in tables.

These factors, r_i and q_i , are reported in Table 6. The calculated values of ketoprofen volume and surface factors are high compared with the values obtained for the other components.

6. Representation of the ternary system

The validity of the semi-empirical models which represent LLE and LSE have been tested.

The parameters, u_{ij} and u_{ji} of the tested semi-empirical UNIQUAC model are not available in tables and have been evaluated for each particular binary system. The parameters of the system acetone–water are deduced from VLE data using the PROREG regression tool designed by PROSIM

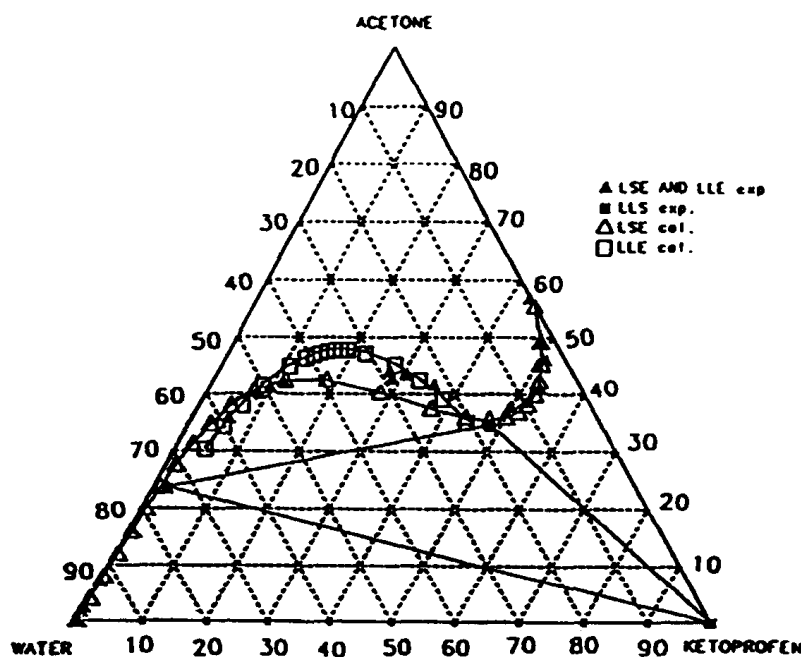


Fig. 6. Predicted LLE and LSE data (after adjustment of the interaction parameters between ketoprofen and water) and experimental data at 20.2 °C.

Table 8

Relative deviations between the calculated and the experimental concentrations of ketoprofen $\left(\frac{(W_{Ke}^{cal} - W_{Ke}^{exp})}{W_{Ke}^{exp}} \right)$ as a function of R_a at 10.1 °C

R_a (kg acetone/ kg acetone–water)	Absolute deviations (kg ketoprofen/kg solution)	Relative deviations on concentration (%)
0	2×10^{-6}	2
0.023	1×10^{-6}	1
0.072	37×10^{-6}	19
0.151	291×10^{-6}	47
0.219	$1\,563 \times 10^{-6}$	72
0.727	0.327	80
0.775	0.292	68
0.811	0.257	58
0.888	0.147	33
0.906	0.102	24
0.960	0.088	20
0.967	0.055	13
1	0.001	0.2

Company (ProSim S.A., 1993). For the systems, ketoprofen–acetone and ketoprofen–water, these parameters were computed from the experimental mutual solubility data, by minimization of the

$$\text{differences } \frac{(\gamma_{Ke}^{calc} - \gamma_{Ke}^{exp})}{\gamma_{Ke}^{exp}} \text{ and } \frac{(\gamma_{solvent}^{calc} - \gamma_{solvent}^{exp})}{\gamma_{solvent}^{exp}}$$

The parameters, a_{ij} and a_{ji} , obtained are given in Table 7.

Table 9

Relative deviations between the calculated and the experimental concentrations of ketoprofen $\left(\frac{(W_{Ke}^{cal} - W_{Ke}^{exp})}{W_{Ke}^{exp}} \right)$ as a function of R_a at 20.2 °C

R_a (kg acetone/ kg acetone–water)	Absolute deviations (kg ketoprofen/kg solution)	Relative deviations on concentration (%)
0	13×10^{-6}	11
0.016	7×10^{-6}	5
0.024	6×10^{-6}	3
0.072	73×10^{-6}	22
0.163	804×10^{-6}	57
0.755	0.303	61
0.786	0.261	50
0.868	0.136	26
0.910	0.072	14
0.941	0.064	13
0.961	0.036	7
1	0.015	4

Table 10

Relative deviations between the calculated and the experimental concentrations of ketoprofen $\left(\frac{(W_{Ke}^{cal} - W_{Ke}^{exp})}{W_{Ke}^{exp}} \right)$ as a function of R_a at 30.2 °C

R_a (kg acetone/ kg acetone–water)	Absolute deviations (kg ketoprofen/kg solution)	Relative deviations on concentration (%)
0	8×10^{-6}	3
0.017	8×10^{-6}	3
0.026	14×10^{-6}	5
0.669	0.408	74
0.730	0.295	51
0.747	0.268	45
0.796	0.156	27
0.896	0.046	8
0.902	0.070	12
0.934	0.048	8
1	0.019	4

The calculated and experimental solubilities in the binary liquid–solid zones are shown at 20.2 °C in Fig. 6. It is important to note that the form of the calculated curve is very similar to the experimental one. Moreover this curve seems able to describe all regions, even the liquid–liquid region. This continuity can be explained by that of the thermodynamic equations used.

However, when comparing with experimental data, the UNIQUAC model gives underestimated concentrations of ketoprofen when the mass ratio of acetone is higher than 0.75. The relative deviations between the calculated and the experimental concentrations of solute $\left(\left(\frac{W_{Ke}^{cal} - W_{Ke}^{exp}}{W_{Ke}^{exp}} \right) * 100 \right)$ as a function of R_a are reported in Tables 8–11, for the different temperatures. For acetone–water mixtures with a high mass ratio of acetone, the deviation increases as R_a decreases. So the concentrations of ketoprofen are underestimated (until 80% at 10.1 °C). For acetone–water mixtures with R_a less than 0.075, there is a good agreement between experimental and

Table 11

Relative deviations between the calculated and the experimental concentrations of ketoprofen $\left(\frac{(W_{Ke}^{cal} - W_{Ke}^{exp})}{W_{Ke}^{exp}} \right)$ as a function of R_a at 48.9 °C

R_a (kg acetone/ kg acetone water)	Absolute deviations (kg ketoprofen/kg solution)	Relative deviations on concentration (%)
0.852	0.007	1.0
0.924	0.002	0.2
0.950	0.003	0.4
0.967	0.005	1
1	0.011	2

Table 12

Relative deviations between the calculated and the experimental concentrations of ketoprofen as a function of R_a at 10.1 °C (after adjustment of the interaction parameters between ketoprofen and water)

R_a (kg acetone/ kg acetone–water)	Absolute deviations (kg ketoprofen/kg solution)	Relative deviations on concentration (%)
	AAD = 2.650×10^{-6}	ARD = 820
0	1.001×10^{-6}	1.164
0.023	1.228×10^{-6}	1.170
0.072	1.865×10^{-6}	937
0.151	3.566×10^{-6}	572
0.219	5.589×10^{-6}	256
	AAD = 0.013	ARD = 2.9
0.727	0.011	3
0.775	0.015	3
0.811	0.005	1
0.888	0.002	0.3
0.906	0.017	4
0.960	0.037	8
0.967	0.013	3
1	0.001	0.2

calculated data (relative error is lower than 10.%). However for R_a higher than 0.075, the ketoprofen concentrations are underestimated too.

According to the principle of the method, the calculated concentrations directly depend on the estimated UNIQUAC parameters. An analysis of the values of these parameters can explain the reported error on the predicted values. In binary mixtures ketoprofen–water, with a low ketoprofen

Table 13

Relative deviations between the calculated and the experimental concentrations of ketoprofen as a function of R_a at 20.2 °C (after adjustment of the interaction parameters between ketoprofen and water)

R_a (kg acetone/ kg acetone water)	Absolute deviations (kg ketoprofen/kg solution)	Relative deviations on concentration (%)
0	AAD = 2.197×10^{-6}	ARD = 481
0.016	916×10^{-6}	738.5
0.024	1048×10^{-6}	691.8
0.072	1111×10^{-6}	628.0
0.163	1644×10^{-6}	487.9
	3099×10^{-6}	219.8
	AAD = 0.009	ARD = 1.7
0.755	0.007	1.5
0.786	0.003	0.5
0.868	0.011	2.1
0.910	0.007	1.5
0.941	0.014	2.6
0.961	0.003	0.6
1	0.015	3.5

Table 14

Relative deviations between the calculated and the experimental concentrations of ketoprofen as a function of R_a at 30.2 °C (after adjustment of the interaction parameters between ketoprofen and water)

R_a (kg acetone/ kg acetone water)	Absolute deviations (kg ketoprofen/kg solution)	Relative deviations on concentration (%)
	AAD = 904.3×10^{-6}	ARD = 376
0	813×10^{-6}	361
0.017	949×10^{-6}	363
0.026	$1\,051 \times 10^{-6}$	403
	AAD = 0.010	ARD = 1.8
0.669	0.005	1
0.730	0.001	0.2
0.747	0.012	2
0.796	0.004	1
0.896	0.011	2
0.902	0.017	3
0.934	0.014	2
1.0	0.019	4

content (hundreds of ppm), the activity coefficients of ketoprofen are very high (about 10 000). It is well known that these semi-empirical models do not give good predictions for high activity coefficients.

So, in order to take into account the overestimation of the interaction parameters, these ketoprofen–water parameters have been re-calculated from experimental data obtained in the ternary system, at each temperature, and in the range of high R_a value ($R_a > 0.70$). Indeed, the highest absolute deviations are obtained in this range.

Tables 12–15 report the absolute and relative deviations between calculated and experimental data, as a function of R_a , after adjustment of the interactions parameters ketoprofen–water and water–ketoprofen respectively at 10.1, 20.2, 30.2 and 48.9 °C. The absolute deviations are considerably reduced for high values of R_a and the agreement is quite good. The same adjusted parameters have been used to calculate the concentrations in the smallest range of R_a . The results remain reasonably good, for the range of considered concentrations. For 48.9 °C, only few experimental points are available

Table 15

Relative deviations between the calculated and the experimental concentrations of ketoprofen as a function of R_a at 48.9 °C (after adjustment of the interaction parameters between ketoprofen and water)

R_a (kg acetone/ kg acetone water)	Absolute deviations (kg ketoprofen/kg solution)	Relative deviations on concentration (%)
	AAD = 0.004	ARD = 0.7
0.852	0.002	0.2
0.924	0.006	1
0.950	0.000	0
0.967	0.003	0.5
1	0.011	2

Table 16

Parameters of the UNIQUAC model for the system studied, LLE

System	i-j	u_{ij}^u (J mol ⁻¹)
Ketoprofen(1)-Acetone(2)	1-2	-1059.12
Acetone(2)-Water(3)	2-1	1404.23
Ketoprofen(1)-Water(3)	1-3	673.18
Water(3)-Ketoprofen(1)	3-1	-125.79
Acetone(2)-water(3)	2-3	3744.80
Water(3)-Acetone(2)	3-2	-866.76

because this temperature is very close to the upper limit of stability of the system. So, in that case, the predicted values must to be regarded with less confidence.

6.1. LLE evaluation method

As LLE data on the binary mixtures of ketoprofen–acetone and ketoprofen–water mixtures, is not available, the parameters of the UNIQUAC model were evaluated from smoothing experimental LLE data at 20.2°C. These parameters are presented in Table 16. They have also been used to calculate the LLE at the other temperatures (10.1 and 30.2 °C) by using PROPHY software (ProSim S.A., 1993).

6.2. LLSE evaluation method

Figs. 6–9 present predicted and experimental curves for both LLE and LSE respectively at 20.2, 10.1, 30.2 and 48.9 °C. They show that liquid–liquid equilibria slightly depend on the temperature.

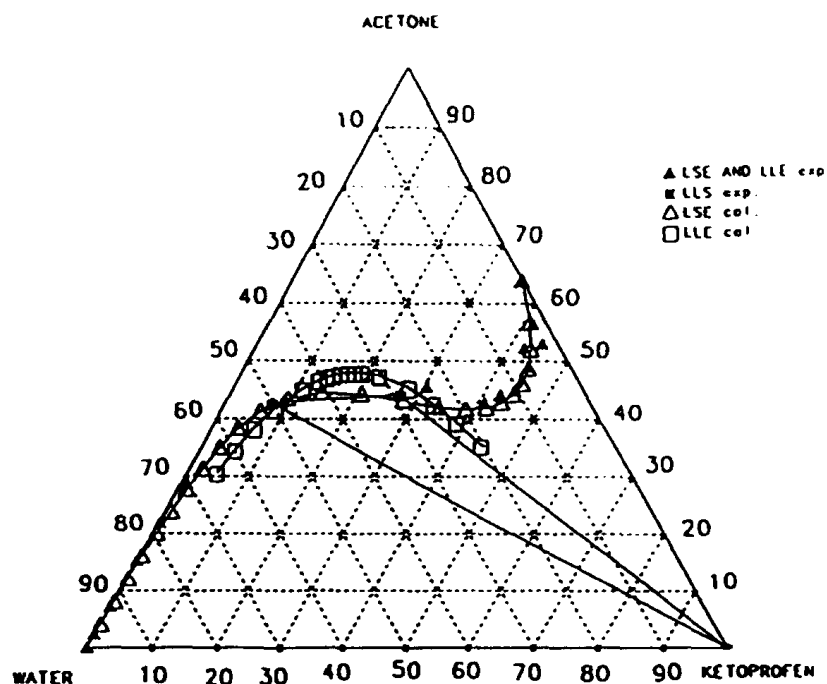


Fig. 7. Predicted LLE and LSE data (after adjustment of the interaction parameters between ketoprofen and water) and experimental data at 10.1 °C.

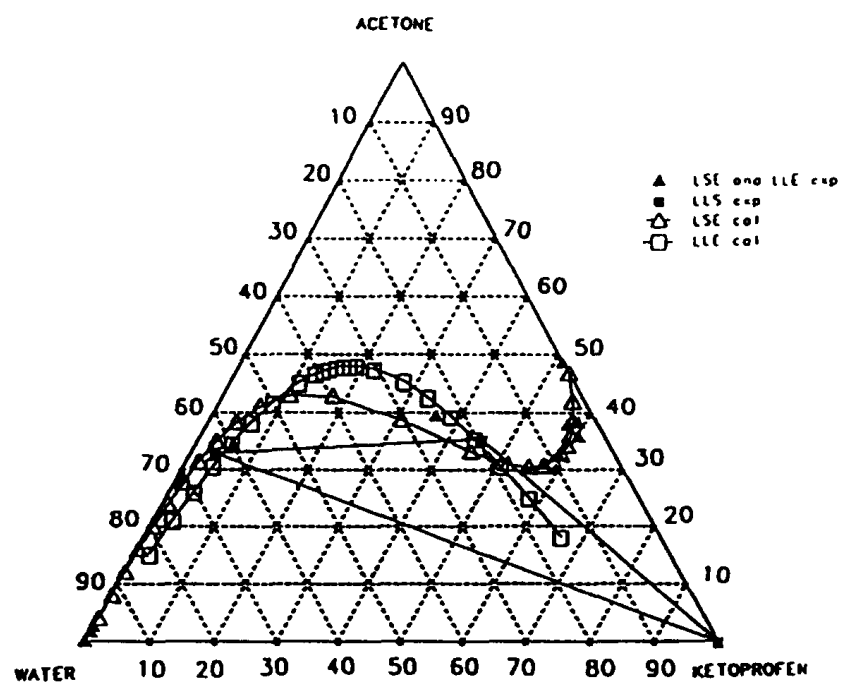


Fig. 8. Predicted LLE and LSE data (after adjustment of the interaction parameters between ketoprofen and water) and experimental data at 30.2 °C.

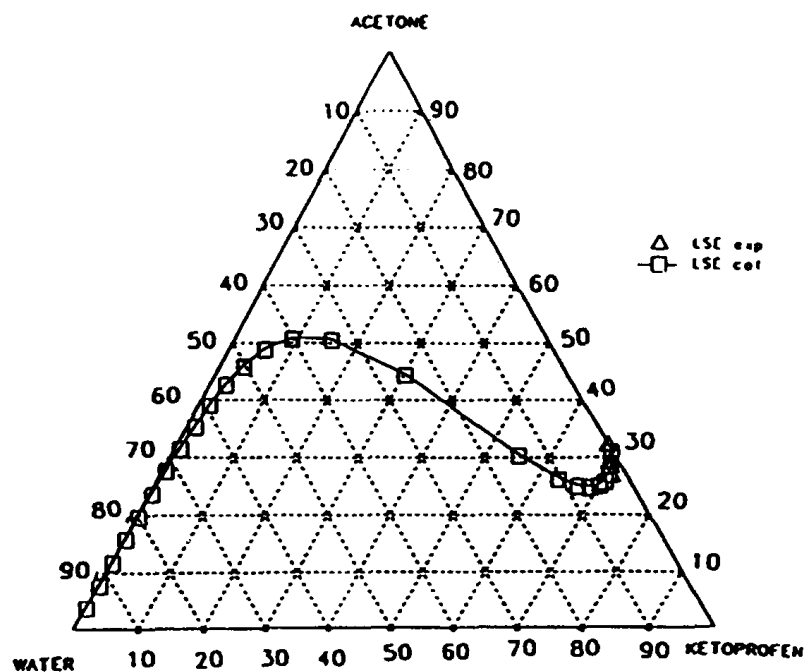


Fig. 9. Predicted and experimental data in LSE at 48.9 °C (after adjustment of the interaction parameters between ketoprofen and water).

The superposition of LLE and LSE predicted curves should allow us to obtain the complete ternary diagram. In the range of high R_a , the intersection point, T2, between the LLE and the LSE predicted curves, is in good agreement with the experimental point. But for small R_a , the intersection between LLE and LSE curves creates a point T1 that does not correspond to the experimental point. The level of agreement between the calculated and experimental intersection points (T1 and T2) depends on the results of prediction of LSE previously discussed. Since T2 corresponds to the experimental point, T1 can be deduced by the following procedure: by creating the first intersection point T2 (in the Fig. 6, for example at 20.2 °C), LLE allows to join the corresponding point T1, by the tie-line. To avoid the discontinuity between LLE and LSE at small R_a values, the tie-line has been extended up to the calculated LSE curve.

7. Conclusion

Experimental and calculated equilibrium data have been determined for the organic system ketoprofen–acetone–water at four temperatures (10.1, 20.2, 30.2 and 48.9 °C).

The experimental diagram exhibits five regions: one homogeneous, three two-phase (two liquid–solid and one liquid–liquid equilibria) and one three-phase zones. Specific experimental procedures have been applied to determine the liquid–liquid and the liquid–liquid–solid equilibria.

The behaviour of the mixtures has been explained by ketoprofen–water, ketoprofen–acetone and acetone–water interactions (hydrogen bonding).

We applied the UNIQUAC model to calculate the LSE and LLE for this system. For LSE, since the interaction parameters, ketoprofen–water and ketoprofen–acetone did not exist, they have been evaluated for each binary system from experimental data. To obtain a better agreement between experimental and calculated data, the interaction parameters ketoprofen–water have been recalculated from experimental data in the ternary system, at each temperature. After adjustment of these last parameters, the results of the semi-empirical model UNIQUAC are in agreement with experimental LSE data. For LLE, we have evaluated the missing parameters from smoothing experimental data at 20.2 °C (PROSIM). The obtained parameters have been used to calculate the LLE at the other temperatures. Finally prediction of the ternary diagram can be carried out by the presented methods.

8. List of symbols

A_k Van der Waals surface area of group or component k (cm²/mol)

AAD average absolute deviation: $AAD = \frac{\sum |W_i^{exp} - W_i^{cal}|}{N_{exp}}$

ARD average relative deviation $AAD = \frac{\sum \left| \frac{W_i^{exp} - W_i^{cal}}{W_i^{exp}} \right| \cdot 100}{N_{exp}}$ (%)

l_i pure-component constant defined in Eq. (4) (–)

N_{exp} number of experimental data (–)

q_i UNIQUAC group surface parameters of pure component i (–)

Q_k	group area parameter for group k (–)
R	ideal gas constant ($\text{J mol}^{-1} \text{ K}$)
R_k	group volume parameter for group k (–)
R_a	acetone mass ratio ($\text{kg of acetone kg}^{-1}$ of acetone–water mixture)
r_i	UNIQUAC group volume parameter of pure component i (–)
T	temperature ($^{\circ}\text{C}$)
T_m	melting temperature of the solid (K)
u_{ij}	UNIQUAC binary interaction parameter (J mol^{-1})
V_k	Van der Waals volume of group or component k ($\text{cm}^3 \text{ mol}^{-1} \times 10^9$)
W_S^*	solubility of solid, S (kg of S kg^{-1} of solution)
x_i	mol fraction of component i (–)
z	coordination number, $z = 10$, (–)

8.1.1. Greek letters

ΔH_{mix}	enthalpy of mixture (cal mol^{-1})
ΔH_m	enthalpy of melting (J mol^{-1})
ϕ_i	molecular volume of component i (–)
γ_i	activity coefficient of component i (–)
γ_i^{C}	combinatorial contribution of activity coefficient of component i (–)
γ_i^{R}	residual contribution activity coefficient of component i (–)
$\nu_k^{(i)}$	integer number of groups of type k in the molecule i (–)
θ_i	molecular surface area of component i (–)
τ_{ij}	UNIQUAC parameter see Eq. (11) (–)

8.1.2. Subscripts

aq	aqueous liquid phase
i,j	components i and j
org	organic liquid phase

8.1.3. Superscripts

cal	calculated
exp	experimental
Ke	ketoprofen
L	liquid phase
S	solid solute

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