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Research Article

Solubility Prediction of Lornoxicam in Different Pure Solvents Using Semi-Empirical Correlations and Thermodynamic Models

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Abstract

The solubility data of Active Pharmaceutical Ingredients in organic solvents is an essential for pharmaceutical crystallization and drug formulation. In this work, two semi-empirical correlations- the Yaws model and λ-h model- and two thermodynamic models – Wilson Model and the Non-random two-liquid model- are used to estimate the solubility of lornoxicam in ethanol and water. The model parameters and correlations coefficients are calculated by optimizing the average relative deviation. The values of these parameters will be helpful to estimate the solubility of lornoxicam at different temperatures where the experimental solubility data is not available. The predicted solubility data of lornoxicam can be further utilized in the pharmaceutical crystallization and drug formulation.

Keywords: *Solubility; crystallization; lornoxicam; thermodynamic model; mixing property.*

1. Introduction

Lornoxicam is a non-steroidal anti-inflammatory drug (NSAID) having low aqueous solubility and high permeability through biological membranes leading to low bioavailability [1]. Several approaches such as complexation with cyclodextrins, solid dispersion, emulsion and co-crystallization are employed to enhance the solubility and subsequently bioavailability of active pharmaceutical ingredients (APIs). The low aqueous solubility of lornoxicam leads to a slow dissolution rate as evident by Noyes –Whitney equation [2]. Nanoparticles exhibited higher saturation solubility as compared to bulk particles which can be described by the Ostwald-Freundlich equation [3]. Several particle engineering based approaches such as solid-lipid particles, nanocrystals and nano-emulsion have been explored recently to enhance the dissolution rate of lornoxicam [4–7].

Noyes-Whitney's equation:

$$\frac{dW}{dt} = \frac{DA(C_S - C)}{L} \tag{1}$$

where $\frac{dW}{dt}$ is the dissolution rate, A is the surface area of the particles, C_s is the drug's saturation solubility, C is the drug's concentration in the dissolution medium, D is the diffusion coefficient, and L is the thickness of the diffusion layer.

Ostwald-Freundlich's equation:

$$\log\frac{C_s}{C_\infty} = \frac{2\sigma V}{2.303RT\rho r} \tag{2}$$

where C_s is the saturation solubility, C_∞ is the solubility of the large particles of the drug, V is the molar volume, σ is the interfacial tension, R is the universal gas constant, T is the absolute temperature, r is the radius of the drug particle and ρ is the density of the drug.

Liquid antisolvent crystallization (LASC) is emerging as a promising approach to prepare the nanoparticles of APIs having poor aqueous solubility. In the liquid antisolvent process, a drug is first dissolved in a suitable solvent followed by its mixing with the antisolvent. To carry out LASC, the solubility of a drug must be known in different solvents. The solubility is measured experimentally at different temperatures which is time-consuming and expensive. Therefore, the prediction of solubility via semi-correlations and thermodynamic models is desirable at different temperatures. Yarraguntla et al. prepared the nanocrystals of lornoxicam via the antisolvent precipitation method [8]. The dissolution rate of the nano-sized drug is substantially increased, from 30.62 % for the raw drug to 60.44 % for the processed drug in 60 minutes. They reported that the average particle size reduced from 3.04 µm to 149 nm.

In this work, the solubility of lornoxicam in different pure solvents using semi-empirical correlations and thermodynamic models has been carried out. The experimental values have been compared with the model predictions. This study will be helpful for the drug formulation techniques to improve the dissolution rate and bioavailability of lornoxicam.

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2. Semi-empirical Correlations and Thermodynamic Models

The equilibrium solubility data of lornoxicam is correlated with the Yaws model, Buchowski-Ksiazaczak (λh) model, Wilson model and NRTL model. The description of these models is given in this section.

2.1 Yaws Model

The solubility data of API can be fitted as a function of temperature by the following semi-empirical correlation also known as the Yaws model [9].

$$\ln x_1 = C_1 + \frac{C_2}{T} + \frac{C_3}{T^2} \tag{3}$$

where C1, C2 and C3 are the model parameters which are estimated by fitting the solubility data with temperature. T is the temperature in Kelvin.

2.2 Buchowski-Ksiazaczak (λh) Model

The solubility of a drug is calculated by two parameters (λ *and* h) model described by the following semi-empirical correlation [10]. This model requires the melting temperature (T_m) of the drug which can be calculated by differential scanning calorimetry (DSC) analysis.

$$\ln\left[1+\lambda\left(\frac{1-x_1}{x_1}\right)\right] = \lambda h\left[\frac{1}{T}-\frac{1}{T_m}\right] \tag{4}$$

2.3 NRTL Model

The solubility of solute can be written as the following form by the NRTL thermodynamic model [11].

$$\ln x_1 = \frac{\Delta_{fus}H}{R}\left(\frac{1}{T_m}-\frac{1}{T}\right) - \ln\gamma_1 \tag{5}$$

where, γ_1 is the activity coefficient for lornoxicam in the mixture which can be computed by the NRTL model

$$\ln\gamma_1 = x_2^2\left[\frac{\frac{\Delta g_{21}}{RT}\left(e^{-\alpha_{12}\frac{\Delta g_{21}}{RT}}\right)^2}{\left(x_1+x_2e^{-\alpha_{12}\frac{\Delta g_{21}}{RT}}\right)^2} + \frac{\frac{\Delta g_{12}}{RT}\left(e^{-\alpha_{12}\frac{\Delta g_{12}}{RT}}\right)^2}{\left(x_2+x_1e^{-\alpha_{12}\frac{\Delta g_{12}}{RT}}\right)^2}\right] \tag{6}$$

where, α_{12} represent the non-randomness of the mixture and the value of this lies between 0.2 to 0.47. Δg_{12} and Δg_{21} are adjustable energy interaction energy parameters.

2.4 Wilson Model

The Wilson equation is also widely used to describe the behavior of the solid-liquid phase equilibrium. The activity coefficient by the Wilson thermodynamic model is calculated by the following expression [12].

$$\ln\gamma_1 = -\ln\left(x_1+\wedge_{12}x_2\right) + x_2\left[\frac{\wedge_{12}}{x_1+\wedge_{12}x_2} - \frac{\wedge_{21}}{x_2+\wedge_{21}x_1}\right] \tag{7}$$

$$\wedge_{12} = \frac{v_2}{v_1}\exp\left(-\frac{\Delta\lambda_{12}}{RT}\right) \tag{8}$$

$$\wedge_{21} = \frac{v_1}{v_2}\exp\left(-\frac{\Delta\lambda_{21}}{RT}\right) \tag{9}$$

v_1 and v_2 are the mole volume of lornoxicam and solvent respectively.

The model parameters are estimated using the non-linear regression method. To examine the applicability and accuracy of these models, the average relative deviation (ARD%) as shown by equation (10) has been optimized and calculated.

$$ARD\% = \frac{100}{N}\sum_{i=1}^{N}\left|\frac{x_i^{\exp}-x_i^{cal}}{x_i^{\exp}}\right| \tag{10}$$

where $x_i^{\exp}$ and x_i^{cal} represent the experimental and calculated solubility of lornoxicam respectively. N stands for the number of experimental points. Shakeel et al. reported the experimental data of the solubility of lornoxicam in ethanol and water [13].

2.5 Thermodynamic Function of Mixing

The mixing properties such as mixing enthalpy, mixing entropy and mixing Gibbs free energy for ideal binary solutions can be estimated by the given equations [14] :

$$\Delta_{mix}G^{id} = RT\sum_i^N x_i\ln x_i \tag{11}$$

$$\Delta_{mix}H^{id} = 0 \tag{12}$$

$$\Delta_{mix}S^{id} = -R\sum_i^N x_i\ln x_i \tag{13}$$

where x_i is the mole fraction of component i.

In the real binary system, the mixing properties can be calculated from the ideal ones given the known excess properties

$$\Delta_{mix}G = \Delta_{mix}G^{id} + G^E \tag{14}$$

$$\Delta_{mix}H = \Delta_{mix}H^{id} + H^E \tag{15}$$

$$\Delta_{mix}S = \Delta_{mix}S^{id} + S^E \tag{16}$$

where G^E, H^E, and S^E refers to the excess properties, which can be computed by the following equations:

$$G^E = RT\sum_i^N x_i\ln\gamma_i \tag{17}$$

$$G^E = RT(x_1\ln\gamma_1 + x_2\ln\gamma_2) \tag{18}$$

$$G^E = -RT[x_1\ln(x_1+x_2\Lambda_{12}) + x_2\ln(x_2+x_1\Lambda_{21})] \tag{19}$$

$$H^E = -T^2\left[\partial(G^E/T)/\partial T\right] \tag{20}$$

$$H^E = x_1x_2\left[\frac{\Delta\lambda_{12}\Lambda_{12}}{(x_1+\Lambda_{12}x_2)} + \frac{\Delta\lambda_{21}\Lambda_{21}}{(x_2+\Lambda_{21}x_1)}\right] \tag{21}$$

$$S^E = \frac{H^E-G^E}{T} \tag{22}$$

3. Results and Discussions

In this work, the solubility of lornoxicam is predicted by different semi-empirical correlations and thermodynamics models. In table 1, the experimental data and model predictions are reported. Table 2 shows that coefficient of correlation (R^2) of these models. It is evident from Figure 1 that the Yaws model can accurately predict the solubility of lornoxicam in ethanol and water. The average relative error of Yaws models is found to be 1.67 % and 2.24 % for ethanol and water respectively. The values of A, B and C are found 5.5944, -5152.7, 1190.15 and 5.4293, -5427.08, 5074.63 for ethanol and water respectively. With these values of parameters, the solubility at any temperature can be calculated.

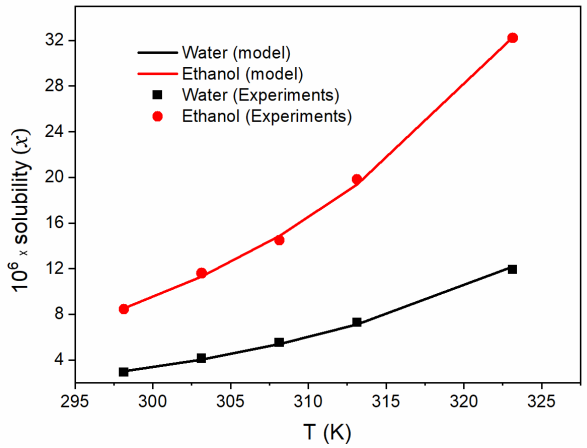

Figure 1: Solubility estimation by Yaws model for ethanol and water and comparison with experiments [13].

Table 1: A comparison between experimental data and model values.

T	Shakeel et al.	Yaws	$(\lambda - h)$	NRTL	Wilson
Solubility of lornoxicam in water, $x \times 10^6$					
298.15	2.91	3.002	1.53	2.59	2.47
303.15	4.12	4.05	2.61	3.72	3.62
308.15	5.52	5.4	4.37	5.28	5.22
313.15	7.27	7.14	7.22	7.41	7.45
323.15	11.9	12.17	18.8	12.46	14.69
Solubility of lornoxicam in ethanol, $x \times 10^6$					
298.15	8.43	8.51	5.73	7.41	6.72
303.15	11.6	11.3	8.95	10.46	9.85
308.15	14.5	14.9	13.8	14.60	14.27
313.15	19.8	19.4	20.88	20.17	20.42
323.15	32.2	32.3	46.24	33.37	40.47

Table 2: Coefficient of correlation value for different models.

API-solvent system	Coefficient of Correlation (R^2 value) Yaws model	$(\lambda - h)$ model	NRTL model	Wilson model
Lornoxicam-water	0.9469	0.2526	0.8104	0.5230
Lornoxicam-ethanol	0.9972	0.3314	0.8301	0.4849

Buchowski-Ksiazaczak ($\boldsymbol{\lambda h}$) model is found to predict the solubility of lornoxicam in ethanol and water with the highest average relative error. To correlate the solubility data with this model, the fusion temperature (T_m) is required. Kharwade et al. reported the fusion temperature of lornoxicam 479.8 K measured by differential scanning calorimetry [15]. Figure 2 shows the solubility of lornoxicam in ethanol and water. The average relative deviation of the predicted value from the experimental value is found to be 21.8 % and 32.66 % for ethanol and water respectively. The parameters value, λ *and* h to minimize the average relative deviation are found 0.1565, 51389 and 0.3262, 29629,55 for ethanol and water respectively.

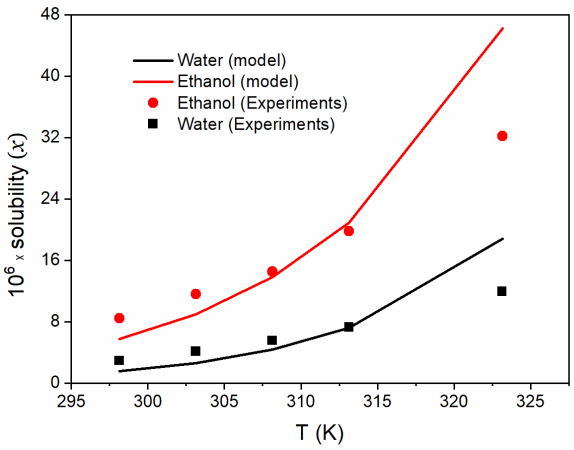

Figure 2: Solubility estimation by Buchowski-Ksiazaczak ($\boldsymbol{\lambda h}$) model for ethanol and water and comparison with experiments [13].

Wilson model is a thermodynamic model based upon activity coefficient to estimate the solid-liquid equilibria. The model parameters $\Delta\lambda_{12}$ *and* $\Delta\lambda_{21}$ are estimated to predict the solubility of lornoxicam at different temperatures. The ΔH_f value is required to estimate the solubility which is reported to be 54.3 kJ/mol [15]. The molar volume of lornoxicam is calculated by dividing the molar mass by the density at room temperature. The density of lornoxicam is estimated by the following expression

$$\rho = \frac{zM}{VN_A} \tag{23}$$

where z is the number of formula of lornoxicam in the crystal unit cell, M is the molar mass, V is the volume of the unit cell and N_A is Avogadro number. Nijhawan et al. reported the crystallographic parameters of lornoxicam [16]

The values of model parameters ($\Delta\lambda_{12}$ *and* $\Delta\lambda_{21}$) are 150.5255, 45333.59 for ethanol and 2767 .707, 47771.45 for water respectively. The average relative deviation is found 10.27 % and 11.73 % for ethanol and water respectively.

The NRTL model is derived from the concept of local composition and is commonly used to describe solid-liquid equilibria. As evident from figure 4, the NRTL model gives good fitting of the experimental solubility data of lornoxicam. The average relative deviation is found 8.11 % for ethanol and 9.23 % for water. The Δg_{12} and Δg_{21}, adjustable energy interaction parameters, are found 3374.12 and 43081.98 for ethanol and 5997.511 and 43209.33 for water. Figure 5 and Figure 6 show the comparison of experimental data with predicted values by each model for ethanol and water respectively.

Kui and Yajun [17] measured the solubility of 2-chlorobenzenesulfonamide in different solvents ad found that NRTL model gave the best fitting performance as

compared to $(\lambda - h)$ model and Wilson model. The authors did not correlate the solubility data with the Yaws model In our work also, NRTL model also gave better results as compared with $(\lambda - h)$ model and Wilson model. However, Yaws model, as it is a semicorrelation rather than based on the complete theoretical principle, gave best result.

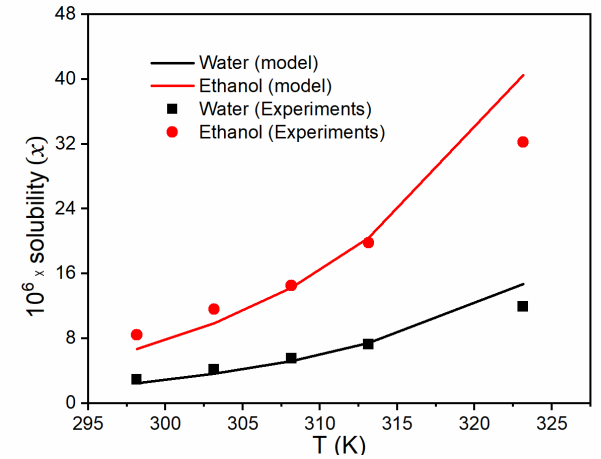

Figure 3: Solubility estimation by Wilson model for ethanol and for water and comparison with experiments [13].

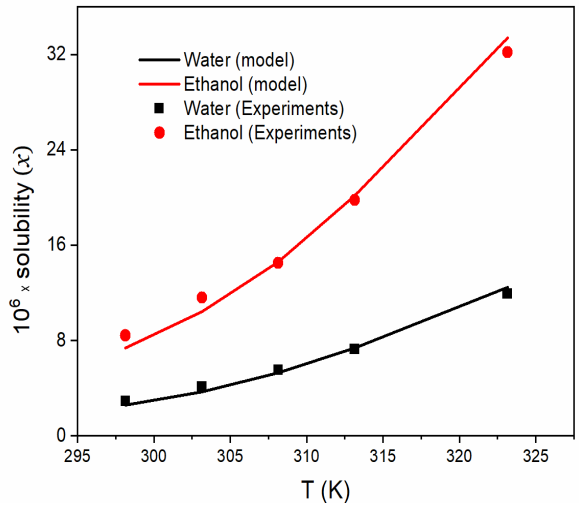

Figure 4: Solubility estimation by NRTL model and for ethanol and for water water and comparison with experiments [13].

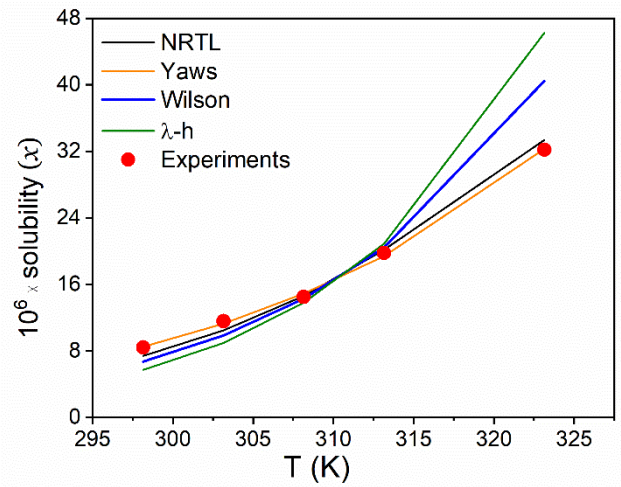

Figure 5: A comparison of experimental solubility data [13] of lornoxicam in ethanol with the predicted values from Yaws model, $\lambda - h$ model, Wilson and NRTL model.

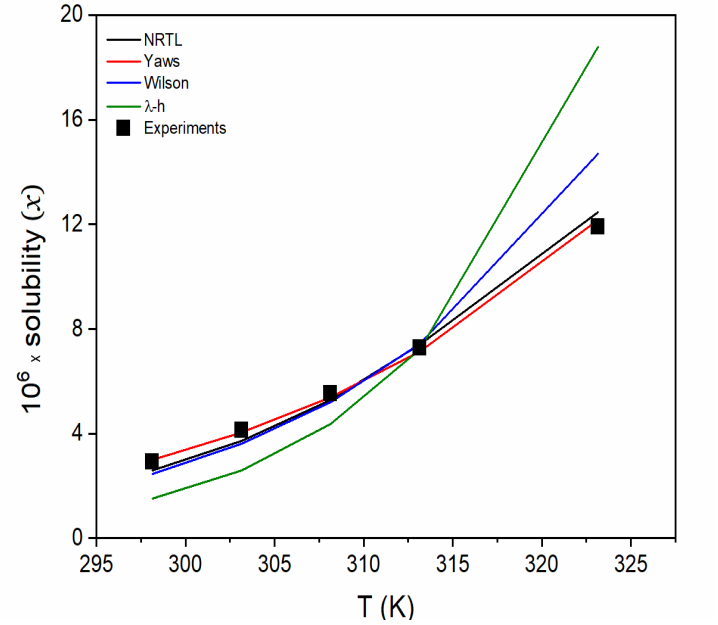

Figure 6: A comparison of experimental solubility data [13] of lornoxicam in water with the predicted values from Yaws model, $\lambda - h$ model, Wilson and NRTL model.

The enthalpy of mixing, entropy of mixing and Gibbs free energy of mixing in ethanol and water are estimated and shown in Table 3. The Gibbs free energy of mixing in all mono-solvents is negative indicating a spontaneous and favorable mixing process of lornoxicam in ethanol and water. The enthalpy of mixing of lornoxicam is positive which means that dissolution is an endothermic process.

Table 3: The thermodynamic properties of lornoxicam in ethanol and water.

T/K	$\Delta_{mix}G$ (kJ/mol)	$\Delta_{mix}H$ (kJ/mol)	$\Delta_{mix}S$ $(kJ/mol.K)$
Ethanol			
298.15	-0.1637	0.0011	5.528×10^{-4}
303.15	-0.2299	0.0015	7.6348×10^{-4}
308.15	-0.3189	0.0022	10.42×10^{-4}
313.15	-0.4371	0.0031	14.06×10^{-4}
323.15	-0.7945	0.0059	24.77×10^{-4}
Water			
298.15	-0.0570	0.0068	2.1403×10^{-4}
303.15	-0.0814	0.0100	3.0150×10^{-4}
308.15	-0.1148	0.0144	4.1945×10^{-4}
313.15	-0.1599	0.0206	5.7644×10^{-4}
323.15	-0.2999	0.0406	1.54×10^{-4}

4. Conclusion

In this work, the solubility of lornoxicam in ethanol and water has been modeled using two semi-empirical correlations- Yaws model, Buchowski-Ksiazaczak ($\boldsymbol{\lambda h}$) model - and two thermodynamic models – NRTL model and Wilson Model. The solubility data is required for antisolvent crystallization and different formulation techniques. Each model predicted the solubility increased monotonously with increasing temperature. The best prediction was given by the Yaws model followed by the NRTL model. Based upon the thermodynamic mixing properties, it can be concluded that dissolution of lornoxicam in ethanol and water is spontaneous, endothermic and entropy-driven.

Nomenclature:

A	Surface area of the particle (m^2)
C	Concentration of solute (-)
C_1, C_2, C_3	Constants in Yaws model (-)
C_s	saturation solubility (mol/m^3)
D	diffusion coefficient (m^2/s)
L	thickness of the diffusion layer (m)
C_∞	Solubility of large particles of drug (mol/m^3)
V	Molar volume (m^3)
T	Temperature (K)
R	Universal gas constant (J/mol K)
ρ	Density of drug (kg/m^3)
σ	Interfacial tension (N/m)
λ, h	Constants in Buchowski-Ksiazaczak model (-)
x_1	Drug mole fraction (-)
T_m	Melting temperature of drug (K)
γ_1	Activity coefficients (-)
$\Delta_{fus}H$	Fusion enthalpy (J/m)
x_2	Mole fraction of solvent (-)
$\Delta g_{12}, \Delta g_{21}$	adjustable energy interaction energy parameters in NRTL model (-)
α_{12}	non-randomness of the mixture (-)
$\Delta\lambda_{12}, \Delta\lambda_{21}$	adjustable energy interaction energy parameters in Wilson model (-)
$\Delta_{mix}G^{id}$	Gibbs free energy for ideal solution (J/mol)
$\Delta_{mix}H^{id}$	Enthalpy of mixing for ideal solution (J/mol)
$\Delta_{mix}S^{id}$	Entropy of mixing for ideal solution (J/mol K)
S^E , G^E , H^E	Excess Entropy, Gibbs Free Energy and Enthalpy

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