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The determination and correlation of the solubility of naproxen in acetone and water mixtures

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ABSTRACT

The equilibrium solubility of the pharmaceutical substance, (S)-(+)-6-Methoxy-alpha-methyl-2-naphthaleneacetic acid (naproxen) in solvent consisting of acetone and water at different volume ratios is determined under different temperatures from 0 °C to 20 °C in increments of 5 °C. NRTL and Wilson models can describe the equilibrium of vapor–liquid and liquid–liquid systems successfully. In this paper they are used to correlate solid–liquid equilibrium for naproxen in acetone and water mixtures. The results show that NRTL and Wilson models correlate the solubilities of naproxen in acetone and water mixtures successfully under different temperatures. The interaction parameters between naproxen and acetone for Wilson and NRTL models are obtained.

1. Introduction

Today research on thermodynamic properties of pharmaceutical substance is a very active area. The solid–liquid equilibrium regarding the solid solubility in the solvent, which is an important branch of thermodynamics, has been registered broad research interests in recent years [1,2]. As basis of a crystallization process study, solubilities data are quite helpful in the final yield prediction [3]. Naproxen has been widely used in the treatment of rheumatic diseases. It is a propionic acid derivative with analgesic and anti-inflammatory activities. Naproxen has been well studied in rheumatoid arthritis and found to be effective as aspirin but better tolerated, it is also effective in degenerative joint diseases of the hip and knee, although further well designed studies are needed to define more clearly its relative place compared with newer drugs such as diclofenac and diflunisal [4,5]. The solubility of naproxen has been studied in ethanol + water, propylene glycol + water and ethanol + propylene glycol mixtures. The solubility of naproxen in ethyl ethanol mixtures under several temperatures has been studied and is correlated with Jouyban–Acree model [6–9].

So far, lots of theoretical models for fluid phase equilibrium have been proposed, as van Lear theory, Wilson equation, NRTL equation, UNIQUAC model, UNIFAC model etc. The more commonly used are summarized as follows [10]:

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

ΔH_{tp} represents the change of enthalpy under the experimental conditions. ΔC_p means the heat capacity tolerance under the experimental conditions. ΔV represents the change of molar volume under the experimental conditions, and P shows the total pressure of phase equilibrium. $P - P_{tp}$ indicates the pressure correction term. T_{tp} says melting temperature. x is the solubility expressed in mole fraction and γ is activity coefficient.

Generally, the pressure correction term and the thermal tolerance in formula (1) can be ignored. And the temperature of the triple point is usually very close to the melting temperature under atmospheric pressure, formula (1) can be simplified as [11]:

$$\ln(\gamma x) = \frac{\Delta H_m}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) \quad (2)$$

ΔH_m represents the melting enthalpy, and T_m is the melting temperature.

In formula (2) activity coefficient γ is the function of solvent composition. It can be gotten according to the Wilson equation and the NRTL equation which is commonly used to carry out regressions and associations correlating the solubility data [12–15].

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Table 1
Solid–liquid equilibrium data in naproxen (1) + water (2) + acetone (3) ternary system.

	$x_1 \times 10^3$	x_2	x_3
0 °C	0.720	0.804	0.196
	2.72	0.731	0.267
	8.09	0.633	0.359
	13.6	0.570	0.416
	19.3	0.497	0.484
	28.6	0.395	0.577
	33.3	0.342	0.625
	36.4	0.302	0.662
5 °C	0.930	0.803	0.196
	3.48	0.730	0.267
	9.96	0.631	0.359
	15.3	0.569	0.416
	21.5	0.496	0.483
	29.8	0.394	0.576
	34.5	0.342	0.624
	37.9	0.302	0.661
10 °C	1.17	0.803	0.196
	4.29	0.729	0.266
	12.5	0.630	0.358
	17.9	0.568	0.415
	24.3	0.494	0.481
	31.8	0.393	0.575
	35.7	0.341	0.623
	38.7	0.301	0.660
15 °C	1.34	0.803	0.196
	5.42	0.729	0.266
	14.5	0.628	0.357
	20.5	0.566	0.413
	27.3	0.493	0.480
	35.3	0.392	0.573
	38.9	0.340	0.621
	43.0	0.300	0.657
20 °C	1.53	0.803	0.196
	6.27	0.728	0.266
	16.3	0.627	0.356
	23.6	0.564	0.412
	33.6	0.490	0.477
	42.9	0.389	0.568
	48.4	0.337	0.615
	52.9	0.297	0.650

In this paper Wilson model and the NRTL model associate the solubility of Naproxen in acetone and water mixture with minimal associated error successfully.

2. Experimental

2.1. Materials

Sparingly soluble naproxen was selected as the solute and acetone as organic solvent in the study. Naproxen (Cat. No. 265467, >99.5%) was purchased from Nanjing Chemlin Chemical Industry Co., Ltd. Acetone (Cat. No. C072011231, ≥99.0%) was purchased from Nanjing Chemical Reagent Co., Ltd. Distilled water was used to prepare mixed solvent. All the chemicals were used as received.

Table 2
the required parameters in Wilson equation.

Naproxen			Acetone	Water	The interaction parameters of water–acetone
$\Delta_m H$ (J mol^{-1})	T_m (K)	V^L (cm^3 mol^{-1})	V^L (cm^3 mol^{-1})	V^L (cm^3 mol^{-1})	Δg_{32} (J mol^{-1})
31730 [18]	429	192.2	75.1	18.016	1223.32

Table 3
the model parameters for naproxen + acetone system.

Wilson model		NRTL model		
Δg_{13} (J mol^{-1})	Δg_{31} (J mol^{-1})	Δg_{13} (J mol^{-1})	Δg_{31} (J mol^{-1})	α_{13}
9811.4	−2306.1	48056	−28491	0.0385

2.2. Experimental details

The experiments were carried out in a jacketed vessel, which was made of perspex. A digital cryostat (HH-4, Guohua Electric Appliance Co., Ltd.) was used to control the temperature. Circulating water in the jacket was used to maintain the system with a constant temperature. The temperature of process vessel was monitored with a digital thermometer which had a resolution of ±0.1 °C. The solubility of naproxen in different solvent systems (mixture of acetone and water at different volume ratios) was determined under different temperatures from 0 °C and 20 °C in increments of 5 °C. Excess amount of solute was put into the vessel containing solvent with certain volume and then stirred for 1.5 h. Repeated experiments proved that 1.5 h are enough to saturate the solvent systems.

3. Results and discussion

For multicomponent systems, activity coefficient equation according to Wilson model could be written as Eq. (3).

$$\ln \gamma_i = 1 - \ln\left(\sum_j^n (\Lambda_{ij} x_j)\right) - \sum_k^n \left(\frac{\Lambda_{ki} x_k}{\sum_j^n (\Lambda_{kj} x_j)}\right) \quad (3)$$

$$\Lambda_{ij} = \frac{V_j}{V_i} \exp\left[-\frac{\Delta g_{ij}}{RT}\right] \quad (4)$$

x_1 is the solubility expressed in mole fraction of component i, x_2 is an adjustable parameter, and it is related to the liquid molar volume of pure components i and j. V_i is the liquid molar volume of pure liquids of component i. Δg_{ij} is the interaction parameters between components i and j, which can be obtained from the regression of phase equilibrium experimental data.

Given naproxen is almost insoluble in water, the energy parameters Λ_{12}, Λ_{21} between naproxen and water molecules can be ignored, ($\Lambda_{12} = \Lambda_{21} = 0$), in the naproxen (1) + water (2) + acetone (3) ternary system, Eq. (3) is thus simplified to

$$\ln \gamma_1 = 1 - \ln(x_1 + x_3\Lambda_{13}) - \frac{x_1}{x_1 + x_3\Lambda_{13}} - \frac{x_3\Lambda_{31}}{x_1\Lambda_{31} + x_2\Lambda_{32} + x_3} \quad (5)$$

Then x_i can be obtained from the experiment. Interaction parameters Δg_{32} in $\Lambda_{32} = (V_2/V_3)\exp(-\Delta g_{32}/RT)$ in Eq. (5) were obtained from the relevant literature [16]. From literature [16] the binary interaction parameter of water + acetone in Wilson equation is $\Delta g_{32} = 1223.32$ J/mol. Therefore, the interaction parameters Δg_{13} and Δg_{31} of naproxen + acetone in Wilson model were gotten from the regression of solubility data.