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SHORT ARTICLE

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Solubility of Florfenicol in Different Solvents at Temperatures from (278 to 318) K

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ABSTRACT: The solubilities of florfenicol in water, methanol, ethanol, acetone, tetrahydrofuran, 1-propanol, and water + acetone solvent mixtures from (278 to 318) K were measured with the mole fraction at atmospheric pressure. The light extinction method was used to determine the dissolution process. Results of these measurements were correlated with a semiempirical equation. For all systems, the semiempirical equation provided an accurate mathematical representation of the experimental data.

INTRODUCTION

D-(Threo)-1-(methylsulfonylphenyl)2-dichloroacetamide-3-fluoro-1-propanol (florfenicol) is a primarily bacteriostatic broad-spectrum antibiotic that is effective against many Gram-positive and Gram-negative organisms. The molecular structure of florfenicol was illustrated in Figure 1. In industrial manufacturing, florfenicol is usually purified by antisolvent addition crystallization. To determine the proper solvent and to design an optimized crystallization process, it is essential to know its solubility in different solvents.[1] In addition, the relatively low solubility (approximately 1 $\text{mg}\cdot\text{mL}^{-1}$) of florfenicol in water decreases its bioavailability for the treatment of disease of swine and poultry.[2] It is known that particle size plays an important role in the dissolution rate of poorly soluble drugs. The reduction of particle size to micro- and nanometer range has been in practice for improving the solubility and bioavailability of poorly soluble drugs.[3] For the preparation of micro- and nanometer size particles, the antisolvent precipitation technique is a common and effective method.[4,5]According to the operation procedure of this technique, selection of the proper solvent and antisolvent is critical. To select a suitable solvent and antisolvent, it is necessary to know its solubility in different solvent mixtures. In this study, the solubilities of florfenicol in water, methanol, ethanol, acetone, tetrahydrofuran, 1-propanol, and water + acetone solvent mixtures were measured from (278 to 318) K by the light extinction method at atmospheric pressure. The light extinction method is much faster and more reliable than the traditional analysis methods.[6] A semiempirical equation was found to provide an accurate mathematical representation of the experimental data.

EXPERIMENTAL SECTION

Materials. White crystalline powder of florfenicol ($C_{12}H_{14}Cl_2FNO_4S$, CAS No. 73231-34-2, MW 358.21) supplied by Boyahua Science and Technology Co., Ltd. China was prepared by recrystallization from ethanol for two times and has a melting point of (426.15 ± 0.5) K. Its mass fraction purity was higher than 99.8 %. Methanol, ethanol, acetone, tetrahydrofuran, and 1-propanol used for experiments were of analytical reagent grade from Beijing Chemical Works, China, and distilled water was used. All of the solvents used in the experiments have a minimum purity of 99.0 %.

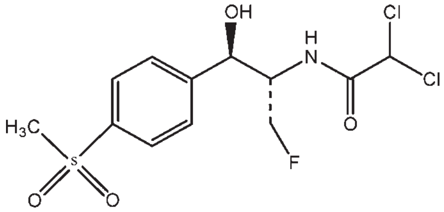

Figure 1. Chemical structure of florfenicol.

Apparatus and Procedures. The solubility of florfenicol was determined by the laser method.[7,8] The laser set consists of a laser generator, a photoelectric transformer, and a digital display. The experiment was performed in a cylindrical double-jacketed glass vessel. This vessel was maintained at a desired temperature by circulating water through the outer jacket from a thermostatic bath. A mercury-in-glass thermometer was inserted into the inner chamber of the vessel with an uncertainty of ± 0.05 K. The masses of florfenicol and solvents were determined using an analytical balance (Sartorius CP224S, Germany, uncertainty of 0.1 mg).

The laser method is based on sequentially adding known masses of a solid to a magnetically stirred solution kept at a predetermined temperature. During the experiments, the glass vessel was monitored by a laser beam. Along with the dissolution of the particles, the intensity of the laser beam increased gradually. When the last portion of florfenicol just disappeared, the laser intensity reached the maximum. Then additional florfenicol of known mass about (0.5 to 5) mg was introduced into the vessel. This procedure was repeated until the penetrated laser intensity could not return to the maximum; in other words, the last addition of solute could not dissolve completely. The total amount of the florfenicol consumed and the temperature were recorded. The same experiment was conducted three times, and the mean values were used to calculate the mole fraction

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Table 1. Experimental Mole Fraction Solubility (x_1^{P}) of Florfenicol in Different Pure Solvents from (278 to 318) K and Calculated Solubility (x_1^{cal}) Obtained from Equation 1

T/K	$10^3\,x_1^{\mathrm{P}}$	$10^2(x_1^{\mathrm{P}} - x_1^{\mathrm{cal}})/x_1^{\mathrm{P}}$	T/K	$10^3\,x_1^{\mathrm{P}}$	$10^2(x_1^{\mathrm{P}} - x_1^{\mathrm{cal}})/x_1^{\mathrm{P}}$
			Water		
278.80	0.0248	2.02	303.13	0.0696	1.15
283.85	0.0286	−3.15	308.13	0.0881	0.45
289.10	0.0362	−0.83	313.25	0.114	0.88
293.95	0.0464	2.80	317.50	0.140	−0.71
298.70	0.0549	−1.82			
			Methanol		
278.55	4.08	−0.25	302.95	10.5	0.00
283.50	4.88	−0.41	308.43	13.2	0.00
288.85	5.98	−0.50	314.70	17.0	−0.59
293.80	7.24	−0.69	319.65	21.0	−0.48
298.65	8.78	−0.57			
			Ethanol		
278.55	1.26	0.00	302.70	3.79	−0.53
283.45	1.53	−3.27	308.05	4.80	−1.04
288.8	2.12	4.72	313.35	6.14	−0.16
293.7	2.59	2.32	317.75	7.46	−0.27
298.45	3.15	0.32			
			Acetone		
279.25	26.1	0.00	304.15	45.8	−0.40
284.35	29.4	0.68	308.95	51.8	0.58
289.10	32.7	0.92	313.50	57.9	0.69
294.45	36.8	0.54	319.25	66.4	0.30
297.75	39.6	0.00			
			Tetrahydrofuran		
279.65	29.3	0.00	303.65	44.7	0.00
284.55	31.7	0.00	308.45	49.2	0.00
289.35	34.2	−0.29	313.05	54.2	0.00
294.50	37.4	−0.53	318.75	61.1	−0.33
297.65	39.8	0.00			
			1-Propanol		
278.35	0.80	−1.37	303.55	2.68	−1.12
284.05	1.06	0.00	308.27	3.39	−0.88
289.00	1.34	0.00	313.35	4.36	−0.69
293.50	1.65	−0.61	317.75	5.44	−0.37
298.65	2.11	−0.95			

solubility (x_1^{P}) based on eq 1 for pure solvents.

$$x_1^{\mathrm{P}} = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

where m_1 and m_2 represent the mass of the solute and solvent, and M_1 and M_2 are the molecular weight of the solute and solvent, respectively. For water + acetone solvent mixtures, the mole fraction solubility (x_1^{m}) is based on eq 2, and the composition (mole fraction) of the acetone + water solvent mixture (x_2^0) was defined by eq 3.

$$x_1^{\mathrm{m}} = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (2)$$

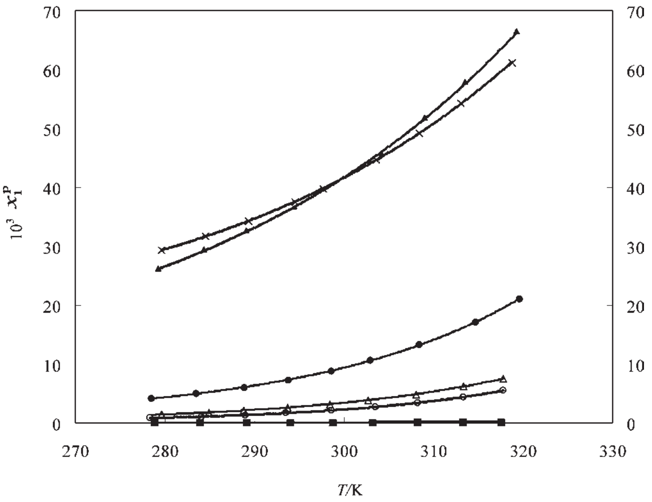

Figure 2. Experimental mole fraction solubility ($10^3\,x_1^{\mathrm{P}}$) of florfenicol in different pure solvents: ×, tetrahydrofuran; ▲, acetone; ●, methanol; △, ethanol; ○, 1-propanol; ■, water; solid lines, calculated from eq 4 with the parameters listed in Table 3.

$$x_2^0 = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \quad (3)$$

where m_1, m_2, and m_3 represent the mass of the solute, organic solvent, and water. M_1, M_2, and M_3 represent the mole weight of the solute, organic solvent, and water, respectively. The uncertainty of the experimental solubility values is about 2.0 %. The uncertainty in the solubility values can be due to uncertainties in the temperature measurements, weighing procedure, and instabilities of the water bath.

■ RESULTS AND DISCUSSION

The mole fraction solubilities of florfenicol determined experimentally in water, methanol, ethanol, acetone, tetrahydrofuran, and 1-propanol are listed in Table 1 and more visually expressed in Figure 2. The solubilities in water + acetone solvent mixtures are listed in Table 2 and more visually expressed in Figure 3. The relationship between temperature and solubility of the florfenicol is correlated with a modified semiempirical equation:[9,10]

$$\ln x_1 = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \quad (4)$$

where T is the absolute temperature, and A, B, and C are empirical constants. The difference between experimental and calculated results is also presented in Tables 1 and 2. The values of the three parameters A, B, and C together with the root-mean-square deviation (rmsd) are listed in Tables 3 and Table 4. The rmsd is defined as follows:

$$\mathrm{rmsd} = \left[\sum_{i=1}^{n} \frac{(x_1 - x_1^{\mathrm{cal}})^2}{N}\right]^{1/2} \quad (5)$$

where N is the number of experimental points; x_1^{cal} is the solubility calculated from eq 4; and x_1 is the experimental value of solubility.

From the tables and figures, we could draw the following conclusions: The solubilities of florfenicol increase significantly

Table 2. Experimental Mole Fraction Solubility (x_1^{m}) of Florfenicol in Acetone + Water at Various Contents of Acetone (x_2^0) between (278 and 318) K, Experimental Mole Fraction Solubility (x_1^{m}), and Calculated Solubility (x_1^{cal}) Obtained from Equation 2

T/K	$10^3\ x_1^{\mathrm{m}}$	$10^2(x_1^{\mathrm{m}} - x_1^{\mathrm{cal}})/x_1^{\mathrm{m}}$	T/K	$10^3\ x_1^{\mathrm{m}}$	$10^2(x_1^{\mathrm{m}} - x_1^{\mathrm{cal}})/x_1^{\mathrm{m}}$
$x_2^0 = 0.0341$					
278.66	0.0489	1.02	303.35	0.193	3.11
283.20	0.0625	1.12	308.43	0.250	0.80
287.95	0.0795	−0.63	313.25	0.328	0.92
293.15	0.106	0.00	318.75	0.441	−0.23
299.15	0.147	−0.68			
$x_2^0 = 0.0731$					
278.90	0.120	0.83	303.45	0.535	1.31
283.30	0.156	0.00	308.45	0.711	−0.70
288.00	0.208	0.48	312.95	0.950	0.84
293.10	0.284	0.70	318.15	1.30	0.77
299.15	0.407	0.00			
$x_2^0 = 0.1172$					
279.00	0.337	1.19	303.60	1.57	0.00
283.45	0.443	−0.23	308.20	2.09	0.96
288.00	0.59	−0.68	312.75	2.81	3.20
293.08	0.815	−0.25	317.80	3.58	−2.51
299.15	1.18	−0.85			
$x_2^0 = 0.1707$					
279.32	1.06	−0.94	304.05	4.64	−0.65
283.35	1.37	0.73	308.35	5.98	−0.84
288.85	1.90	0.53	313.15	8.04	0.25
293.73	2.54	0.79	317.60	10.5	0.00
298.15	3.27	−0.31			
$x_2^0 = 0.2367$					
278.05	3.19	0.00	303.97	11.4	0.00
283.45	4.19	0.24	307.95	13.8	0.73
289.37	5.57	−0.72	311.50	16.1	−0.62
294.15	7.03	−0.85	316.65	20.4	−0.49
298.65	8.79	−0.23			
$x_2^0 = 0.3166$					
279.25	8.50	0.47	303.50	22.5	0.44
283.20	9.95	0.00	307.95	26.6	0.00
288.85	12.4	−0.81	312.95	32.3	0.31
293.60	15.1	0.00	317.40	38.1	−0.26
297.80	18.0	0.56			
$x_2^0 = 0.4157$					
278.65	17.5	0.57	303.00	37.7	1.06
283.45	20.3	0.49	308.95	45.2	0.44
288.80	23.7	−0.84	313.15	52.1	1.54
293.03	27.1	−0.37	317.80	58.8	−1.02
298.50	32.4	0.31			
$x_2^0 = 0.5490$					
278.00	29.9	0.33	303.80	56.6	0.53
283.50	34.2	0.00	307.95	62.5	0.32
289.30	39.3	−0.25	311.45	68.0	0.29
294.00	44.3	0.00	316.85	77.1	−0.13
298.40	49.5	0.40			

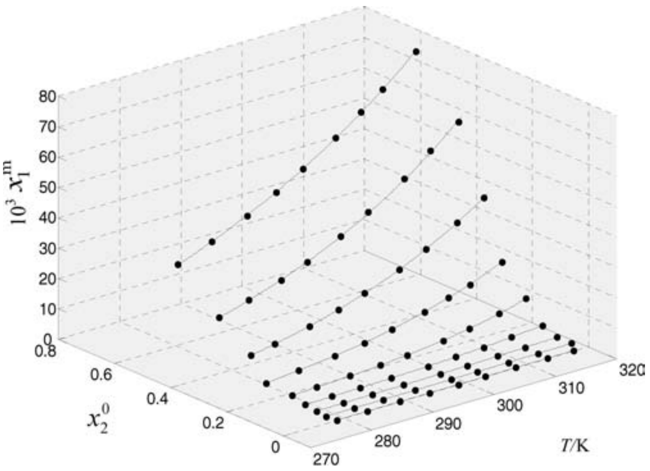

Figure 3. Variation of experimental mole fraction solubility ($10^3\ x_1^{\mathrm{m}}$) with temperature (T) at various contents of acetone (x_2^0) in acetone + water solvent mixtures. Solid lines, calculated from eq 4 with the parameters listed in Table 4.

Table 3. Parameters of Equation 4 for Florfenicol in Different Pure Solvents

solvent	A	B	C	10^5 rmsd
water	−405.50	14144	61.121	0.08589
methanol	−243.12	7585.0	37.372	5.416
ethanol	−147.50	2875.0	23.182	4.667
acetone	−134.81	4098.3	20.683	23.57
tetrahydrofuran	−178.61	6384.1	27.026	10.00
1-propanol	−232.35	6396.8	35.931	2.033

Table 4. Parameters of Equation 4 for Florfenicol in Acetone + Water at Various Contents of Acetone (x_2^0)

x_2^0	A	B	C	10^5 rmsd
0.0341	−251.46	6617.0	38.682	0.2403
0.0731	−242.57	5852.3	37.748	0.5207
0.1172	−147.07	1570.0	23.696	4.312
0.1707	−223.94	5207.7	35.235	2.261
0.2367	−111.97	1135.4	18.149	6.298
0.3166	−98.379	1212.8	15.849	7.572
0.4157	−125.01	3033.4	19.551	37.71
0.5490	−78.339	1498.8	12.338	16.33

with an increase of acetone in the solvent mixture, and the solubility in pure water is the lowest. The acetone and water can be used as an effective proper solvent and antisolvent in the antisolvent precipitation. From the values of the root-mean-square deviation (rmsd) listed in Tables 3 and 4, it can be seen that all of the experimental data fit well with eq 4. The experimental solubility and correlation equation in this work can be used as essential data and model in the practice of improving the solubility of florfenicol in water and some other correlative research.

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