

Correlation of Solubilities in Mixed-Solvents with Local-Composition-Regular Solution Theory

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Abstract

The solubility of a solute in solvent is a common protocol in industries that process food and active pharmaceutical ingredients (API). Therefore, solid-liquid equilibrium data are necessary to improve the processing of active components with desirable solvents and to reduce the use of organic solvents that can contaminate the product. However, determination of suitable solvent systems can be complex because processing requirements involve multi-components. The aim of this study was to correlate solubility data of active pharmaceutical ingredients in mixed-solvents with local composition-regular solution theory (LC-RST) model. The studied models were paracetamol-water- alcohol (273 K to 313 K) dan L-hydroxyproline-water-alcohol (293 K to 318 K). LC-RST correlated better for both systems relative to Wilson model. The fitting parameters could be used to explain local composition relationship between solute and solvents. The potential application of correlation is for selection of vegetable oil based mixed solvents for separation processes in support of green and sustainable development.

Keywords

Correlation model, active pharmaceutical ingredients, solid-liquid equilibria

1.0 Introduction

Dipolar aprotic solvents [1] and non-polar solvents (organic solvents) are commonly used in the production of pharmaceutical ingredients (API) and foods. In fact, the knowledge of solid-liquid equilibrium data is a prerequisite for the selection of suitable solvents and the dissolution of active components still is a major challenging for the formulation scientists [2]. Solid-liquid equilibrium data can be obtained with experiments, however these required massive time, and materials can be expensive [2, 3]. Besides, the environmental problems caused by the organic solvents are always concerned by the researchers. On conditions that a solid-liquid equilibrium data can be predicted by a mathematical model, the suitable solvent and process conditions can be selected without performing any experiment.

In the previous study [4], regular solution theory (RST) was modified to correlate solid-liquid equilibrium in ternary system. RST was used because it was possible to predict the phase behaviour of non-polarity or non-specific interactions solutions [5, 6]. However, the limitation of RST was on local composition and temperature dependence. Therefore, a new correlation equation that can consider local composition-regular solution theory (LC-RST) with temperature dependence for solid-liquid equilibrium in ternary system was developed.

The aim of this paper was focusing on the correlation of LC-RST on APIs solubility in mixed solvents. The fitting parameters were reduced to a minimum number and quality of correlation was compared with Wilson model. Two group of ternary systems in the total of six systems were chosen from literature were used as the experimental data. The selected group systems were paracetamol-water- alcohol and L-hydroxyproline-water-alcohol. These solutes were selected due their high demand among manufacturers in the pharmaceutical industries. Paracetamol has been used during Covid-19 outbreak [7], while L-hydroxyproline has been used for inhibition of inflammation [8].

2.0 Materials and Methods

2.1 Material

Properties of materials used in this study were obtained from the literature and are tabulated in Table 1.

Table 1: Properties of materials

	Solubility parameter (MPa ^{0.5})	Molecular weight (g/mol)	dHfus (J/mol) x 10 ³	Melting point (K)	Molar volume (cm ³ /mol)
Solutes					
Paracetamol	27.8 ^b	151.2 ^a	27.0 ^a	443.55 ^a	128.8 ^b
L-hydroxyproline	31.9 ^e	131.13 ^c	23.1 ^c	429.37 ^c	94.0 ^d
Solvents					
Water	47.8	18.01			18.0
Isopropanol	23.2 ^f	60.096			92.8 ^g
Ethanol	26.5 ^f	46.07			59.1 ^g
1-Propanol	24.6 ^f	60.095			75.6 ^g

^a Paracetamol molecular weight, dHfus, Melting point [9]

^b Paracetamol molar volume and solubility parameter [10]

^c L-hydroxyproline molecular weight, dHfus, Melting point [11]

^d L-hydroxyproline molar volume [12]

^e L-hydroxyproline solubility parameter [13]

^f Isopropanol, ethanol and 1-propanol molar volume and solubility parameter [14]

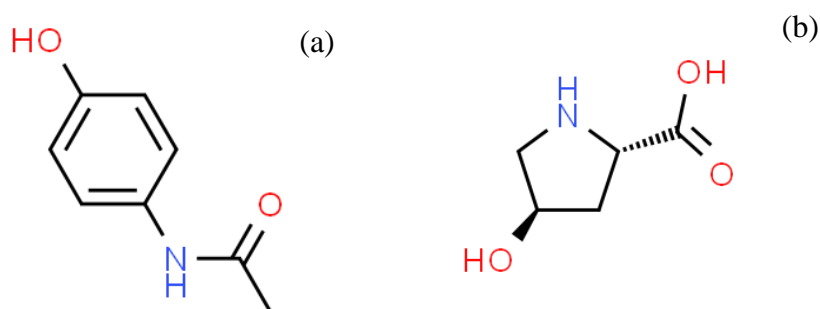


Fig 1. Molecular structure for (a) paracetamol and (b) L-hydroxyproline

Experimental data for paracetamol-water-ethanol [20], paracetamol-water-isopropanol [10], paracetamol-water-1-propanol [21], L-hydroxyproline-water-methanol, L-hydroxyproline-water-ethanol, and L-hydroxyproline-water-1 propanol [15] were obtained from the literature.

Theory

2.1. Solubility calculation model

API solubility in a liquid solvent can be described using standard thermodynamic expressions for solid–liquid equilibria. The solubility of API in a mixed solvent (x_i) is given by eq. (1) [4, 16], where dH_{fus} is the enthalpy of melting of the API, T_m is the melting temperature of the API, R is the universal gas constant, T is the thermodynamic temperature, ΔC_p is the change in heat capacity of the API between its liquid state and solid state ($\Delta C_p = C_{pL} - C_{pS}$) and γ_i is the activity coefficient of the API in the liquid solvent.

$$\ln \frac{1}{x_i} = \ln \gamma_i + \frac{dH_{fus}}{RT_m} \left(\frac{T_m}{T} - 1 \right) - \frac{\Delta C_p}{R} \left(\frac{T_m}{T} - 1 \right) + \frac{\Delta C_p}{R} \ln \frac{T_m}{T} \quad (1)$$

For the application of eq. (1), the pure API was assumed as the solid phase. The triple point temperature and melting point temperatures of the API are generally very close to each other and so the melting point was used as data. The activity coefficient, γ_i for the nonideality between API and mixed solvent can be calculated from several models, such as UNIFAC [17], PC-SAFT [18], COSMO-RS [19], but the API properties (dH_{fus} , T_m , molar volume V^L , solubility parameter δ) are still necessary data. Therefore, a correlation form of regular solution theory (LRST) model was applied as a simple and general model [4].

2.2. Local Composition Regular Solution Theory (LC-RST) model

The activity coefficient γ can be calculated using regular solution theory (RST) [5] as shown in the following equations.

$$RT \ln \gamma_k = V_k^L (\delta_k - \bar{\delta})^2 \quad (2)$$

$$\bar{\delta} = \sum_i \Phi_i \delta_i \quad (3)$$

$$\Phi_i = \frac{x_i V_i^L}{\sum x_i V_i^L} \quad (4)$$

where δ is the solubility parameter and Φ is the volume fraction. The advantage of these equations is that the activity coefficient can be predicted from only from the physical properties of the pure substances in the solvent mixture. However, RST is not able to predict negative deviations from Raoult's law ($\gamma_i < 1$) because the right-hand side of Eq. (2) is always positive. RST theory also lacks temperature dependence in the activity coefficients. To overcome limitations in the RST model, local composition theory and temperature dependence are considered. The local composition is the relationship between solute and solvents. For the explanation of the relationship, the interactions were between the central element and surrounding by elements, therefore a more reliable correlation can be made. Local composition RST (LC-RST) was developed and shown as follows:

$$RT \ln \gamma_k = V_k^L \sum_i \sum_j (A_{ik} - \frac{1}{2} A_{ik}) \Phi_i \Phi_j \quad (5)$$

$$A_{ij} = (\delta_i - \delta_j)^2 + 2l_{ij} \delta_i \delta_j \quad (6)$$

l_{ij} are fitting parameters and assumed to have linear relationship with temperature [4]:

$$l_{ij} = m_{ij}T + b_{ij} \quad (7)$$

where i , j , and k are the notations for solute and solvents in the solution. However, l_{ij} is considered to be not equal to l_{ji} in accordance with local composition models.

There are 12 fitting parameters in eq. (5) for a ternary system, however, in this work, the significant parameters were screened based on the objective function (OF) considering the incremental (step-wise) contribution to eq. (8):

$$OF = \sum (x_{calc} - x_{exp})^2 \quad (8)$$

Equations were solved with visual basic application (VBA) and solver in Microsoft Office Excel.

2.3. Wilson model

For the Wilson model, the activity coefficient γ can be calculated by the following formula [5]:

$$\ln \gamma_k = -\ln \left(\sum_j^N x_j \Lambda_{kj} \right) + 1 - \sum_i^N \frac{x_i \Lambda_{ik}}{\sum_j^N x_j \Lambda_{ij}} \quad (9)$$

$$\Lambda_{ij} = \frac{V_j^L}{V_i^L} \exp \left(-\frac{\Delta g_{ij}}{RT} \right) \quad (10)$$

where Δg_{ij} is the fitting parameter. In this equation, the activity coefficient γ is also calculated by considering the local composition. The Wilson equation contains its own temperature dependence for the local composition.

3.0 Results and Discussion

Fig. 2 shows the step-wise decrease of the objective function according to the number of fitting parameters in the LC-RST model for the paracetamol-water-isopropanol system. When 12 fitting parameters were used (Fig. 2), the lowest SSQ was obtained, however, the incremental decrease in the SSQ for more than six parameters was small. From Fig. 2, it could be concluded that six fitting parameters were sufficient for correlating the data, because the SSQ increased greatly when less than six fitting parameters were used. This approach was also performed for other systems in this paper.

Referring to Fig. 3, LC-RST showed good correlation for both paracetamol-water-isopropanol system and L-hydroxyproline-water-methanol systems. LC-RST described the trends of the data well, which is due to the consideration of local composition and corrected temperature as in Eq. (7). LC-RST was also able to correlate temperature sensitive (Fig. 3a) and non-sensitive systems (Fig. 3b). Even though Wilson model does consider local composition and has built-in temperature dependence, it performed less well than the LC-RST model in correlating the studied systems. For temperature insensitive systems, the Wilson model did not correlate the data well (Fig. 4b). In the Wilson model, the activity coefficient γ is based on purely local composition effects and does not incorporate molecular properties contained in the solubility parameter (e.g. dispersion, polar, hydrogen bond contributions) of the solutes and solvents, which might be the reason for large deviations in correlations.

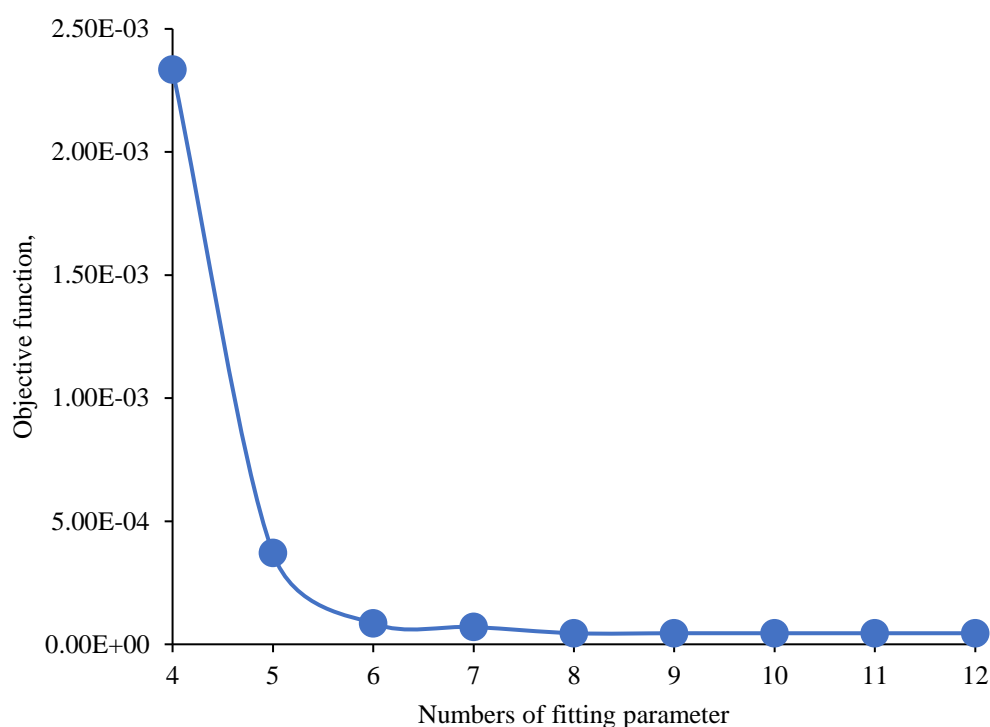


Fig. 2: Number of fitting parameters used in local composition regular solution theory (LC-RST) model for correlating solid liquid equilibrium (paracetamol-water-isopropanol) at 278.15 K to 313.15 K.

Table 2 and Table 3 show the fitting parameters of the LC-RST model for correlating the studied systems. The fitting parameters for both systems were reduced from 12 to 6, which meant the insignificant parameters were removed from the model. For paracetamol-water-alcohol system, paracetamol (1) had local composition interactions with water (2) and alcohol (3) either with temperature effect ("m" term) or without temperature effect ("b" term) as shown by the parameters ($l_{12,b}$, $l_{21,m}$ and $l_{13,m}$). However, local interaction of alcohol to paracetamol was affected by temperature in linear relation with intercept ($l_{31,m}$ and $l_{31,b}$), which can interpret that the solubility of paracetamol in alcohol was greatly improved as temperature increased relative to water. The local relationship between water and alcohol was rather simple, with only $l_{32,m}$ being required to describe the data, which might be related to lower interactions between alcohol-water (3-2) compared with those of API-water (1-2, 2-1) or API-alcohol (1-3, 3-1) interactions.

As for L-hydroxyproline-water-alcohol systems, the local composition relationship between solute and solvents were similar to those discussed above. However, local relationships which were represented by fitting parameters were different, which might be due to the molecular

structure of the solutes (Fig. 1). It was noticed that the local interaction between water and L-hydroxyproline ($l_{21,m}$ and $l_{21,b}$) was also linear in temperature. Such relationships usually occur for high solubility of the solute in solvent, namely, water-L-hydroxyproline and alcohol-paracetamol.

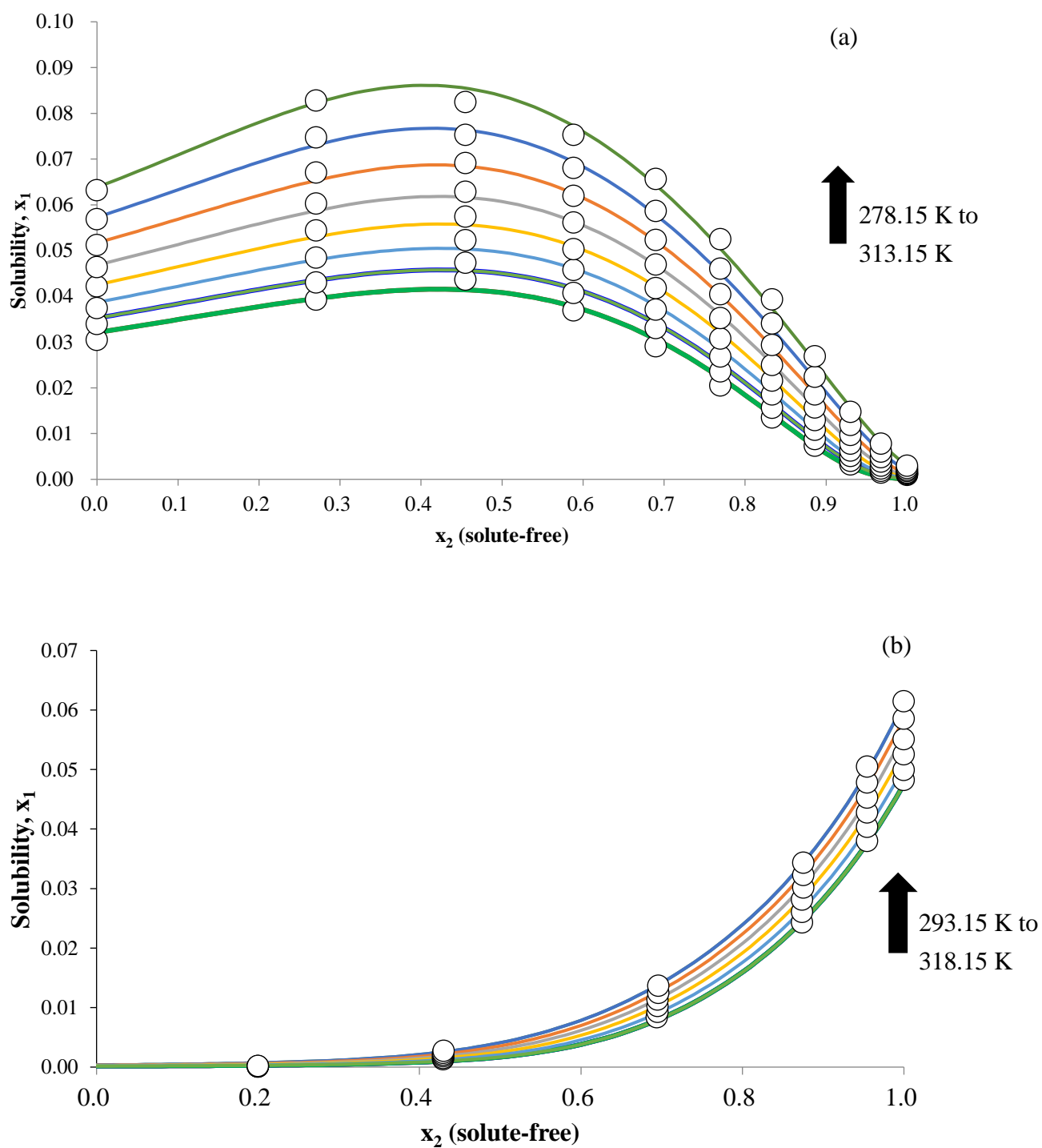


Fig. 3: Solid-liquid equilibrium for (a) paracetamol-water-isopropanol at 278.15 K to 313.15 K [10], (b) L-hydroxyproline-water-methanol at 293.15 K to 318.15 K [15]. Markers: experimental data, solid line: local composition regular solution theory (LC-RST) model, 1: paracetamol, 2: water.

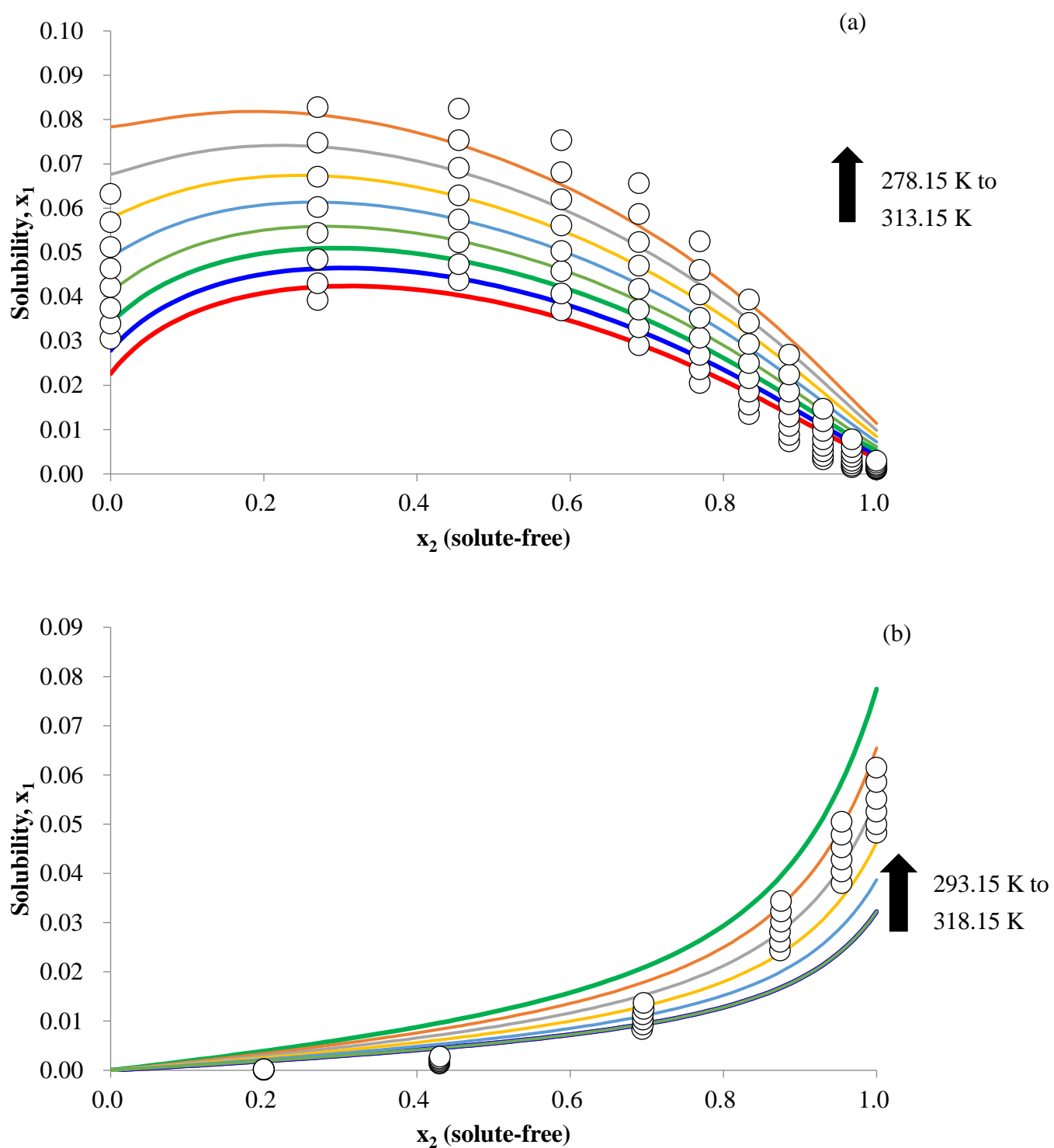


Fig. 4: Solid-liquid equilibrium for (a) paracetamol-water-isopropanol at 278.15 K to 313.15 K [10], (b) L-hydroxyproline-water-methanol at 293.15 K to 318.15 K [15]. Markers: experimental data, solid line: Wilson model, 1: paracetamol, 2: water.

Table 2: SSQ significant fitting parameters of local composition regular solution theory (LC-RST) model for paracetamol-aqueous alcohol systems at 278.15 K to 313.15 K.

	paracetamol-water-ethanol [20]	paracetamol-water-isopropanol [10]	paracetamol-water-1-propanol [21]
$l_{12,b}$	-2.5916E-01	-3.1058E-01	-9.3229E-01
$l_{21,m}$	-3.9995E-04	-4.1694E-04	-4.2196E-04
$l_{13,m}$	3.8472E-04	4.8977E-04	-6.7593E-04
$l_{31,m}$	3.9372E-04	3.5809E-04	7.3191E-05
$l_{31,b}$	-1.2219E-01	-1.2619E-01	-4.3381E-02
$l_{32,m}$	-7.3780E-04	-1.3807E-03	-3.2654E-04
SSQ	7.3344E-05	9.6896E-05	3.4417E-05

Table 3: SSQ significant fitting parameters of local composition regular solution theory (LC-RST) model for L-hydroxyproline-aqueous alcohol systems at 293.15 K to 318.15 K.

	L-hydroxyproline-water-methanol [15]	L-hydroxyproline-water-ethanol [15]	L-hydroxyproline-water-1-propanol [15]
$l_{12,m}$	-3.5065E-03	-2.8265E-03	-1.7502E-02
$l_{21,m}$	-1.3733E-03	-1.1738E-03	-1.0064E-02
$l_{21,b}$	2.1062E-01	1.7925E-01	2.3103E+00
$l_{13,m}$	-7.1078E-03	-5.4328E-03	-7.7043E-02
$l_{31,m}$	2.545E-04	1.7004E-04	9.3781E-04
$l_{23,m}$	-1.6598E-03	-1.8350E-03	-1.8941E-03
SSQ	5.2437E-06	4.9075E-05	7.3962E-05

4. Conclusions

Local composition regular solution theory (LC-RST) model, which considers parameter related to local composition and temperature dependence, was used to correlate solid-liquid equilibrium data in ternary systems. The fitting parameters of LC-RST could be reduced from 12 to 6 using step-wise parameter fitting technique. For comparison, LC-RST model showed better correlation for paracetamol-water-alcohol and L-hydroxyproline-water-alcohol than Wilson model. Analysis of the fitting parameter of the LC-RST model were useful for understanding local composition in temperature sensitive and temperature insensitive pharmaceutical compound solubilities in mixed-solvents.

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