Solubility of Cefazolin Sodium Pentahydrate in Binary System of Ethanol + Water Mixtures

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Using a laser monitoring observation technique, the solubilities of cefazolin sodium pentahydrate in binary ethanol + water solvent mixtures were determined by the synthetic method from 277.35 K to 310.05 K, respectively. Results of these measurements were correlated by the semiempirical equation. For the eight group data studied, the semiempirical equation was found to provide an accurate mathematical representation of the experimental data.

Introduction

The cephalosporin antibiotic, cefazolin sodium pentahydrate [CASRN 115850-11-8], 3-[[5-methyl-(1,3,4-thiadiazol-2-yl)thio]-methyl]-7-[2-(1H-tetrazol-1-yl)acetamido]-3-cephem-4-carboxylic sodium salt (Figure 1), is a white or almost white powdered crystal. During the manufacture in order to purify cefazolin sodium pentahydrate, the solubility of cefazolin sodium pentahydrate in solvents are needed. Only solubility in binary 2-propanol + water solvent mixtures and some pure solvents such as dichloromethane, 1-butanol, 1-propanol, ethanol, methanol, and *N*,*N*-dimethylformamide have been reported in the literature.[1,2] In this work, we report the solubilities of cefazolin sodium pentahydrate in binary ethanol + water solvent mixtures in the temperature range from 273.15 K to 308.15 K at atmospheric pressure.

Experimental Section

Materials. A white crystalline powder of cefazolin sodium pentahydrate obtained from North China Pharmaceutical Co., Ltd., with a melting/decomposition point of 185.6 °C, measured with a NETZSCH STA449C differential scanning calorimeter, was prepared by recrystallization from an ethanol solution. Its mass fraction purity, determined by HPLC according to BP2000, is higher than 0.996. Ethanol was analytical research grade reagents from Tianjin Chemical Reagent Co. Distilled deionized water of HPLC grade was used.

Apparatus and Procedure. The apparatus for solubility measurement is the same as described in the literature.[1,2] Solubilities were measured by a synthetic method.[3−5] A laser beam was used to determine the solubility of solute in binary solvents mixture at a known temperature. The laser monitoring system consisted of a laser generator, a photoelectric transformer, and a light intensity display. The solubility apparatus consisted of a jacketed glass vessel maintained at a desired temperature by water circulated from a water bath with a thermoelectric controller (type 501, China). The jacket temperature could be maintained within ± 0.05 K of the required temperature. Continuous stirring was achieved with a magnetic stir bar. A condenser was connected to the vessels to prevent the solvents from evaporating. A mercury-in-glass thermometer was inserted into the inner chambers of the vessels for the measurement of the temperature. The thermometer had an uncertainty of ± 0.05 K.

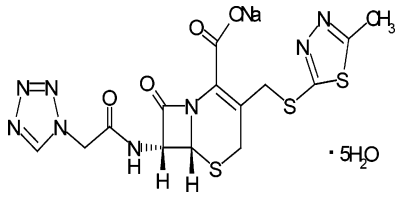

Figure 1. Structure of cefazolin sodium pentahydrate.

An analytical balance (type TG332A, China) with an uncertainty of ± 0.0001 g was used during the measurement. Predetermined excess amounts of cefazolin sodium pentahydrate and solvent of known mass were placed in the jacketed vessel. The contents of the vessel were stirred continuously at an invariable and required temperature, and the solvent was added to the vessel simultaneously. When the last portion of solute just disappeared, the intensity of the laser beam penetrating the vessel reached the maximum, and the solvent mass consumed in the measurement would be recorded. Together with the mass of solute, the solubility would be obtained. The saturated mole fraction solubility of the solute (x_A) in binary ethanol + water solvent mixtures can be obtained as follows:

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_B/M_B + m_C/M_C} \quad (1)$$

$$x_C = \frac{m_C/M_C}{m_C/M_C + m_B/M_B} \quad (2)$$

In which m_A, m_B, and m_C represent the mass of solute, water, and ethanol, respectively. M_A, M_B, and M_C are the molecular weight of solute, water, and ethanol, respectively. The same solubility experiment was conducted three times. The uncertainty of the experimental solubility values is about 0.5 %.

Results and Discussion

The solubility data of cefazolin sodium pentahydrate in binary ethanol + water solvent mixtures at the temperature range from

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Table 1. Experimental Solubilities (x_A) of Cefazolin Sodium Pentahydrate in Binary Ethanol (B) + Water (C) Solvent Mixtures at the Temperature Range from 277.35 K to 310.05 K

T/K	$10^3\,x_A$	$(x_A - x_A^{calc})/x_A$	*T*/K	$10^3\,x_A$	$(x_A - x_A^{calc})/x_A$
	$x_C = 0.1001$			$x_C = 0.1945$	
277.35	2.469	−0.0200	277.35	2.199	−0.0282
281.65	3.487	0.0076	281.65	3.024	−0.0008
285.15	4.460	−0.0020	285.15	3.975	0.0329
289.25	6.180	0.0276	289.25	5.259	0.0306
292.75	8.119	0.0497	292.75	6.735	0.0353
297.55	10.47	−0.0340	297.55	8.583	−0.0579
300.95	13.13	−0.0450	300.95	10.94	−0.0533
303.95	16.09	−0.0490	303.95	13.80	−0.0313
306.65	21.09	0.0368	306.65	18.22	0.0549
310.05	26.19	0.0228	310.05	22.13	0.0102
	$x_C = 0.3008$			$x_C = 0.4001$	
277.35	1.806	0.0123	277.35	1.368	0.0405
281.65	2.293	−0.0111	281.65	1.604	−0.0302
285.15	2.811	−0.0262	285.15	1.889	−0.0650
289.25	3.758	0.0024	289.25	2.588	0.0115
292.75	4.898	0.0386	292.75	3.323	0.0472
297.55	6.491	0.0021	297.55	4.205	−0.0199
300.95	8.131	−0.0026	300.95	5.416	0.0110
303.95	9.631	−0.0396	303.95	6.698	0.0223
306.65	12.27	0.0161	306.65	7.855	−0.0026
310.05	15.40	0.0058	310.05	9.785	−0.0201
	$x_C = 0.5024$			$x_C = 0.5924$	
277.35	0.7914	−0.0286	277.35	0.5051	−0.0211
281.65	0.9937	0.0075	281.65	0.6314	0.0261
285.15	1.195	0.0219	285.15	0.7542	0.0435
289.25	1.501	0.0357	289.25	0.8666	−0.0219
292.75	1.807	0.0272	292.75	0.9962	−0.0744
297.55	2.206	−0.0579	297.55	1.419	0.0018
300.95	2.699	−0.0686	300.95	1.819	0.0375
303.95	3.592	0.0252	303.95	2.171	0.0192
306.65	4.267	0.0174	306.65	2.593	0.0141
310.05	5.370	0.0135	310.05	31.56	−0.0286
	$x_C = 0.7025$			$x_C = 0.7930$	
277.35	0.2759	0.0206	277.35	0.1463	−0.1083
281.65	0.3128	−0.0313	281.65	0.2050	0.0340
285.15	0.3581	−0.0606	285.15	0.2718	0.1162
289.25	0.4986	0.0583	289.25	0.3260	0.0571
292.75	0.6029	0.0510	292.75	0.3808	−0.0128
297.55	0.7797	0.0147	297.55	0.5126	−0.0510
300.95	0.9345	−0.0286	300.95	0.6532	−0.0612
303.95	1.127	−0.0504	303.95	0.8130	−0.0755
306.65	1.385	−0.0383	306.65	1.042	−0.0422
310.05	19.65	0.0551	310.05	16.26	0.1140

277.35 K to 310.05 K are presented in Table 1. The solubility data in binary ethanol + water solvent mixtures are described by the semiempirical equation:[6−8]

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

where x is the mole fraction solubility of cefazolin sodium pentahydrate; T is the absolute temperature; and A, B, and C are the parameters. The calculated solubility values of cefazolin sodium pentahydrate x^{calc} are also given in Table 1. The values of parameters A, B, and C are listed in Table 2 together with the root-mean-square deviations (RMSDs). The RMSD is defined as

$$\mathrm{RMSD} = \left[\frac{1}{n}\sum_{i=1}^{n}(x_i^{calc} - x_i^{exptl})^2\right]^{1/2} \tag{4}$$

where n is the number of experimental points, x_i^{calc} represents the solubilities calculated from eq 4, and x_i^{exptl} represents the experimental solubility values.

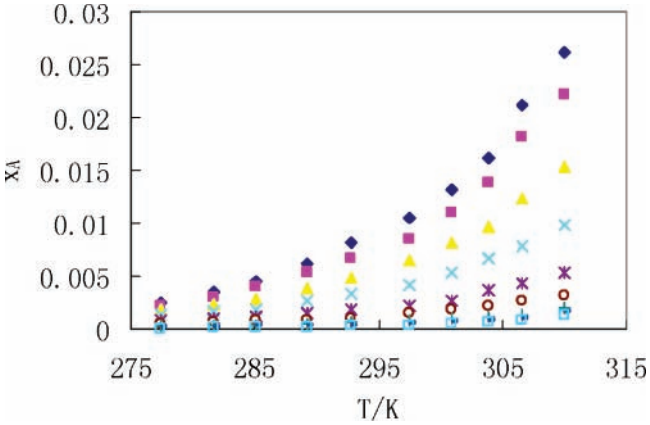

Figure 2. Solubility of cefazolin sodium pentahydrate in binary system of ethanol + water mixture along temperature: ◆, x_C = 0.1001; ■, x_C = 0.1945; △, x_C = 0.3008; ×, x_C = 0.4001; *, x_C = 0.5024; ○, x_C = 0.5924; +, x_C = 0.7025; −, x_C = 0.7930; □, x_C = 0.8902.

Table 2. Curve-Fitting Parameters of Cefazolin Sodium Pentahydrate in Binary Ethanol (C) + Water (B) Solvent Mixtures at the Temperature Range from 277.35 K to 310.05 K

T/K	A	B	C	10^4 RMSD
0.1001	−142.67	862.03	23.746	4.753
0.1945	−316.57	8591.3	49.687	4.393
0.3008	−424.61	13587	65.648	1.535
0.4001	−553.27	19485	84.685	1.085
0.5024	−696.96	26112	105.90	0.872
0.5924	−797.34	30569	120.80	0.482
0.7025	−898.70	34792	136.00	0.458
0.7930	−917.96	35014	139.19	0.663

From Table 1 and Figure 2, we can draw the following conclusions: (i) The solubility of cefazolin sodium pentahydrate in binary ethanol + water solvent mixtures is a function of temperature, and solubility increases with an increase of temperature. (ii) The solubility decreases with the increasing mole fraction of ethanol in the solvent mixture. (iii) The calculated solubilities of cefazolin sodium pentahydrate 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 cefazolin sodium pentahydrate.

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