Solubility of Rifapentine in the Binary System of Acetic Acid and *n*-Octanol Solvent Mixtures

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The solubility of rifapentine in acetic acid and *n*-octanol solvent mixtures was measured at temperatures ranging from (278.15 to 323.15) K. The mole fraction of *n*-octanol in the solvent mixtures (x_3) range from 0.0 to 0.5993. For the seven group data studied, the experimental solubility data were well-correlated with the data, calculated by means of a semiempirical equation.

Introduction

Rifapentine is a brick red powdered crystal and has been mostly used in the fields of pharmaceutics. Rifapentine is a semisynthetic antibiotic belonging to the rifamycin group. It has an antibacterial spectrum similar to rifampicin, but its antituberculosis power is 9-fold stronger than that of rifampicin; its orally toxic reaction is lower; and its half-lifetime is longer. Because of its strong bacteriostatic activity to *Staphylococcus aureus*, it has also been used for some tolerant *S. aureus* infections recently and has great potential.[1] During the manufacture to purify rifapentine, the solubility values of rifapentine in solvents are needed. The use of binary solvent mixtures is a highly versatile and very powerful means of altering (increasing or decreasing) the solubility of a solute. Binary solvent mixtures can alter the solubility of an extremely wide variety of solutes. In some cases, solubility can be improved by several orders of magnitude in solvent mixtures.[2,3] However, only solubilities in some pure solvents such as methanol, ethanol, acetone, chloroform, and dichloromethane were reported in the literature.[4] In this work, the solubility data of rifapentine in binary acetic acid and *n*-octanol solvent mixtrure were measured in the temperature range from (278.15 to 325.15) K under atmospheric pressure, where the concentrations were determined by ultraviolet−visible spectrophotometry (UV−vis).[5]

Experimental Section

Materials. A brick red crystalline rifapentine powder ($C_{47}H_{64}N_4O_{12}$, molecular mass 877.04) used to measure the solubility was purchased from Leshan San Jiu-Long March Pharmaceuticals Co., Ltd., China. It was prepared by recrystallization from a methanol-*n*-octanol solution three times at 298.15 K under atmospheric pressure. It was washed with ethanol, dried in a vacuum at 333.15 K for 24 h, and stored in a desiccator. Its mass fraction, determined by HPLC, is better than 99.0 %. Acetic acid and *n*-octanol were analytical grade reagents from Chengdu Chemical Reagent Co. Their mass fraction was better than 99.5 %.

Apparatus and Procedures. The mesurement apparatus of the solubility is similar to that described in the literature.[6] A 150 mL jacketed vessel was used to determine the solubility. The temperature fluctuation was controlled within 0.05 K through a thermostatted bath (type 501, China). A mercury-in-glass thermometer (uncertainty of ± 0.05 K) was used for the measurement of the temperature in the vessel. The mixtures of rifapentine and solvent in the vessel were stirred with a magnetic stirrer. To prevent the evaporation of the solvent, a condenser vessel was introduced. The concentration of the rifapentine was

Table 1. Mole Fraction Solubility (x_1) of Rifapentine in the Binary System of the Acetic Acid (2) + *n*-Octanol (3) Mixture between (278 and 323) K

T/K	10^2x_1	$10^2(x_1 - x_1^{calcd})$	*T*/K	10^2x_1	$10^2(x_1 - x_1^{calcd})$
		$x_3 = 0.0000$			
278.15	5.23	0.000	303.15	7.07	0.022
283.15	5.58	−0.025	308.15	7.55	0.030
288.15	5.95	−0.036	313.15	8.05	0.019
293.15	6.32	−0.032	318.15	8.58	0.018
297.15	6.70	−0.005	323.15	9.13	0.023
		$x_3 = 0.1001$			
278.15	4.67	−0.011	303.15	6.23	−0.015
283.15	4.94	0.008	308.15	6.56	−0.011
288.15	5.24	0.010	313.15	6.91	−0.011
293.15	5.56	0.001	318.15	7.27	−0.011
297.15	5.89	−0.007	323.15	7.62	0.001
		$x_3 = 0.2008$			
278.15	4.14	0.017	303.15	4.87	0.004
283.15	4.27	0.016	308.15	5.03	0.008
288.15	4.40	0.018	313.15	5.20	0.006
293.15	4.55	0.011	318.15	5.38	0.001
297.15	4.71	0.006	323.15	5.57	−0.006
		$x_3 = 0.2998$			
278.15	3.53	−0.026	303.15	3.89	−0.007
283.15	3.60	−0.018	308.15	3.96	−0.001
288.15	3.67	−0.016	313.15	4.04	0.003
293.15	3.74	−0.012	318.15	4.12	0.008
297.15	3.81	−0.010	323.15	4.21	0.011
		$x_3 = 0.4005$			
278.15	2.76	−0.012	303.15	3.07	0.013
283.15	2.81	−0.005	308.15	3.15	0.021
288.15	2.87	−0.001	313.15	3.23	0.027
293.15	2.93	0.004	318.15	3.31	0.013
297.15	3.00	0.010	323.15	3.40	0.027
		$x_3 = 0.5011$			
278.15	2.03	0.010	303.15	2.36	0.024
283.15	2.10	0.000	308.15	2.44	0.023
288.15	2.17	0.003	313.15	2.52	0.022
293.15	2.24	−0.001	318.15	2.61	0.018
297.15	2.31	−0.005	323.15	2.70	0.007
		$x_3 = 0.5993$			
278.15	1.40	0.004	303.15	1.71	0.006
283.15	1.45	0.004	308.15	1.78	0.008
288.15	1.51	0.005	313.15	1.87	0.007
293.15	1.57	0.005	318.15	1.95	0.006
297.15	1.64	0.003	323.15	2.04	0.007

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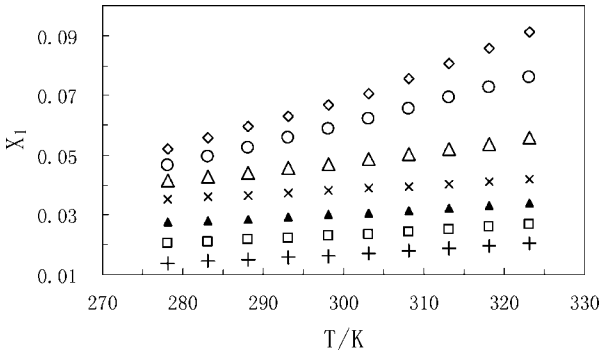

Figure 1. Solubility of rifapentine in the binary system of the acetic acid + *n*-octanol mixture along temperature: ◇, $x_3 = 0.0000$; ○, $x_3 = 0.1001$; Δ, $x_3 = 0.2008$; ×, $x_3 = 0.2998$; ▲, $x_3 = 0.4005$; □, $x_3 = 0.5011$; +, $x_3 = 0.5993$.

examined by UV−vis analysis. The masses of the samples and solvents were determined using an analytical balance (Sartorius CP124S, Germany) with an uncertainty of ± 0.1 mg.

In this experiment, the solubility measurement of rifapentine is carried out by adding masses of rifapentine to a stirred solution kept at a fixed temperature. At the beginning, predetermined amounts (about 50.0 g) of mixed solvent (acetic acid + *n*-octanol) were loaded into the jacketed vessel, and then an excess amount of rifapentine was transferred into the solvent. After attaining equilibrium, the stirrer was turned off to let the solution settle for 2 h. Then the upper portion (about 10.0 mL) was taken and filtered, and after that, the filtrate (1.0 g) was diluted into a 50 mL volumetric flask. To prepare the solutions for UV−vis analysis, they were diluted to 50 mL with the same system.[7] An average value was taken from three measurements for each temperature. The uncertainty of the mass fraction solubility values was estimated to less than 1 %.

The mean values were used to calculate the mole fraction solubility x_1 based on eq 1. The composition of solvent mixtures x_3 was defined as eq 2

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (1)$$

$$x_3 = \frac{m_3/M_3}{m_2/M_2 + m_3/M_3} \quad (2)$$

where m_1, m_2, and m_3 repersent the mass of the solute, acetic acid, and *n*-octanol, respectively, and M_1, M_2, and M_3 are the molecular weight of the solute, acetic acid, and *n*-octanol, respectively.

Sample Analysis. To determine the rifapentine concentration in the solution, the absorbance of the standard and sample was measured at 474 nm because the maximum absorption wavelength (λ_{max}) of rifapentine is 474 nm. The working curve for the concentration estimation of rifapentine is prepared by using the standard solutions in the appropriate concentration range from (0.020 to 0.20) mg·mL^{-1}.[5]

Table 2. Parameters of Equation 2 for Rifapentine in the Binary System of the Acetic Acid (2) + *n*-Octanol (3) Mixture between (278 and 323) K

x_3	A	B	C	10^4rmsd
0.0000	−53.24	1307.4	8.1	2.80
0.1001	−8.25	−593.2	1.3	0.95
0.2008	−35.28	944.5	5.1	1.09
0.2998	−20.80	470.3	2.8	1.32
0.4005	−44.90	1470.4	6.4	2.03
0.5011	−34.71	901.2	4.9	1.40
0.5993	−54.50	1604.5	7.9	0.56

Results and Discussion

The solubilities of rifapentine in acetic acid and *n*-octanol mixtures at different temperatures are presented in Table 1 and are more visually expressed in Figure 1.

The temperature dependence of rifapentine solubility in solvents was described by the modified empirical equation.[8,9]

$$\ln(x_1) = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \quad (3)$$

where x_1 is the mole fraction solubility of rifapentine; T is the absolute temperature; and A, B, and C are the parameters. The calculated solubility values of rifapentine (x^{calcd}) are also given in Table 1. The values of parameters A, B, and C and the root-mean-square deviations (rmsd) are listed in Table 2. The rmsd is defined as

$$\mathrm{rmsd} = \left[\frac{\sum_{i=1}^{N}\left(x_{1,i} - x_{1,i}^{calcd}\right)^2}{N}\right]^{1/2} \quad (4)$$

where N is the number of experimental points.[10]

From Table 1 and Figure 1, we can draw the following conclusions: (1) The solubility of rifapentine in binary acetic acid + *n*-octanol solvent mixtures is a function of temperature, and solubility increases with the increase of temperature. (2) The solubility decreases with the increasing mole fraction of *n*-octanol in the solvent mixture. (3) The calculated solubilities of rifapentine show good agreement with the experimental values, and the experimental solubility and correlation equation in this work can be used as essential data and models in the purification process of rifapentine.

Literature Cited

(1) He, X. B.; Wang, J. P.; Liu, X. Q.; Chen, X. J. High-performance liquid chromatography assay of rifapentine in human serum. *J. Chromatogr.* **1996**, *681*, 412–415.
(2) Gao, Y. Y.; Ying, T. Solubility of Irbesartan Form B in Aqueous Ethanol Mixture. *J. Chem. Eng. Data* **2008**, *53*, 535–537.
(3) Wu, J. H.; Wang, J. k.; Zhang, M. J.; Qian, Y. X. Solubility of Cefazolin Sodium Pentahydrate in Binray System of Ethanol + Water Mixtures. *J. Chem. Eng. Data* **2006**, *51*, 1404–1405.
(4) Zhou, K.; Li, J.; Ren, Y. S. Solubility of Rifapentine in Different Organic Solvents. *J. Chem. Eng. Data* **2008**, *53*, 998–999.
(5) Wang, L. H.; Cheng, Y. Y. Solubility of Puerarin in Water, Ethanol and Acetone from (288.2 to 328.2). *J. Chem. Eng. Data* **2005**, *50*, 1375–1376.
(6) Li, X. N.; Yin, Q. X.; Chen, W.; Wang, J. K. Solubility of Hydroquinone in Different Solvents from 276.65 and 345.10 K. *J. Chem. Eng. Data* **2006**, *51*, 127–129.
(7) Kulkarni, A. R.; Soppimath, K. S.; Aminabhavi, T. M. Solubility Study of Azadirachta indica A. Juss. (Neem) Seed Oil in the Presence of Cosolvent/Nonionic Surfactant at (298.15, 303.15, 308.15, and 313.15) K. *J. Chem. Eng. Data* **1999**, *44*, 836–838.
(8) Ren, B.-Z.; Yuan, X.-L.; Li, C.; Zhao, H.-K. Solubility of Tripolycyanamide and Cyanuric Acid in Ethanediol, N,N-Dimethylformamide, and N,N-Dimethylacetamide from (301.07 to 363.35) K. *J. Chem. Eng. Data* **2004**, *49*, 890–891.
(9) Daneshfar, A.; Ghaziaskar, H. S.; Homayoun, N. Solubility of Gallic Acid in Methanol, Ethanol, Water, and Ethyl Acetate. *J. Chem. Eng. Data* **2008**, *53*, 757–758.
(10) Wang, L. H.; Song, Y. T.; Chen, Y.; Cheng, Y. Y. Solubility of Artemisinin in Ethanol + Water from (278.2 to 343.2) K. *J. Chem. Eng. Data* **2007**, *52*, 757–758.

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