Solubility of Clindamycin Phosphate in Binary Water−Ethanol Solvent

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The solubilities of clindamycin phosphate in different solvents were measured using a static method. The RP-HPLC was used to determine the concentration of clindamycin phosphate in the liquid phase. The solubility data were correlated with the combined nearly ideal binary solvent (CNIBS)/Redlich−Kister equation which provided an accurate mathematical representation of the experimental data.

Introduction

Clindamycin phosphate is (2*S*-*trans*)-methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside-2-(dihydrogen phosphate), (CAS No. 24729-96-2). It is a white or almost white crystalline powder, and Figure 1 shows the chemical structure. Clindamycin phosphate is the third generation product of lincomycin and has a lot of advantages relative to these two products, and as a semisynthetic antibiotic drug of Gram-positive and Gram-negative bacteria, it is widely used in clinical applications. In industrial manufacture, the purification step includes ion-change resin adsorption and crystallization from solution.[1] To determine the proper solvent and to design an optimized separation process, it is necessary to know its solubility in different solvents.[2] However, no experimental solubility data on clindamycin phosphate in aqueous + organic solvents have been reported. In this work, solubility data of clindamycin phosphate in water, ethanol, and different water + ethanol mixtures were experimentally determined using an analytical method.

Analytical and synthetic methods are two ways of measuring the solubility.[3,4] The advantage of the synthetic method is the short time for measurement, but its disadvantage is lower precision. To obtain more precise solubility data, an analytical method was used, using high-performance liquid chromatography (HPLC).

Experimental Section

A. Reagents and Apparatus. A crystalline powder of clindamycin phosphate ($C_{18}H_{34}ClN_2O_8PS$, relative mole mass 504.96) was obtained from North China Pharmaceutical Co., Ltd., China. Its mass fraction was better than 99.0 %, determined by HPLC. It was dried in a vacuum at 80 °C for 24 h and stored in a desiccator. Ethanol was analytical purity grade from Tianjin Chemical Reagent Co., and distilled deionized water was used. The concentration measurements were carried out on HPLC (Agilent Technologies 1200, USA) with an XDB C18 reverse-phase column (4.6 mm × 150 mm, 5 μm) eluted ahead with methanol + water. The masses of the samples and solvents were determined by an analytical balance (Mettler Toledo AB204-N, Switzerland) with an accuracy of 0.0001 g.

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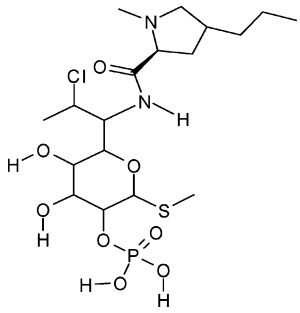

Figure 1. Molecular structure of clindamycin phosphate.

B. Sample Preparation. An excess amount of clindamycin phosphate was added to the solvents in a jacketed glass vessel. Between the outer and inner walls of the vessel, water at a desired temperature was circulated from a water bath with a thermoelectric controller within 0.05 K (type 501A, China). A condenser was connected with the vessel to prevent solvent evaporation. A mercury-in-glass thermometer which had an uncertainty of 0.05 K was inserted into the inner wall of the vessels for temperature measuring.

The solution was stirred by a magnetic stirrer continuously. To confirm the exact time consumed of attaining equilibrium, the concentrations of clindamycin phosphate in pure ethanol at 283.15 K with different stirring times were measured, and the concentrations kept almost identical after nearly 1 h. The stirrer was turned off to let the solution settle for 0.5 h. Then the quantitative upper portion was taken by a heated piette with an accuracy of 0.01 mL into 100 mL of distilled deionized aqueous solution to prepare the samples for HPLC analysis. All the measurements were repeated three times.

C. Sample Analysis. HPLC analysis[5,6] was performed by an external standard method. More than 20 μL of clindamycin phosphate dilution that was extracted from the samples was injected into an HPLC for quantity analysis. The mobile phase was acetonitrile (1) + water (2) with a volume fraction, Φ_1, of 0.3, containing potassium dihydrogen phosphate (10.54 g·L^{-1}). The HPLC conditions were set as follows: wavelength of determination, 210 nm; column temperature, 303.15 K; flow rate of the mobile phase, 1.0 mL·min^{-1}; retention time, 8 min. The calibration curve for the estimation of clindamycin phosphate was prepared by using the standard solutions in the concentration range of (0.01 to 4.0) mg·mol^{-1} (at room temperature). The uncertainty in the measurement of the concentration of clindamycin phosphate was less than 2 %.

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Table 1. Experimental Solubilities (x_A) and Calculated Solubilities (x_A^{calcd}) of Clindamycin Phosphate in Binary Ethanol + Water Solvent Mixtures from T = (278.15 to 343.15) K

x_C^0	$10^3 x_A$	$10^3 x_A^{calcd}$	x_C^0	$10^3 x_A$	$10^3 x_A^{calcd}$
	T = 278.15 K			T = 283.15 K	
0.0000	0.006	0.47	0.0000	0.09	0.59
0.1499	1.37	1.48	0.1499	1.48	1.69
0.3085	1.7	2.08	0.3085	2.57	2.5
0.4502	3.8	2.76	0.4502	4.54	3.49
0.6150	5.81	6.09	0.6150	6.78	7.59
0.7518	18.48	18.49	0.7518	21.42	21.27
1.0000	176.08	176.1	1.0000	179.86	179.87
	T = 288.15 K			T = 293.15 K	
0.0000	0.09	1.01	0.0000	0.11	1.24
0.1499	1.71	1.74	0.1499	2.84	2.61
0.3085	3.61	2.15	0.3085	3.74	3.15
0.4502	5.19	3.34	0.4502	6.08	4.37
0.6150	7.53	9.78	0.6150	9.4	11.24
0.7518	34.33	33.86	0.7518	36.93	36.55
1.0000	185.89	185.88	1.0000	199.57	199.53
	T = 298.15 K			T = 303.15 K	
0.0000	0.14	1.25	0.0000	0.24	1.82
0.1499	3.22	3.07	0.1499	4.18	3.79
0.3085	4.1	4.39	0.3085	5.72	4.93
0.4502	8.76	6.46	0.4502	9.17	7.14
0.6150	13.6	15.32	0.6150	15.12	17.51
0.7518	43.2	42.84	0.7518	50.89	50.32
1.0000	202.92	202.93	1.0000	209.42	209.42
	T = 308.15 K			T = 313.15 K	
0.0000	0.31	1.20	0.0000	0.34	1.24
0.1499	4.57	4.22	0.1499	5	4.8
0.3085	6.16	7.16	0.3085	7.37	8.2
0.4502	12.99	10.45	0.4502	14.07	11.6
0.6150	19.49	21.4	0.6150	20.86	22.81
0.7518	51.27	50.80	0.7518	53.43	52.95
1.0000	216.65	216.66	1.0000	222.86	222.85
	T = 318.15 K			T = 323.15 K	
0.0000	0.42	1.04	0.0000	0.45	0.36
0.1499	5.44	4.96	0.1499	5.55	4.09
0.3085	7.98	9.69	0.3085	11.03	13.37
0.4502	17.28	14.34	0.4502	24.52	22.29
0.6150	25.74	27.6	0.6150	35.61	36.57
0.7518	60.87	60.43	0.7518	63.74	63.56
1.0000	227.87	227.89	1.0000	231.77	231.79
	T = 328.15 K			T = 333.15 K	
0.0000	0.47	0.67	0.0000	0.56	0.99
0.1499	6.73	5.92	0.1499	7.62	6.9
0.3085	14.73	16.00	0.3085	16.12	17.29
0.4502	25.58	24.27	0.4502	27.23	25.95
0.6150	37.64	38.32	0.6150	39.82	40.54
0.7518	66.81	66.65	0.7518	69.05	68.87
1.0000	234.95	234.95	1.0000	240.71	240.72
	T = 338.15 K			T = 343.15 K	
0.0000	0.74	1.39	0.0000	1.12	1.78
0.1499	8.72	8.80	0.1499	11.4	10.62
0.3085	19.74	19.83	0.3085	21.79	23.17
0.4502	28.97	28.19	0.4502	34.51	32.79
0.6150	42.91	43.83	0.6150	50.63	51.71
0.7518	76.5	76.18	0.7518	91.47	91.18
1.0000	251.87	251.87	1.0000	292.39	292.4

Results and Discussion

The solubility data for clindamycin phosphate in ethanol (B) + water (C) mixtures at different temperatures are listed in Table 1. The mole fraction solubility is given by[7]

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

x_A^{calcd} is a calculated value; x_{Ai} is the saturated mole fraction solubility of the solute in pure solvent i; and x_C^0 refers to the initial mole fraction of the solvent mixture when the solute (A) was not present.

For describing how the experimental solubility of solute dissolved in a binary solvent mixture varies with binary solvent composition, Acree and co-workers[8−10] suggested a mathematical representation for isothermal solubility data based on the combined nearly ideal binary solvent (CNIBS)/Redlich−Kister model

$$\ln x_A = x_B^0 \ln(x_A)_B + x_C^0 \ln(x_A)_C + x_B^0 x_C^0 \sum_{i=0}^{N} S_i (x_B^0 - x_C^0)^i \quad (2)$$

Here S_i is the model constant and N can be equal to 0, 1, 2, and 3, respectively. Depending on the values of N, four equations can be obtained from eq 2. x_B^0 and x_C^0 refer to the initial mole fraction of the solvent mixture when the solute (A) was not present. For $x_B^0 = (1 - x_C^0)$ in eq 1, $N = 2$ and subsequent rearrangements result in eq 3

$$\ln x_A = \ln(x_A)_B + [\ln(x_A)_C - \ln(x_A)_B + S_0 + S_1 + S_2]x_C^0 + [-S_0 + 3S_1 + 5S_2]x_C^{02} + [-2S_1 - 8S_2]x_C^{03} + [-4S_2]x_C^{04} \quad (3)$$

This can be simplified as

$$\ln x_A = B_0 + B_1 x_C^0 + B_2 x_C^{02} + B_3 x_C^{03} + B_4 x_C^{04} \quad (4)$$

Correlated experimental solubility data (x_A) with eq 4 and the calculated solubilities (x_A^{calcd}) are listed in Table 1. For comparing the experimental points with calculated values by the (CNIBS)/Redlich−Kister model, the solubility data of clindamycin phosphate in binary ethanol + water solvent from temperatures (278.15 to 343.15) K are presented in Figure 2

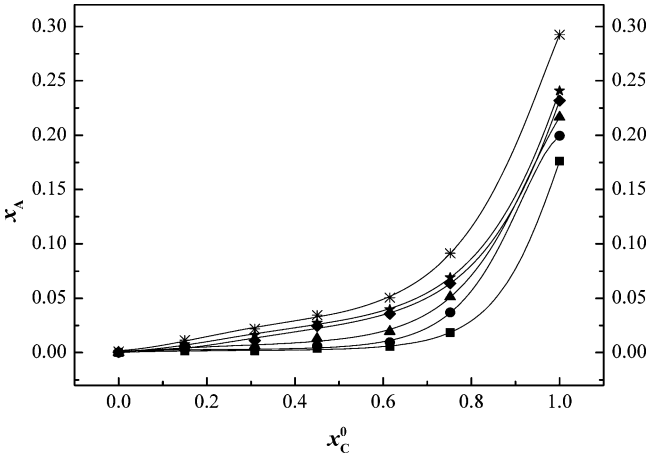

Figure 2. Correlation of clindamycin phosphate solubilities in binary ethanol + water with the (CNIBS)/Redlich−Kister mode: ■, T = 278.15 K; ●, T = 293.15 K; ▲, T = 308.15 K; ◆, T = 323.15 K; ★, T = 333.15 K; *, T = 343.15 K.

Table 2. Curve Fitting Parameters of Clindamycin Phosphate in Binary Ethanol + Water in the Temperature Range from T = (278.15 to 343.15) K

T/K	B_0	B_1	B_2	B_3	B_4	10 % dev[a]
278.15	−7.652	12.617	−42.386	63.843	−28.159	0.3299
283.15	−7.433	11.130	−34.872	52.278	−22.819	0.39889
288.15	−6.893	6.625	−27.878	55.276	−28.812	0.99838
293.15	−6.691	9.119	−36.745	64.922	−32.217	0.84432
298.15	−6.685	9.766	−32.691	54.233	−26.219	0.84859
303.15	−6.306	8.396	−31.219	55.411	−27.845	1.10897
308.15	−6.723	12.762	−36.678	52.910	−23.800	1.02417
313.15	−6.689	13.812	−39.965	56.352	−25.011	0.97771
318.15	−6.865	15.452	−41.536	55.612	−24.141	1.15232
323.15	−7.941	22.574	−49.298	51.868	−18.667	1.04042
328.15	−7.303	20.527	−47.604	52.611	−19.679	0.63339
333.15	−6.920	18.174	−41.138	44.951	−16.491	0.64442
338.15	−6.580	17.700	−42.9150	49.66	−19.248	0.40424
343.15	−6.332	17.225	−42.447	50.173	−19.848	0.84723

partly. The values of the five parameters, B_0, B_1, B_2, B_3, and B_4, and average percent deviations (% dev[a]) in absolute form are listed in Table 2. The % dev[a] is expressed in absolute form as

$$|\Delta x_i\,\%| = \frac{100}{n}\sum_{i=1}^{n}\left[\frac{|x_i^{\mathrm{calcd}} - x_i|}{x_i}\right] \qquad (5)$$

Here, n is the number of experimental points and x_i^{calcd} and x_i represent the solubility values of calculated results from eq 4 and experiments, respectively.

From Figure 2, Table 1, and Table 2, it is easy to conclude the following: (i) With an increase in temperature, the solubility of clindamycin phosphate in binary ethanol + water solvent mixtures increases. (ii) The solubility decreases with the proportion of the increase of ethanol, and the lowest solubility happens in pure ethanol. (iii) By the correct correlation with the proper model, the calculated solubility values show good agreement with the experimental values; this could be used as essential data and models in the purification process of clindamycin phosphate.

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