Solubility of Rifapentine in Different Organic Solvents

Kun Zhou,* Jun Li, and Yong sheng Ren

College of Chemical Engineering, Sichuan University, Chengdu, Sichuan 610065, People's Republic of China

The solubility of rifapentine in methanol, ethanol, acetone, chloroform, and dichloromethane was measured at temperatures ranging from (278 to 323) K under the atmospheric pressure. The solubility of rifapentine in the above solvents increased in the order chloroform > methanol > dichloromethane > ethanol > acetone. 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. It has no smell and is tasteless. Figure 1 shows the chemical structure of this compound. It was approved for the treatment of pulmonary tuberculosis by the US FDA in June 1998.[1,2] Rifapentine is a rifamycin derivative with excellent activity against *Mycobacterium tuberculosis* in vitro and in animals.[3,4] The drug has the advantage of a half-life five times longer than rifampicin, and it is recommended for use in intermittent therapy.[5] During the manufacture and purification of rifapentine, the cooling or evaporative crystallization process is used. Therefore, the solubilities of rifapentine in different solvents are required.[6] However, the solubility data are not reported. In this work, the solubility data of rifapentine in methanol, ethanol, acetone, chloroform, and dichloromethane were measured by an ultraviolet–visible spectrophotometry system (UVV) from (278 to 323) K under atmospheric pressure.[7]

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–water solution three times. 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 %. Other reagents were analytical grade reagents from Chengdu Chemical Reagent Co. Their mass fractions were better than 99.5 %.

Apparatus and Procedures. The measurement apparatus of the solubility is similar to that described in the literature.[8,9] 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 examined by UVV analysis. The masses of the samples and solvents were determined using an analytical balance (Sartorius CP124S, Germany) with an uncertainty of ± 0.1 mg.

* Corresponding author. E-mail: kun.zhou925@gmail.com.

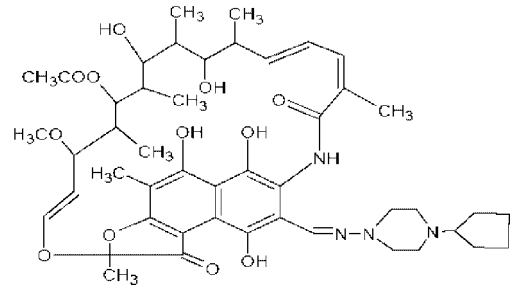

Figure 1. Chemical structure of rifapentine.

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 of solvent (about 50.0 g) 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 was taken, filtered, and diluted into a 50-mL volumetric flask.[10] To prepare the solutions for UVV analysis, they were diluted to 50 mL with the same system.[11] The uncertainty of the mass fraction solubility values was estimated to less than 1 %. An average value was taken from three measurements for each temperature.

The mean values are used to calculate the mole fraction solubility x_1 based on

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \tag{1}$$

where m_1 and m_2 represent the mass of rifapentine and solvent and M_1 and M_2 are the molecular weight of rifapentine and the solvent, 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.

Results and Discussion

The solubilities of rifapentine in methanol, ethanol, acetone, chloroform, and dichloromethane at different temperatures are presented in Table 1 and more visually expressed in Figure 2.

10.1021/je7007457 CCC: $40.75
Published on Web 03/19/2008

Table 1. Mole Fraction Solubility (x_1) of Rifapentine in Pure Solvents between (278 and 323) K

T/K	10^3x_1	$10^3(x_1 - x_1^{calcd})$	T/K	10^3x_1	$10^3(x_1 - x_1^{calcd})$
		Methanol			
278.15	22.0	0.033	303.15	24.9	0.022
283.15	22.4	–0.016	308.15	25.7	0.021
288.15	22.9	–0.027	313.15	26.7	0.029
293.15	23.5	–0.028	318.15	27.8	0.011
297.15	24.2	–0.005	323.15	29.0	−0.043
		Ethanol			
278.15	0.515	−0.002	303.15	0.604	−0.001
283.15	0.525	0.002	308.15	0.625	0.001
288.15	0.541	0.003	313.15	0.651	–0.001
293.15	0.562	0.000	318.15	0.677	–0.001
297.15	0.583	–0.002	323.15	0.703	0.001
		Acetone			
278.15	0.523	0.001	303.15	0.576	0.007
283.15	0.530	–0.002	308.15	0.609	–0.003
288.15	0.536	0.000	313.15	0.635	–0.001
293.15	0.549	–0.002	318.15	0.668	–0.002
297.15	0.563	0.000	323.15	0.701	0.002
		Chloroform			
278.15	25.4	0.209	303.15	29.9	0.262
283.15	26.5	0.106	308.15	30.8	0.222
288.15	28.1	–0.559	313.15	31.6	0.149
293.15	28.7	–0.183	318.15	32.6	–0.065
297.15	29.3	0.056	323.15	33.4	–0.207
		Dichloromethane			
278.15	15.9	–0.027	303.15	20.9	0.029
283.15	16.5	0.058	308.15	22.4	0.002
288.15	17.5	–0.031			
293.15	18.4	0.029			
297.15	19.6	–0.061			

The temperature dependence of rifapentine solubility in pure solvents was described by the modified empirical equation.[12,13]

$$\ln(x_1) = a + \frac{b}{T/\mathrm{K}} + c\ln(T/\mathrm{K}) \quad (2)$$

where x_1 is the mole fraction solubility of rifapentine; T is the absolute temperature; and a, b, and c are the parameters. The different values between the experimental solubility and the calculated solubility of rifapentine ($x - x^{calcd}$) 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

$$\mathrm{rmsd} = \left[\frac{1}{N}\sum_{i=1}^{N}(x_{1,i} - x_{1,i}^{calcd})^2\right]^{1/2} \quad (3)$$

where N is the number of experimental points.

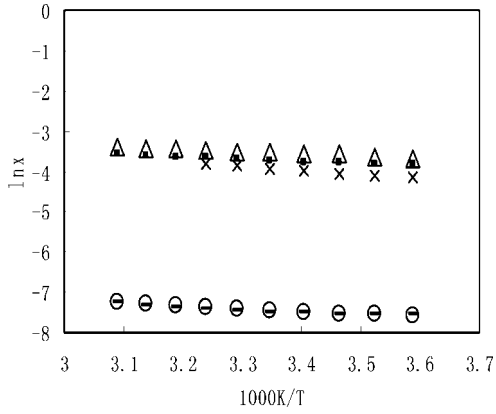

Figure 2. Solubility of rifapentine in different solvents: □, methanol; △, chloroform; ×, dichloromethane; ○, ethanol; −, acetone.

Table 2. Parameters of Equation 2 for Rifapentine in Different Solvents

solvent	a	b	c	10^3rmsd
methanol	–94.8	3607	13.9	25.3
ethanol	–70.9	2291	9.8	1.6
acetone	–174.2	6950	25.2	2.7
chloroform	22.3	–1596	–3.6	8.4
dichloromethane	–167	6306	24.9	32

The solvents selected in this study, methanol, ethanol, acetone, chloroform, and dichloromethane, are typical and representative. From Table 1, the solubility results indicate that ethanol and acetone are not good solvents for rifapentine. To obtain high output, relatively high solubility of the compound is required. Therefore, the alcohol and acetone are not suitable for rifapentine, but they may be used as cosolvents to help the recovery of the product.

From Table 1 and Table 2, the solubility of rifapentine in these five solvents decreases in the order chloroform > methanol > dichloromethane > ethanol > acetone. The solubility values in ethanol and acetone are almost equal, which is lower than that in methanol, chloroform, and dichloromethane. According to the values of the rmsd, it can be seen that the solubility of rifapentine in these solvents under consideration can be fitted with eq 2 very well. The experimental solubility and correlation equation in this work can be used as fundamental data and models in the purification process of rifapentine.

Literature Cited

(1) Renato, C.; Vittorio, A. Piperazinylimino Rifamycins, United States Patent 4002752, 1977.
(2) Prasad, B.; Bhutani, H.; Singh, S. Study of the interaction between rifapentineand isoniazid under acid conditions. *J. Pharm. Biomed. Anal.* **2006**, *41*, 1438–1441.
(3) Dickinson, J. M.; Mitchison, D. A. In vitro properties of rifapentine (MDL473) relevant to its use in intermittent chemotherapy of tuberculosis. *Tubercle* **1987**, *68*, 113–118.
(4) Ji, B.; Truffot-Pernot, C.; LaCroix, C. Effectiveness of rifampin, rifabutin, and rifapentine for preventive therapy of tuberculosis in mice. *Am. Rev. Respir. Dis.* **1993**, *148*, 1541–1546.
(5) Miyazaki, E.; Chaisson, R. E.; Bishai, W. R. Analysis of Rifapentine for Preventative Therapy in the Cornell Mouse Model of Latent Tuberculosis. *Antimicrob. Agents Chemother.* **1999**, *43*, 2126–2130.
(6) Nebuloni, M.; Via, C.; Occelli, E.; Cavalleri, B. ; Via, P. Pure Crystalline Form of Rifapentine, European Patent 0536197, 1992..
(7) Wang, L. H.; Cheng, Y. Y. Solubility of Puerarin in Water, Ethanol and Acetone from (288.2 to 328.2) K. *J. Chem. Eng. Data* **2005**, *50*, 1375–1376.
(8) 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.
(9) Wang, S.; Li, Q. S.; Li, Y. L. Solubility of D-*p*-hydroxyphenylglycine in water, methanol, ethanol, carbon tetrachloride, toluene, and *N*,*N*-dimethylformamide between 278 K and 323 K. *J. Chem. Eng. Data* **2006**, *51*, 2201–2202.
(10) Mohsen-Nia, M.; Modarress, H.; Razzaghi, D. Solubility of 1,3,5-Trioxane in Methanol, Ethanol, and 2-Propanol. *J. Chem. Eng. Data* **2004**, *49*, 1613–1614.
(11) 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.
(12) Hao, H. X.; Wang, J. K.; Wang, Y. L. Solubility of Dexamethasone Sodium Phosphate in Different Solvents. *J. Chem. Eng. Data* **2004**, *49*, 1697–1698.
(13) Nie, Q.; Wang, J. K.; Wang, Y. L. Solubility of 11α-hydroxy-16α,17α-epoxyprogestrone in different solvents between 283 K and 323 K. *J. Chem. Eng. Data* **2005**, *50*, 989–992.

Received for review December 18, 2007. Accepted January 23, 2008.

JE7007457