

Modeling of Ternary Solid-Liquid-Equilibria for Pharmaceutical and Food Systems

Karima Bitchikh, Abdeslam-Hassen Meniai*, Wahida Louaer

Laboratoire de l'Ingénierie des Procédés de l'Environnement (LIPE), Faculté du Génie des Procédés Pharmaceutiques
 Université Constantine 3, BP B60 Centre Djefaal Amar Khroub 25100 Algeria
 meniai@yahoo.fr

The present work deals with the modeling of solid-liquid equilibria (SLE) using the NRTL and the UNIFAC thermodynamic models for activity coefficient calculation, for a number of ternary systems involving pharmaceutical and food compounds such as salicylic acid, nicotinic acid, caffeine, urea, vanillin, etc. as the solutes and water-ethanol and water-methanol as the solvent pairs, at different temperatures.

For the UNIFAC model interaction parameters were available whereas for the NRTL model they were retrieved from the experimentally measured values using the Simplex method to minimize an objective function expressed as a summation of the squared differences between the experimental and the calculated values, to be used to predict the SLE data for the considered systems with a quite good agreement.

1. Introduction

The reliability of any design concerning separation equipments depends upon the availability and accuracy of phase equilibria data. However the experimental measuring of such data is not always an easy task, encouraging the development and test of predictive thermodynamic models.

In the present study liquid-solid systems involving pharmaceutical or food compounds are considered. This has been motivated by the scarcity of such phase equilibrium data in the literature.

In general most of the techniques used for the determination of any solute in a given solvent are not very complex but they require a great skill and care, due to the difficulty to reach a complete state of equilibrium of the solid in the liquid solution. Therefore it is necessary to maintain an intimate and prolonged contact between both phases.

The modelling of the solid-liquid equilibria for the different considered systems consisting of water, a hydrophilic organic solvent and a solute, was carried out using two different thermodynamic models, namely the UNIFAC and the NRTL. The experimental data concerning these systems has been obtained from the literature (Hamedi et al, 2006).

2. Solid-Liquid Equilibria modelling

At a fixed temperature and pressure, the solid-liquid equilibrium is conditioned by the isoactivity criterion. For a given constituent A, this condition is expressed as follows:

$$x_A^S \gamma_A^S f_{A, \text{pure}}^S = x_A^L \gamma_A^L f_{A, \text{pure}}^L \quad (1)$$

with S and L denoting the solid and liquid states, x_A the molar fraction of constituent A, γ_A the activity coefficient and $f_{A, \text{pure}}$ the fugacity of pure constituent in each phase.

This leads to the following solubility equation:

$$\ln(x_i \gamma_i) = \frac{\Delta H_{tp}}{R} \left(\frac{1}{T_{tp}} - \frac{1}{T} \right) - \frac{\Delta C_p}{R} \left(\ln \frac{T_{tp}}{T} - \frac{T_{tp}}{T} + 1 \right) - \frac{\Delta V}{RT} (P - P_{tp}) \quad (2)$$

where T_{tp} and ΔH_{tp} are the temperature and the enthalpy at the triple point respectively, ΔC_p and ΔV_p represent the differences in heat capacity and volume for the liquid with the solid.

However it is usual in most cases to neglect the effects of pressure and the variation of the heat capacity on the solubility and to consider safely the fusion temperature instead of the triple point which is generally not known for many constituents. These assumptions lead to the following general solubility equation:

$$\ln(x_i \gamma_i) = \frac{\Delta H_m}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) \quad (3)$$

Therefore thermodynamic models are needed for the calculation of the activity coefficient, where among the well known ones, namely NRTL and UNIFAC were tested in the present work. Briefly they are described as follows.

3. Thermodynamic models

3.1 NRTL (Non Random Two Liquids) model

This model was originally proposed by Renon and Prausnitz (1968). It is mainly based on the introduction of the local composition concept with the hypothesis of a non random molecular distribution, similarly to the propositions put forward by Wilson (1968) and Scott (1956). For a mixture of n constituents, n different elementary cells with different central molecules are considered.

According to this model, the activity coefficient for a constituent is expressed as follows:

$$\ln \gamma_i = \frac{\sum_k \tau_{ji} G_{ji} x_j}{\sum_k G_{ki} x_k} + \sum_j \frac{x_j G_{ij}}{\sum_k G_{kj} x_k} \left(\tau_{ij} - \frac{\sum_l \tau_{lj} G_{lj} x_l}{\sum_k G_{kj} x_k} \right) \quad (4)$$

$$\text{with } G_{ji} = \exp\left(-\alpha_{ji} \cdot \frac{C_{ji}}{RT}\right) \text{ and } \tau_{ji} = \frac{C_{ji}}{RT}$$

with α_{ji} the randomness parameter and $C_{ji} = g_{ji} - g_{ii}$, g_{ij} being the molar free energy due to the interaction between molecule i and j .

3.2 Interaction parameters calculation

As mentioned previously phase equilibria data are not always available and are not easy to measure for most systems. The prediction of such data is mainly based on the use of reliable thermodynamic models. However most of these models require interaction parameters which also are not always available and have to be calculated from experimental values.

Therefore in the present study, the opportunity was taken to calculate these interaction parameters by minimizing an objective function defined as follows:

$$F = \sum_{i=1}^N (x_{exp} - x_{calc})^2 \quad (5)$$

with x_{exp} and x_{calc} the experimental and the calculated solid solute solubilities in the solvent, respectively.

x_{calc} is obtained from Equation 3 as follows:

$$x_{calc} = \exp\left[\frac{\Delta H_m}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right)\right] / \gamma \quad (6)$$

The activity coefficient γ is expressed according to the considered thermodynamic model (NRTL) and it involves the required interaction parameters.

The objective function was minimized using a version of the Simplex method modified by Nelder and Mead, (1965).

3.3 UNIFAC (UNIQUE Functional –group Activity Coefficient)

The original version of the UNIFAC model as first introduced by Fredenslund et al. (1975) was used in the present work. It is based on a group contribution concept where the activity coefficient is defined as follows:

$$\ln \gamma_i = \ln \gamma_i^C + \ln \gamma_i^R \quad (7)$$

$$\ln \gamma_i^C = \ln \frac{\Phi_i}{x_i} + \frac{Z}{2} q_i \ln \frac{\Theta_i}{\Phi_i} + l_i \frac{\Phi_i}{x_i} \sum_j x_j l_j \quad (7a)$$

With

$$l_i = \frac{Z}{2} (r_i - q_i) - (r_i - 1); Z=10 \quad (7b)$$

x_i represents the molar fraction of constituent i and the summations are all over the constituents, Θ and Φ are the surface area and volume fractions, respectively, r_i and q_i are the molecular volume and surface area, respectively and can be calculated as follows :

$$\Theta = \frac{q_i \cdot x_i}{\sum_j q_j \cdot x_j}; \Phi = \frac{r_i \cdot x_i}{\sum_j r_j \cdot x_j} \quad (7c)$$

where $V_K^{(i)}$ is the number of type k groups in molecule i , R_k and Q_k are the group volume and surface parameters which are readily available in standard tables or can be calculated from the following relationships:

$$R_K = \frac{V_{wk}}{15.17}; Q_K = \frac{A_{wk}}{2.5 \times 10^9} \quad (7d)$$

with V_{wk} and A_{wk} the volume and the surface area of the considered group.

The residual term is given as follows:

$$\ln \gamma_i^R = \sum_k v_k^i (\ln \Gamma_k - \ln \Gamma_k^{(i)}) \quad (7e)$$

Where Γ_k and $\Gamma_k^{(i)}$ are the residual activity coefficients of group k in the mixture and in pure liquid i , respectively. The residual activity coefficient of group k is then expressed as follows:

$$\ln \Gamma_k = Q_k \left(1 - \ln \left(\sum_m \Theta_m \cdot \Psi_{mk} \right) - \sum_n \frac{\Theta_m \cdot \Psi_{km}}{\sum_n \Theta_n \cdot \Psi_{nm}} \right) \quad (8)$$

$$\Theta_m = \frac{Q_m \cdot X_m}{\sum_n q_n \cdot x_n}; X_m = \frac{\sum_j v_m^{(j)} \cdot x_j}{\sum_j \sum_n v_n^{(j)} \cdot x_j} \quad (8a)$$

with Θ_m the group surface fraction in the mixture and X_m the group molar fraction in the solution. The interaction parameter between m and n groups is then calculated from the following:

$$\Psi_{mn} = \exp \left(-\frac{u_{mn} - u_{nn}}{RT} \right) = \exp \left(-\frac{a_{mn}}{T} \right) \quad (8b)$$

Ψ_{mn} is the Boltzmann factor corresponding to the interaction parameter a_{mn} ($a_{mn} = U_{mn} - U_{nm}$).

4. Results and discussion

The minimization of the objective function defined in Equation 8 lead to the following results:

Table 1: NRTL Interaction parameters ($\alpha(i, j) = 0.2$)

System	T (K)	Interaction parameters					
		$\tau(1,2)$	$\tau(2,1)$	$\tau(1,3)$	$\tau(3,1)$	$\tau(2,3)$	$\tau(3,2)$
Water (1)-Ethanol (2)- Vanillin(3)	303.15	-221.23	259.53	-254.32	306.09	134.12	-130.48
Water (1)-Ethanol (2)- Vanillin (3)	318.15	-160.68	181.26	-228.90	269.95	185.92	167.59
Water (1)-Methanol (2)- Vanillin (3)	303.15	-229.95	272.41	-212.43	247.23	148.56	-137.99
Water (1)-Methanol (2)- Vanillin (3)	318.15	-206.26	238.48	-237.28	282.25	58.98	-57.06
Water (1)-Ethanol (2)- Urea (3)	303.15	-187.19	213.92	-188.43	215.47	40.25	-39.77
Water (1)-Ethanol (2)- Phenyl urea (3)	30315	-164.45	187.51	-118.19	128.32	194.66	-178.72
Water (1)-Ethanol (2)- Caffeine (3)	303.15	-306.82	376.80	-274.24	329.13	15.12	-15.23
Water (1)-Ethanol (2)- Nicotic acid (3)	303.15	-29.81	29.39	99.73	-95.44	142.20	-126.38
Water (1)-Ethanol (2)-Salicylic acid (3)	303.15	-266.16	321.28	72.46	75.40	100.17	103.32

These parameters were used to predict the solid-liquid equilibria and the results concerning the systems Ethanol (Methanol)-Water- Solute are shown in the following figures:

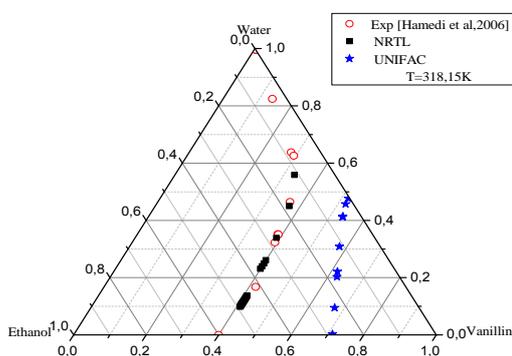


Figure 1: Solubility of Vanillin in Water-Ethanol

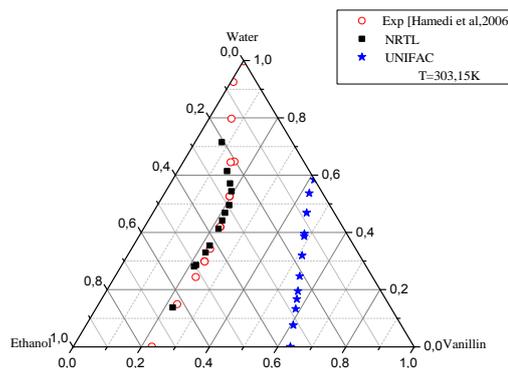


Figure 2: Solubility of Vanillin in Water-Ethanol

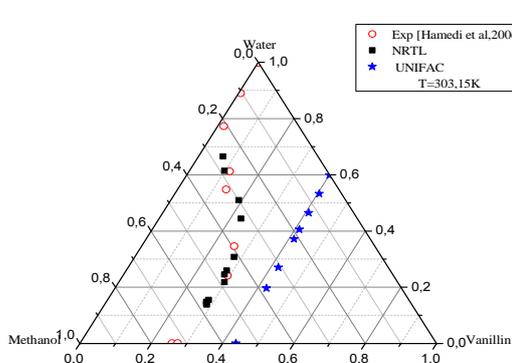


Figure 3: Solubility of Vanillin in Water-Methanol

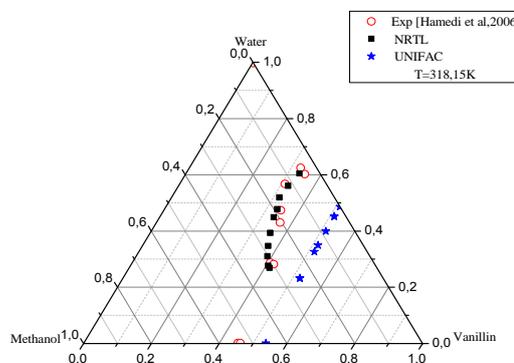


Figure 4: Solubility of Vanillin in Water-Methanol

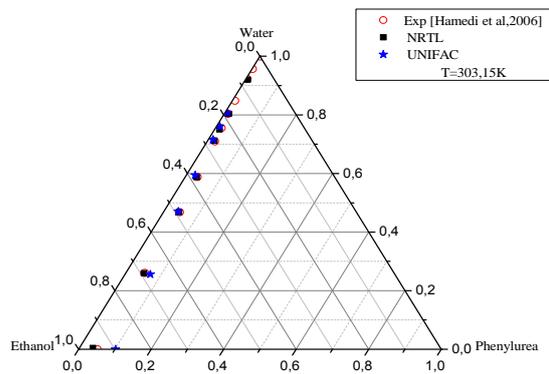


Figure 5: Solubility of Phenyl urea in Water-Ethanol

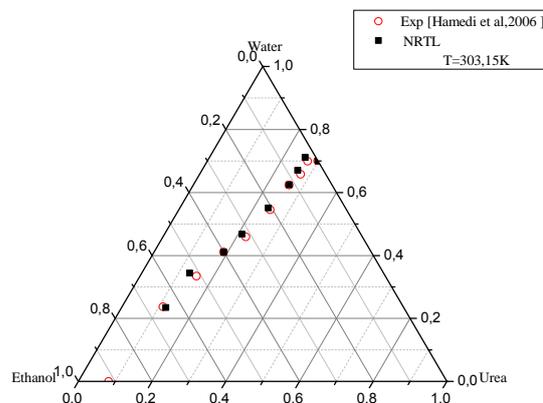


Figure 6: Solubility of Urea in Water-Ethanol

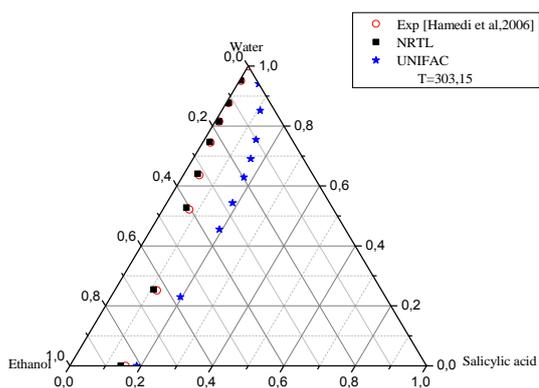


Figure 7: Solubility of Salicylic acid in Water-Ethanol

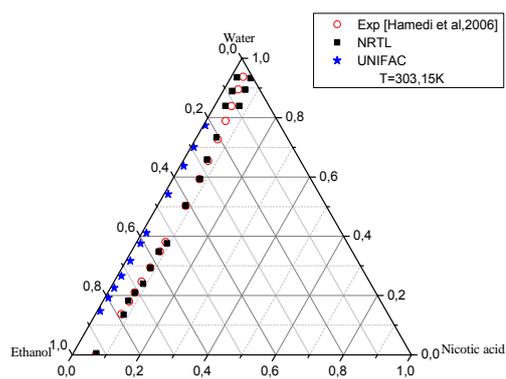


Figure 8: Solubility of Nicotic acid in Water-Ethanol

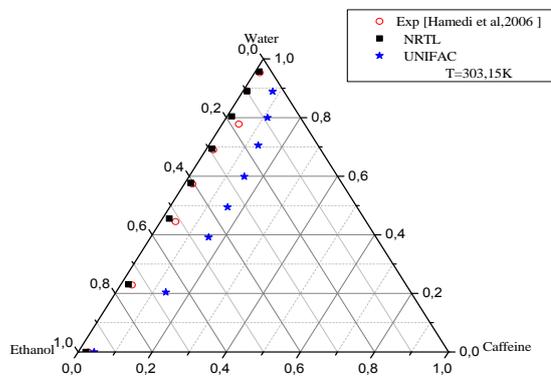


Figure 9: Solubility of Caffeine in Water-Ethanol

The obtained results for the different ternary systems are in a quite good agreement with the reported experimental values, confirming the reliability of the calculated interaction parameters for the NRTL model.

Figures 1, 2, 3 & 4 show the behaviour of Vanillin in two different solvent mixtures (Water+ Ethanol and Water + Methanol) at two different temperatures of 303.15 and 318.15 K. The molecule of this solute represents an important class where the three functional groups (hydroxyl, aldehyde and methoxyl) are present in the aromatic cycle. From the figures it is clear that Vanillin is more soluble with the presence of methanol molecules than with larger and linear ethanol ones. A better solubility is obtained at the greater temperature of 318.15 K, compared to 303.15 K and less alcohol is required.

Urea and Phenyl urea solutes can be considered as from the same family. However Urea has a great capacity to modify water molecule structure to an important extent and can be used in a number of applications such as in dermatology and bacteriology. Phenyl urea can be used as an herbicide. From Figures 5 and 6 it can be seen that these two solutes show different behaviors as far as the solubility in water-ethanol mixtures is concerned. Having a better affinity towards water, Urea dissolves easily in mixtures where ethanol concentrations are low, whereas the aromatic nucleus reduced greatly its solubility in the alcoholic solvent.

Salicylic acid, Nicotic acid and Caffeine are generally slightly soluble in water and ethanol, explaining the shapes of the solubility curves which are very near to the water-ethanol side, as shown in the corresponding figures 7, 8 and 9. The different shapes of the equilibrium curves may be explained by the differences in the chemical structures of the solutes.

The solubilities of all the considered solutes, excepted Urea due to the non availability of the required interaction parameters, were also calculated. Clearly the obtained results showed large deviations with the experimental values, indicating the non reliability of this model to retrieve solubility data for these system types.

5. Conclusion

The use of NRTL for the modelling of solid-liquid equilibria for different ternary systems led to results in a quite good agreement with the corresponding experimental values reported from the literature. This did also enable the calculations of the required molecular interaction parameters which are now available for further computer experiments, determining the solubility curves for the considered systems.

The obtained results can also be used to examine the behaviour of a given solute in a solvent mixture made of water (solvent) and alcohol such as methanol and ethanol (antisolvent).

References

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