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Solubility of *β*-Artemether in Methanol + Water and Ethanol + Water from (288.85 to 331.95) K

Yang Zhang, Yanbin Jiang,* Kaixia Li, and Yu Qian

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China

The solubility of *β*-artemether in methanol + water and ethanol + water was measured over the temperature range from (288.85 to 331.95) K under atmospheric pressure using a gravimetric method. The experimental data were satisfactorily correlated with a modified empirical logarithmic equation. The experimental solubility data show good agreement with the calculated values. The relative average deviations (RADs) between the experimental and calculated values are less than 3 %.

Introduction

β-Artemether (CAS no. 71963-77-4) is an important active pharmaceutical ingredient that can be used as an antimalaria drug. Malaria is a parasite disease caused by plasmodium; 300 to 500 million cases of malaria occur annually, and more than 1 million people die of malaria.[1] The key problem for this disease is drug resistance of the plasmodium, especially for quinine and chloroquine. *β*-Artemether was found to be an effective antimalaria active pharmaceutical ingredient without report of drug resistance and recommended by WHO.[2]

The manufacturing process for *β*-artemether includes the synthesis of *β*-artemether from artemisinin and the separation from the mother liquor. The artemisinin is reduced to dihydroartemisinin, and dihydroartemisinin is esterified to *β*-artemether; then, *β*-artemether is purified. Crystallization is the key purification process for quality control of *β*-artemether, and fundamental solubility data of *β*-artemether are crucial for the crystallization process. Although it is well known that *β*-artemether is insoluble in water and soluble in some organic solvents, for example, methanol, ethanol, acetone, and so on, there were no detailed solubility data reported. In this study, to provide fundamental data for process and product quality control of *β*-artemether crystallization, the experimental solubility data of *β*-artemether in methanol + water and ethanol + water were determined using a gravimetric method[3−5] under atmospheric pressure and were correlated using the modified empirical logarithmic equation.

Experimental Section

Materials. *β*-Artemether was obtained from Guangzhou Hanfang Pharmaceutical with stated mass fraction purity of > 99.5 %. The melting point of *β*-artemether was 360.25 K, which was measured using a differential scanning calorimeter (DSC, TA SDT Q600). Potassium nitrate, methanol, and ethanol were of analytical grade and were purchased from Guangdong Guanghua Chemical Reagents. All of the chemicals were used as obtained. Redistilled water was used in all experiments.

Table 1. Comparison of Mass Fraction Solubility Data of Potassium Nitrate in Water at Different Temperature among Reference 7 ($\boldsymbol{w}_{\mathrm{ref}}{}^{7}$), Reference 8 ($\boldsymbol{w}_{\mathrm{ref}}{}^{8}$), and This Work ($\boldsymbol{w}$)

T/K	w	$w_{\mathrm{ref}}{}^{7}$	$w_{\mathrm{ref}}{}^{8}$	$100\lvert(w - w_{\mathrm{ref}})/w\rvert$	$100(1/n)\cdot\sum_{i=1}^{n}\lvert(w - w_{\mathrm{ref}})/w\rvert$
293.65	0.242	0.243		0.24	
300.85	0.301	0.298		0.98	
303.85	0.325	0.320		1.41	1.56
308.65	0.365	0.356		2.35	
313.35	0.403	0.391		2.80	
283.15	0.174		0.173	0.39	
293.15	0.245		0.240	2.10	
303.15	0.320		0.314	1.75	1.27
313.15	0.393		0.390	0.85	

Solubility Measurement. The apparatus used for the solubility determination was a small glass cell (50 mL) fitting with a calibrated thermometer with an uncertainty of ± 0.1 K and a magnetic stirrer. The cell was immersed in a thermostat water bath (THD 0506, Ningbo Tianheng Instrument Factory) controlled and maintained with an uncertainty of ± 0.05 K. To prevent solvent evaporation, the cell was sealed using a rubber plug. For each measurement, excess quantities of *β*-artemether and prepared solvent mixture were charged to the cell, and the cell was heated to a constant temperature with continuous stirring for 3 h, which was enough for establishing the equilibrium of the solute−solvent mixture; stirring was then stopped, and the cell was kept undisturbed for 1 h to ensure that the crystal had separated and the equilibrium was established. A small amount of crystal was left undissolved in the lower portion of the cell; about 2 mL of the upper clean portion was withdrawn to a weighed measuring vial (m_1) using a preheated warmed syringe. The vial was weighed (m_2) and put in a vacuum oven at 313.15 K; a filter cloth covered the vial so as to avoid dust contamination. After the solvent was completely dried, the vial was reweighed (m_3). All of the weights were measured using an electronic balance (AL 104, Mettler Toledo) with an uncertainty of 0.1 mg. The mole fraction of solubility of the *β*-artemether can be determined from eq 1[6]

$$x = [(m_3 - m_1)/M_{\mathrm{solute}}]/[(m_3 - m_1)/M_{\mathrm{solute}} + (m_2 - m_3)w/M_{\mathrm{solvent}} + (m_2 - m_3)(1 - w)/M_{\mathrm{W}}] \quad (1)$$

where m_1, m_2, and m_3 stand for the masses of the vial, the vial containing the sample, and the vial containing the solid solute, M_{solute}, M_{w}, and M_{solvent} stand for the molecular weights of the *β*-artemether, water, and ethanol (or methanol), and w is the

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* Corresponding author. Tel: +86-20-87112051. E-mail: cebjiang@scut.edu.cn.

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Table 2. Solubility (x) of β-Artemether in Methanol (w) + Water ($1 - w$)[a]

T/K	10^3x	$100[(x - x_c)/x]$	T/K	10^3x	$100[(x - x_c)/x]$	T/K	10^3x	$100[(x - x_c)/x]$
				$w = 1.0000$				
289.45	26.34	0.82	303.55	64.91	−0.63	317.35	222.44	−0.85
291.15	29.47	2.81	306.35	82.43	0.92	319.45	297.35	6.27
294.05	34.28	1.09	308.25	98.79	3.05	322.05	355.20	−3.75
296.95	40.49	−0.59	310.15	116.23	2.74			
299.05	46.30	−1.39	312.95	149.20	2.15			
300.75	51.88	−2.09	315.65	186.54	−1.46			
				$w = 0.7973$				
288.85	6.60	1.05	303.55	9.87	−2.18			
290.85	6.58	−2.02	306.25	11.53	−0.44			
293.85	6.95	−2.55	312.75	17.47	0.37			
296.25	7.88	3.57	315.55	21.30	−0.61			
298.65	8.66	5.09	317.75	24.65	−3.77			
300.15	8.72	0.29	319.55	31.31	4.71			
				$w = 0.6001$				
289.35	0.97	−2.83	303.65	1.60	−1.73	317.75	3.19	1.83
291.05	1.10	4.76	306.55	1.80	−2.02	319.55	3.48	0.96
293.95	1.15	0.39	308.45	2.02	1.22	322.05	3.89	−1.68
296.95	1.26	−0.48	310.35	2.23	2.48			
298.95	1.35	−0.68	313.25	2.55	2.17			
300.75	1.45	−0.21	315.95	2.80	−1.91			

[a] x is experimental data, and x_c is calculated values from eqs 2 and 3; both are mole fractions. w is the mass fraction of methanol in methanol + water.

Table 3. Solubility (x) of β-Artemether in Ethanol (w) + Water ($1 - w$)[a]

T/K	10^3x	$100[(x - x_c)/x]$	T/K	10^3x	$100[(x - x_c)/x]$	T/K	10^3x	$100[(x - x_c)/x]$
				$w = 1.0000$				
289.05	39.54	2.89	303.95	90.27	−0.80	318.95	251.43	5.55
290.85	42.61	0.47	306.95	109.99	0.51	322.65	315.32	3.23
293.95	49.22	−2.58	308.45	116.51	−3.15	326.05	386.92	0.23
296.95	59.25	−1.25	310.45	132.85	−2.64	328.65	441.77	−4.93
299.05	68.16	0.48	313.2	164.43	1.09			
301.05	76.40	0.02	316.25	199.50	0.51			
				$w = 0.8012$				
288.95	15.31	−1.69	308.95	58.56	6.58	325.65	235.17	0.38
290.85	17.40	1.44	312.85	66.77	−11.34	327.55	287.79	1.68
294.05	19.94	−2.31	315.65	88.20	−6.36	329.25	339.93	1.04
296.95	23.69	−1.97	317.75	104.19	−7.93	331.95	442.24	−0.91
298.95	26.00	−5.07	320.35	143.70	1.27			
303.95	45.10	15.68	322.75	185.75	4.59			
				$w = 0.6005$				
288.95	3.48	−2.21	303.85	7.05	1.37	321.45	24.17	−0.58
290.85	3.67	−3.50	306.85	8.29	−0.24	323.35	30.71	6.65
293.85	4.30	0.86	310.65	10.48	−1.44			
296.95	5.04	3.24	313.75	12.80	−3.31			
298.95	5.48	2.14	316.65	15.76	−4.36			
301.95	6.41	2.36	318.55	18.30	−4.44			

[a] w is the mass fraction of ethanol in ethanol + water.

Table 4. Quadratic Polynomial Parameters in Equation *3* for Methanol + Water and Ethanol + Water

	a_i	b_i	c_i
		Methanol + Water	
$i = 1$	$-1.4557 \cdot 10^3$	$2.4133 \cdot 10^3$	−903.16
$i = 2$	9.3229	−15.503	5.7261
$i = 3$	−0.014916	0.024984	$-9.1928 \cdot 10^{-3}$
RAD		0.0197	
		Ethanol + Water	
$i = 1$	−299.37	343.62	−46.460
$i = 2$	2.1642	−2.5393	0.31295
$i = 3$	$-3.9895 \cdot 10^{-3}$	$4.8800 \cdot 10^{-3}$	$-6.8805 \cdot 10^{-4}$
RAD		0.0298	

mass fraction of methanol (or ethanol) in the solution. Each average value of three measurements under the same experimental condition was used as the final experimental solubility data. It is estimated that the uncertainty in experimental solubility values is less than 3 %.

Results and Discussion

Experimental Data. The experimental solubility data of potassium nitrate in water were measured to prove the feasibility of the experimental method mentioned above. The experimental data, along with literature values,[7,8] were given in Table 1. Both relative average deviations (RADs) are less than 3 %. The comparison indicates that the experimental method is reasonable and reliable.

The mole fraction experimental solubility data of β-artemether in methanol + water are listed in Table 2, and the mole fraction experimental solubility data of β-artemether in ethanol + water are listed in Table 3. Where x is the experimental data and x_c is the calculated value from eqs 2 and 3, both x and x_c are mole fractions.

Data Correlation. The empirical logarithmic equation, as shown in eq 2, is widely used to correlate solid−liquid equilibrium data[9]

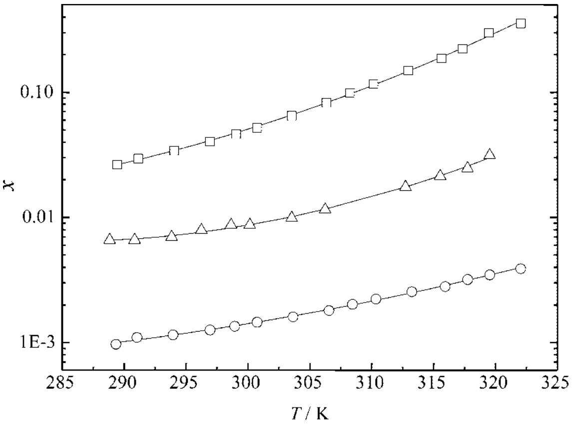

Figure 1. Solubility of β-artemether (x) in methanol (w) + water ($1 - w$): □, $w = 1.0000$; △, $w = 0.7993$; ○, $w = 0.6001$. Solid lines are values calculated from eqs 2 and 3 with parameters from Table 4.

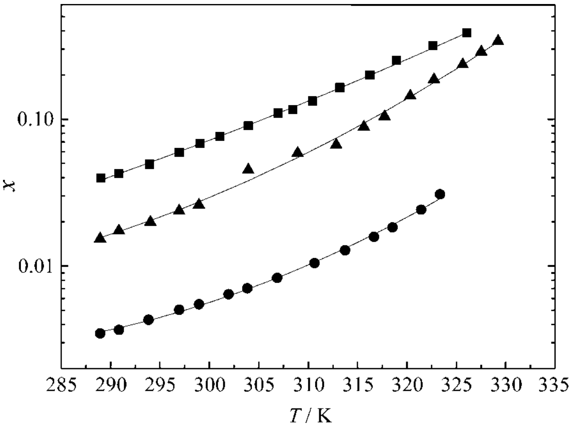

Figure 2. Solubility of β-artemether (x) in ethanol (w) + water ($1 - w$): ■, $w = 1.0000$; ▲, $w = 0.8012$; ●, $w = 0.6005$. Solid lines are values calculated from eqs 2 and 3 with parameters from Table 4.

$$\ln x = A + BT + CT^2 \tag{2}$$

where x is the mole fraction solubility of β-artemether, T is the absolute temperature, and A, B, and C are correlative parameters. Because the empirical logarithmic equation is effective only for constant solvent composition, the values of A, B, and C change with different solvent composition. In this work, it was assumed that A, B, and C were the quadratic polynomial equation of w, as described in eq 3

$$\begin{aligned} A &= a_1w^2 + b_1w + c_1 \\ B &= a_2w^2 + b_2w + c_2 \\ C &= a_3w^2 + b_3w + c_3 \end{aligned} \tag{3}$$

where a_1, a_2, a_3, b_1, b_2, b_3, c_1, c_2, and c_3 are adjustable parameters and w is the mass fraction of methanol (or ethanol) in methanol (or ethanol) + water.

In this work, eqs 2 and 3 were used to correlate the experimental data, and the calculated values, x_c, are listed in Tables 2 and 3 for methanol + water and ethanol + water, respectively. The calculated values of a_i, b_i, and c_i ($i = 1$, 2, and 3) are given in Table 4.

The comparison of the experimental and the calculated values is shown in Figures 1 and 2 for methanol + water and ethanol + water, respectively. It is found that the solubility of β-artemether in both methanol + water and ethanol + water dramatically increases with increasing temperature and significantly decreases with increasing water fraction. Therefore, in the crystallization process of β-artemether, temperature can play an important role, and water can be used as an excellent antisolvent.

The RAD was selected to show the difference between the experimental data and the calculated values. The RAD was calculated according to eq 4 and listed in Table 4

$$\mathrm{RAD} = \frac{\left[\sum_{i=1}^{n} |(x - x_c)/x|\right]}{n} \tag{4}$$

where x is the mole fraction of solubility of β-artemether, x_c is the calculated value, and n is the number of experimental points. (For methanol + water, $n = 42$, and for ethanol + water, $n = 46$.) As shown in Table 4, both RAD values are less than 3 %, which indicates that the calculated values are in good agreement with the experimental data.

The gravimetric method mentioned above was correctly proven for the measurement of the solubility. The experimental solubility data of β-artemether in methanol (or ethanol) + water were precisely measured. The RAD between the experimental and calculated values is less than 3 % for both systems. This indicates that the solubility data of β-artemether are reasonably correlated by the modified empirical logarithmic equation. The experimental solubility data and correlation equation in this work can provide essential data for the crystallization of β-artemether in methanol (or ethanol) + water.

Note Added after ASAP Publication: This paper was published ASAP on March 25, 2009. A change was made in equation 1. The revised paper was reposted on April 9, 2009.

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