Solubility of Losartan Potassium in Different Binary Solvents from (293.15 to 343.15) K

Kun Guo, Qiuxiang Yin,* Meijing Zhang, and Jingkang Wang

School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, People's Republic of China

The solubility of losartan potassium in mixed 2-propanol + water and 2-propanol + cyclohexane solvents was measured at the temperature ranging from (293.15 to 343.15) K under atmospheric pressure. The experimental data were correlated by the CNIBS/Redlich–Kister model. The results show that the solubility of losartan potassium increases with increasing temperature in these two binary mixed solvents and increases with the increasing mole fraction of water while decreasing mole fraction of cyclohexane, respectively.

Introduction

Losartan potassium, a medicine used for treating hypertension and congestive heart failure, exhibits polymorphism, and Form I grown from the solvent system of 2-propanol + water + cyclohexane is the most stable form.[1–4]

According to the crystallization conditions for losartan potassium described in ref 4, the initial solvent system used was 2-propanol + water mixtures at the beginning of the crystallization process, and the final solvent system was 2-propanol + cyclohexane at the end of the process. Therefore, the solubility of losartan potassium in binary 2-propanol + water and 2-propanol + cyclohexane solvent mixtures is the crucial data for designing and controlling the crystallization process. However, it was found that no experimental solubility data of losartan potassium in these solvents and solvent mixtures were available in the literature.

In this work, the solubility data of losartan potassium in binary 2-propanol + water and 2-propanol + cyclohexane at temperatures ranging from (293.15 to 343.15) K under atmospheric pressure were experimentally determined using the synthetic method and a laser monitoring observation technique.

Experimental Section

Materials. A white crystalline powder of losartan potassium was obtained from Huahai Pharmaceutical Co. Ltd. of China with a mass fraction purity of 0.96. After recrystallization with the method published in ref 4, the mass fraction purity of 0.995 was achieved. 2-Propanol (Kewei, 99.5 %, anhydrous), cyclohexane (Kewei, 99.5 %, anhydrous), and distilled–deionized water were used without further purification.

Apparatus and Procedure. The solubility of losartan potassium in different solvents was measured with the synthetic method.[5,6] The measuring principle and setup were similar to those described in the literature.[7,8] A laser monitoring system was used to determine the disappearance of the last crystal in the solid + liquid mixtures. The equilibrium cell is a cylindrical double-jacketed glass vessel with a working volume of 50 mL. The vessel was continuously stirred with a magnetic stir bar, and the temperature with an uncertainty of ± 0.05 K was controlled to within ± 0.1 K of the desired value by circulating water through the outer jacket from a thermostat. A condenser was connected vertically on the vessel to prevent solvent evaporation. An analytical balance (Metler Toledo AB204-N, Switzerland) with an uncertainty of ± 0.1 mg was used during the mass measurements.

A predetermined excess amount of losartan potassium was added to a certain amount of solvent and placed in the jacketed vessel. The excess undissolved solid solute particles were completely suspended in the vessel by continuous stirring for 1 h under a certain temperature. Then, the same solvent was added dropwise into the vessel through a burette. With the increasing amount of solvent in the vessel, the solid solute gradually dissolved, and the intensity of the penetrated light increased. When the last portion of the solid solute just disappeared, the penetrated light intensity reached its maximum value. Then, the addition of solvent was stopped, and the amount of the solvent used in the experiment was recorded. Together with the mass of solute, the solubility in mole fraction (x_0) could be calculated by eq 1, and the composition of the solvent mixture (x_2^0, x_3^0) was defined by eqs 2 and 3

$$x_0 = \frac{m_0/M_0}{m_0/M_0 + m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (1)$$

$$x_2^0 = \frac{m_2/M_2}{m_1/M_1 + m_2/M_2} \quad (2)$$

$$x_3^0 = \frac{m_3/M_3}{m_1/M_1 + m_3/M_3} \quad (3)$$

where m_0 and M_0 denote the mass of losartan potassium used in the experiment and its molecular weight. m_1, m_2, m_3 and M_1, M_2, M_3 denote the masses of 2-propanol, water, and cyclohexane used in the experiment and their molecule weights, respectively. For the case of 2-propanol + water, $m_3 = 0$ in eq 1, while for the case of 2-propanol + cyclohexane, $m_2 = 0$. All the experiments were repeated three times. The uncertainty in the solubility values is estimated to be 0.5 %.

Results and Discussion

Solubility Data. The solubility data of losartan potassium in 2-propanol + water and 2-propanol + cyclohexane binary mixed solvents at temperatures ranging from (293.15 to 343.15) K are summarized in Tables 1 and 2. In the former binary solvent,

* To whom correspondence should be addressed. E-mail: qxyin@tju.edu.cn. Fax: +86-22-27374971.

10.1021/je700724r CCC: $40.75
Published on Web 04/04/2008

Table 1. Solubility of Losartan Potassium (0) in Binary 2-Propanol (1) + Water (2) Mixtures and Binary 2-Propanol (1) + Cyclohexane (3) Mixtures

2-propanol + water			2-propanol + cyclohexane		
x_2^0	x_0	$(x_0 - x_0^{calcd}/x_0)\cdot 100$	x_3^0	$x_0\cdot 10000$	$(x_0 - x_0^{calcd}/x_0)\cdot 100$
	293.15 K			293.15K	
0.09360	0.01485	−0.1347	0.4166	12.50	0.00576
0.1221	0.02144	−0.4198	0.5882	2.346	−2.262
0.1495	0.02881	2.325	0.6410	1.965	4.835
0.1757	0.03278	−4.088	0.6818	0.9891	−4.229
0.2008	0.04034	2.380	0.7142	0.7683	−2.099
0.2250	0.04425	0.2034	0.7407	0.6509	3.220
0.2482	0.04842	−0.8881	0.7812	0.4691	3.127
0.2706	0.05415	0.2770	0.8108	0.3713	−2.836
	303.15 K			303.15 K	
0.09360	0.01832	−1.255	0.4166	12.68	−0.00394
0.1221	0.02462	2.599	0.5882	3.172	0.8042
0.1495	0.02985	0.7705	0.6410	1.88	4.442
0.1757	0.03378	−5.979	0.6818	1.135	−2.561
0.2008	0.04351	2.528	0.7142	0.9254	6.814
0.2250	0.05085	3.599	0.7407	0.7067	−0.7952
0.2482	0.05273	−4.248	0.7812	0.5393	−7.476
0.2706	0.06021	1.146	0.8108	0.5146	3.642
	313.15 K			313.15 K	
0.09360	0.02014	0.1489	0.4166	13.96	−0.02407
0.1221	0.02627	−1.256	0.5882	3.542	6.867
0.1495	0.03418	3.072	0.6410	1.95	2.849
0.1757	0.03791	−3.77	0.6818	1.382	6.458
0.2008	0.04574	1.202	0.7142	1.131	8.661
0.2250	0.05149	1.165	0.7407	0.883	−2.947
0.2482	0.05604	−1.196	0.7812	0.735	−3.117
0.2706	0.06325	0.3004	0.8108	0.618	6.513
	323.15 K			323.15 K	
0.09360	0.02345	0	0.4166	17.22	−0.03937
0.1221	0.03037	−0.4280	0.5882	4.52	3.829
0.1495	0.03885	1.544	0.6410	2.24	4.382
0.1757	0.04394	−1.684	0.6818	1.436	8.117
0.2008	0.0492	−0.5691	0.7142	1.178	7.563
0.2250	0.05474	2.466	0.7407	0.998	−5.741
0.2482	0.05671	−1.887	0.7812	0.899	−7.588
0.2706	0.06478	0.4322	0.8108	0.612	4.575
	333.15 K			333.15 K	
0.09360	0.03149	−0.1588	0.4166	18.86	−0.02778
0.1221	0.03832	−0.1566	0.5882	5.055	7.862
0.1495	0.04629	2.203	0.6410	3.019	5.703
0.1757	0.04928	−5.032	0.6818	2.146	5.048
0.2008	0.06023	4.034	0.7142	1.714	4.112
0.2250	0.0628	−1.258	0.7407	1.369	−3.185
0.2482	0.0692	−0.3179	0.7812	0.998	−6.064
0.2706	0.0759	0.1976	0.8108	0.7529	9.696
	343.15 K			343.15 K	
0.09360	0.0358	0.1676	0.4166	20.61	−0.01562
0.1221	0.03941	−0.6089	0.5882	5.313	5.337
0.1495	0.0477	0.4822	0.6410	3.892	2.866
0.1757	0.05591	0.3577	0.6818	3.124	5.047
0.2008	0.06243	−0.6727	0.7142	2.256	−3.031
0.2250	0.06887	0.1597	0.7407	1.789	−1.185
0.2482	0.07422	0.1617	0.7812	1.198	4.568
0.2706	0.08014	−0.07487	0.8108	0.8842	0.4411

the mass fraction of water is from 0.03 to 0.10, and the mole fraction of water (x_2^0) is from 0.09360 to 0.2706, respectively. In the latter binary solvent, the mass ratio of cyclohexane/2-propanol is from 1:1 to 6:1, and the mole fraction of cyclohexane (x_3^0) is from 0.4166 to 0.8108, respectively.

From Table 1, it can be seen that within the temperature range under consideration the solubility of losartan potassium in mixed 2-propanol + water solvent increases with both the increase of temperature and the mole fraction of water. The solubility in the mixed 2-propanol + cyclohexane solvent increases with the increase of temperature and decreases with the increase of the mole fraction of cyclohexane at constant temperature.

Acree and co-workers [9–11] suggested the combined nearly ideal binary solvent (CNIBS)/Redlich–Kister model as a possible mathematical representation for describing how the experimental isothermal solubility of a crystalline solute dissolved in a binary solvent mixture varies with binary solvent composition.

$$\ln x_0 = x_B^0 \ln(x_0)_B + x_C^0 \ln(x_0)_C + x_B^0 x_C^0 \sum_{i=0}^{N} S_i (x_B^0 - x_C^0)^i \quad (4)$$

where S_i is the model constant and N is the number of solvents and equals 2 in this work. x_B^0 and x_C^0 refer to the initial mole fraction composition of the binary solvent calculated as if the

Table 2. Parameters of Equation 6 for Losartan Potassium in Binary 2-Propanol + Water and Binary 2-Propanol + Cyclohexane Mixtures

	293.15 K	303.15 K	313.15 K	323.15 K	333.15 K	343.15 K
			2-Propanol + Water			
B_0	0.0114	−0.01316	0.0119	0.06636	0.02445	0.1291
B_1	−0.2776	0.6297	−0.1282	−1.573	−0.1776	−2.559
B_2	5.043	−4.979	3.432	17.80	4.021	23.56
B_3	−20.76	23.44	−13.97	−72.82	−16.27	−83.54
B_4	29.79	−36.86	20.79	105.0	23.73	106.9
R^2	0.997	0.991	0.997	0.997	0.992	0.999
			2-Propanol + Cyclohexane			
B_0	214.1	53.66	41.78	−226.2	84.23	530.6
B_1	−1087	−60.89	69.27	1921	−88.99	−3008
B_2	2116	−274.7	−690.9	−5288	−501.7	6512
B_3	−1857	561.6	1091	6011	1041	−6304
B_4	617.9	−283.5	−520.5	−2449	−547.0	2288
R^2	0.999	0.999	0.998	0.995	0.997	0.998

solute was not present. x_C^0 is equal to x_2^0 or x_3^0, respectively. $(x_0)_i$ is the saturated mole fraction solubility of the solute in pure solvent i. Substitution of $(1 - x_C^0)$ for x_B^0 in eq 4 with $N = 2$ and subsequent rearrangements result in eq 5

$$\ln x_0 = \ln(x_0)_B + [\ln(x_0)_C - \ln(x_0)_B + S_0 + S_1 + S_2]x_C^0 + [-S_0 + 3S_1 + 5S_2](x_C^0)^2 + [-2S_1 - 8S_2](x_C^0)^3 + [-4S_2](x_C^0)^4 \quad (5)$$

which can be written as eq 6

$$\ln x_0 = B_0 + B_1 x_C^0 + B_2(x_C^0)^2 + B_3(x_C^0)^3 + B_4(x_C^0)^4 \quad (6)$$

The solubility data in the above two kinds of binary solvents are correlated by eq 6, and the values of the five parameters B_0, B_1, B_2, B_3, B_4, and R^2 are listed in Table 2. It can be seen that the calculated solubility by the CNIBS/Redlich–Kister model is in good agreement with the experimental values.

Acknowledgment

The authors are very grateful to Huahai Pharmaceutical Co. Ltd. of China for supplying the experimental material of losartan potassium.

Literature Cited

(1) Robert, D. L.; Anthony, O. K.; Cheng, Y. C.; Edward, G. C. Efficient Synthesis of Losartan, A Nonpeptide Angiotensin Il Receptor Antagonist. *J. Org. Chem.* **1994**, *59*, 6391–6394.

(2) Gareth, J. G.; Michael, B. H.; Rene′, I.; Jö rg, K. Novel Syntheses of 2-Butyl-5-chloro-3H-imidazole-4-carbaldehyde: A Key Intermediate for the Synthesis of the Angiotensin II Antagonist Losartan. *J. Org. Chem.* **1999**, *64*, 8084–8089.

(3) Gordon, C. C.; Anil, M. D.; Dorothy, A. L.; James, A. M. Polymorphs of losartan and the process for the preparation of form II of losartan. US 5608075, Mar. 4 1997.

(4) You, h. W.; Ming, h. Z.; Gong, y. H. New polymorph of losartan potassium. CN 1763036, Apr. 26 2006.

(5) Jaroslav, N. *Solid-Liquid Equilibria*; Elsevier Scientific Pub: New York, 1977.

(6) Mohan, R.; Lorenz, H.; Myerson, A. S. Solubility Measurement Using Differential Scanning Calorimetry. *Ind. Eng. Chem. Res.* **2002**, *41* (19), 4854–4862.

(7) Zhan, z. W.; Jing, k. W.; Mei, j. Z. Solubility of erythromycin A dihydrate in different pure solvents and acetone + water binary mixtures between 293 and 323 K. *J. Chem. Eng. Data* **2006**, *51*, 1062–1065.

(8) Dian, Q. L.; Da, Z. L.; Fu, A. W. Solubility of 4-Methylbenzoic Acid between 288 and 370 K. *J. Chem. Eng. Data* **2001**, *46*, 234–236.

(9) William, E. A. Mathematical Representation of Thermodynamic Properties: Part 2. Derivation of the Combined Nearly Ideal Binary Solvent (CNIBS)/Redlich-Kister Mathematical Representation from a Two-Body and Three-Body Interactional Mixing Model. *Thermochim. Acta* **1992**, *198*, 71–79.

(10) William, E. A.; James, W. M.; Anita, I. Z.; Teng, I. L. Mathematical Representation of Thermodynamic Properties. Carbazole Solubilities in Binary Alkane+Dibutyl Ether and Alkane+Tetrahydropyran Solvent Mixture. *Phys. Chem. Liq* **1991**, *23*, 27–35.

(11) William, E. A.; Anita, I. Z. Thermodynamic Properties of Nonelectrolyte Solutions. Part 4. Estimation and Mathematical Representation of Solute Activity Coefficients and Solubilities in Binary Solvents Using the CNIBS and Modified Wilson Equation. *Thermochim. Acta* **1991**, *178*, 151–167.

Received for review December 08, 2007. Accepted February 18, 2008.

JE700724R