Solubility and Metastable Zone of Cefoperazone Sodium in Acetone + Water System

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The solubility and the metastable zone of cefoperazone sodium in acetone + water were determined by the gravimetrical method and the laser monitoring observation technique, respectively. The experimental data can be well correlated by (CNIBS)/Redlich−Kister equation. All results were important for the crystallization process's control of cefoperazone sodium.

Introduction

Cefoperazone sodium belongs to the third generation cephalosporin antibiotics. It plays an antibacterial role by inhibiting the synthesis of bacterial cell wall and possesses many merits such as broad antibacterial spectrum, better curative effect, lower toxicity, and fewer allergic reactions.[1] The quality of cefoperazone sodium can be judged by crystal size, habit, purity, clarity, color grade, specific rotation, and so on. To achieve these quality targets, it depends not only on the synthetic method but also largely on the final crystallization processes. Aimed at supplying valuable thermodynamic data for crystallization processes, the solubility and metastable zone of cefoperazone sodium in acetone + water were studied in this article.

Experimental Section

Materials. A white crystalline powder of cefoperazone sodium supplied by Shandong Pharmaceutical Co., Ltd., China with a melting/decomposition point of (453.15 ± 0.5) K, measured with a NETZSCH DSC-204 differential scanning calorimeter, was recrystallized from an acetone + water solution. Its purity, determined by HPLC according to BP2000, was higher than 99.0 % (mass fraction). The acetone used for experiments was of analytical reagent grade, and distilled deionized water was used.

Solubility Measurements. Solubility of cefoperazone sodium in acetone + water solvents mixture was measured by a gravimetrical method.[2−4] As shown in Figure 1, the solubility apparatus consisted of a jacketed glass vessel maintained at a desired temperature by thermostatic bath that is capable of maintaining the jacket temperature within ± 0.05 K of the required temperature. A mercury-in-glass thermometer with an uncertainty of ± 0.05 K was inserted into the inner chambers of the vessel for the measurement of the solution temperature. Continuous stirring was achieved with a magnetic stir bar. The masses of the solute and solvents were weighed using an analytical balance (Metler Toledo AB204-N, Switzerland) with an accuracy of ± 0.0001 g.

In the experiments, excess amounts of solute were placed in an acetone + water solvents mixture of known composition. The solution was continuously stirred for at least 6 h to ensure solid−liquid phase equilibrium and was kept still for 2 h. Then, the suspension was filtered, and 5 mL of clear saturated solution was sampled with transfer pipet to a previously weighed watch glass. The watch glass was dried in a vacuum oven at 323.15 K for 12 h and weighed. Finally, solubility of cefoperazone sodium in acetone + water was obtained according to the density of acetone + water saturated solution. The same experiment was conducted three times, and the mean values were used to calculate the saturated mole fraction solubility as follows

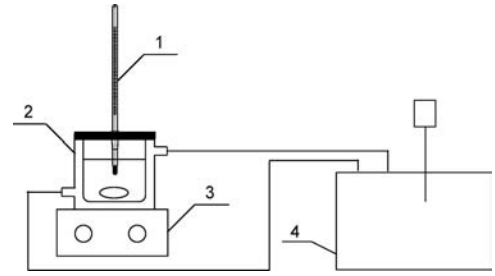

Figure 1. Apparatus for solubility measurements: 1, thermometer; 2, equilibrium vessel; 3, magnetic stirrer; 4, thermostatic bath.

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

where m_A, m_B, and m_C represent the mass of the solute, acetone, and water, respectively, and M_A, M_B, and M_C are the molecular weights of the solute, acetone, and water, respectively.

Metastable Zone Width (MZW) Measurements. MZW of cefoperazone sodium in the acetone + water solvents mixture was measured by laser method. The apparatus is shown in Figure 2. The MZW usually depends on the temperature, the addition rate of antisolvent addition, the stirring rate, the presence of impurities, and the type of measuring technique. In this article, the effect of temperature on MZW was investigated. First the saturated solution was prepared and stirred for 1 h to reach stability. Then, the antisolvent (acetone) was slowly added to the saturated solution through a buret at constant rate of 0.4 $mL \cdot min^{-1}$. A change in the relation between the laser intensity and the amount of acetone added occurred during measurement. When the solid phase appeared, the intensity of the laser beam penetrating the vessel dramatically decreased. As shown in Figure 3, the total amount of the acetone added at the points of B and E was recorded in time during the measurement, and the tangent intersection I of AB and CD can be seen as the end of

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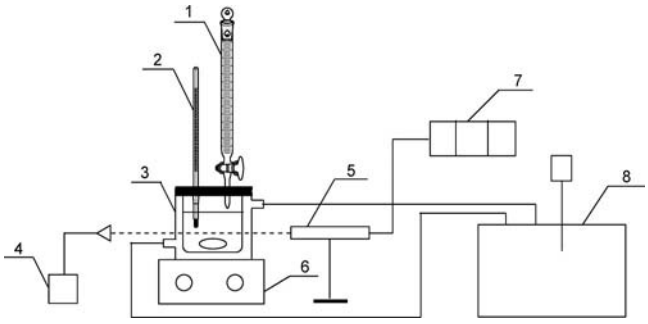

Figure 2. Schematic setup for MZW measurements: 1, buret; 2, thermometer; 3, equilibrium vessel; 4, laser generator; 5, laser receiver; 6, magnetic stirrer; 7, recording display; 8, thermostatic bath.

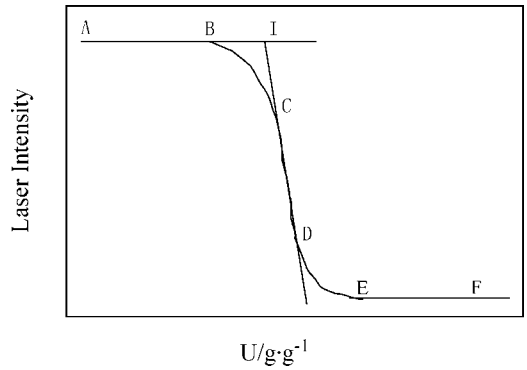

Figure 3. Schematic diagram of recording curve of laser apparatus for MZW measurements: AB, the tangent for the initial recording curve of laser apparatus; CD, the tangent for the recording curve of laser apparatus when crystals start to appear in the solution; I, the intersection I of AB and CD; EF, the tangent for the recording curve of laser apparatus that becomes smooth after a dramatic drop.

Table 1. Mole Fraction Solubility (x_A) of Cefoperazone Sodium in Binary Acetone (B) + Water (C) Solvents Mixture

x_C^0	$10^2 x_A^{exptl}$	$10^2 x_A^{calcd}$	x_C^0	$10^2 x_A^{exptl}$	$10^2 x_A^{calcd}$
	T/K = 288.15			T/K = 298.15	
0.2447	0.0401	0.0546	0.2150	0.0521	0.0471
0.2691	0.0579	0.0669	0.2473	0.0628	0.0679
0.3103	0.0801	0.0986	0.2719	0.0777	0.0888
0.3932	0.2064	0.2219	0.3134	0.1439	0.1369
0.4475	0.3766	0.3539	0.3966	0.3162	0.3008
0.4793	0.4811	0.4453	0.4510	0.4479	0.4724
0.5314	0.5678	0.5995	0.4828	0.6118	0.5991
0.7297	1.0234	1.0227	0.5349	0.8452	0.8452
			0.7325	1.6676	1.6673

experiment, at which the total amount of the acetone added was used for the determination of the supersolubility by the linear interpolation method. Finally, MZW was easily obtained because it is just the region between the solubility curve and the supersolubility curve. The same experiment was conducted three times, and the mean values were used to calculate the MZW as follows[5]

$$\Delta U = U - U^* \tag{2}$$

where U^* and U represent the mass ratio of antisolvent and solvent for saturated solution and supersaturated solution.

Results and Discussion

The solubility data of cefoperazone sodium in acetone + water solvents mixture are presented in Table 1 and described by (CNIBS)/Redlich−Kister equation[6]

$$\ln x_A = B_0 + B_1 x_C^0 + B_2 x_C^{02} + B_3 x_C^{03} + B_4 x_C^{04} \tag{3}$$

in which B_0, B_1, B_2, B_3, B_4, and x_C^0 refer to the equation parameters and the initial mole fraction composition of the binary solvents calculated as if solute A were not present, respectively. The fitting curves are presented in Figure 4. The values of the parameters B_0, B_1, B_2, B_3, and B_4 for eq 3 are listed in Table 2, together with the root-mean-square deviations (rmsd). The rmsd is defined as

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

where n is the number of experimental points, x_i^{calcd} represents the solubilities calculated from eq 3, and x_i^{exptl} represents the experimental solubility values.

The supersolubility data and the MZW are listed in the Table 3, and it is discovered that the MZW for each temperature can also be well correlated by eq 3 in which the variables x_A and x_C^0 should be replaced by ΔU and C, respectively. C represents

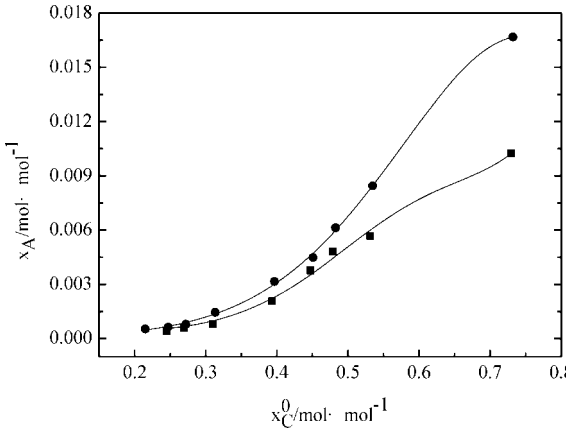

Figure 4. Mole fraction solubility of cefoperazone sodium in acetone (B) + water (C) solvents mixture: ■, T = 288.15 K; ●, T = 298.15 K.

Table 2. Curve Fitting Parameters of Cefoperazone Sodium in Binary Acetone (B) + Water (C) Solvents Mixture

T/K	B_0	B_1	B_2	B_3	B_4	10^3 rmsd
288.15	−5.7028	−32.9092	153.5829	−229.6283	114.9001	0.2143
298.15	−10.4568	14.5115	−7.4148	3.0212	−5.1265	0.1165

Table 3. MZW of Cefoperazone Sodium in Binary Acetone (B) + Water (C) Solvents Mixture

C / g·g^{-1}	U^* / g·g^{-1}	U / g·g^{-1}	ΔU^{exptl} / g·g^{-1}	ΔU^{calcd} / g·g^{-1}
		T/K = 283.15		
0.3730[a]	2.866[a]	5.308	2.442	2.401
0.3371[a]	3.531[a]	5.477	1.946	2.088
0.2965[a]	4.013[a]	6.144	2.131	1.996
0.1926[a]	5.016[a]	7.269	2.253	2.301
0.0816[a]	7.223[a]	10.65	3.427	3.392
0.0617[a]	8.828[a]	12.64	3.812	3.832
		T/K = 293.15		
0.5512[a]	1.188[a]	3.887	2.699	2.701
0.4234[a]	2.829[a]	4.663	1.834	1.809
0.3352[a]	3.960[a]	5.013	1.053	1.146
0.2648[a]	4.950[a]	5.904	0.954	0.857
0.0830[a]	8.712[a]	10.68	1.968	2.002
0.0639[a]	9.900[a]	12.71	2.808	2.789
		T/K = 298.15		
0.8605	1.182	3.538	2.356	2.356
0.5923	2.815	4.248	1.433	1.418
0.4739	3.468	4.503	1.035	1.096
0.3708	3.941	4.900	0.959	0.855
0.2973	4.926	5.629	0.703	0.760
0.0737	7.094	9.023	1.929	1.928

[a] Ref 1.

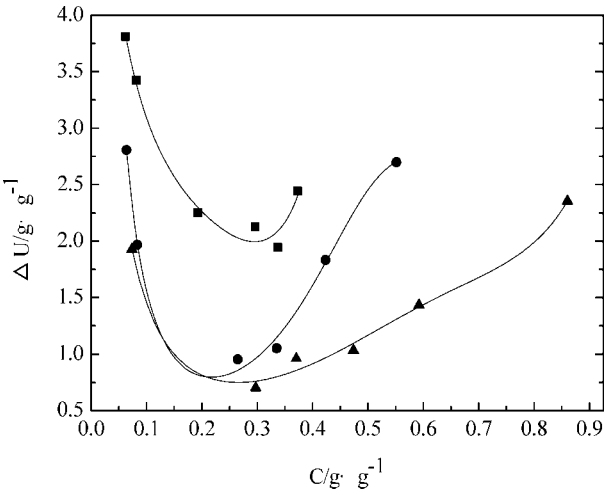

Figure 5. The width of metastable zone at different temperature: ■, T = 283.15 K; ●, T = 293.15 K; ▲, T = 298.15 K.

Table 4. Curve Fitting Parameters of the MZW of Cefoperazone Sodium in Binary Acetone (B) + Water (C) Solvents Mixture

T/K	B_0	B_1	B_2	B_3	B_4	rmsd
283.15	1.9403	−13.2135	69.2915	−208.9159	261.6920	0.0858
293.15	2.6451	−32.2194	116.8846	−148.2346	58.7184	0.0581
298.15	1.8239	−20.1929	64.7432	−79.5180	34.9011	0.0548

the mass ratio of solute and solvent for saturated solution. The fitting curves are visually given in Figure 5, and the values of the parameters B_0, B_1, B_2, B_3, and B_4 are listed in Table 4, together with the root-mean-square deviations (rmsd).

From Table 1 and Figure 4, it can be seen that the solubility of cefoperazone sodium in acetone + water increases with increasing temperature. At constant temperature, the solubility of cefoperazone sodium in acetone + water increases with the mole fraction of water, and the calculated solubility values from eq 3 show good agreement with the experimental values.

From Table 3 and Figure 5, we can draw the following conclusions: (1) In all temperatures under consideration, the MZW of cefoperazone sodium in acetone + water increases with a decrease in temperature. Therefore, a wider metastable zone can be obtained by lower crystallization temperature. (2) At constant temperature, the MZW has a minimum. The reason for this phenomenon needs to be further studied, and the crystallization process should avoid operating within the scope of the minimum, which easily leads to the formation of large numbers of nuclei.

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