Solubility of Deflazacort in Binary Solvent Mixtures

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Experimental solubility data were measured for deflazacort dissolved in binary *n*-hexane + acetone, *n*-hexane + ethyl acetate, *n*-hexane + ethanol, and *n*-hexane + 2-propanol solvent mixtures at 303.15 K and atmospheric pressure by laser monitoring technique. Results of these measurements were used to test the predictive ability of the combined nearly ideal binary solvent (NIBS)/Redlich−Kister model. Computation showed that the model fit the data well.

Introduction

Deflazacort, 21-acetoxy-11β-hydroxy-2′-methyl-(16β)-pregna-1,4-dieno[17,16-*d*]oxazole-3,20-dione (Figure 1) is an oxazoline derivative of prednisolone with anti-inflammatory and immunosuppressive activity. It has been prescribed for the treatment of rheumatoid arthritis and asthma and for other applications.[1,2] Deflazacort is usually purified by crystallization. Solvent selection is important for the optimization of the crystallization process, so it is necessary to get the solubility data of deflazacort in solvents and solvent mixtures. Unfortunately, the solubility data of deflazacort in solvent mixtures have never been reported.

In the present study, experimental solubility data were measured for deflazacort dissolved in binary *n*-hexane + acetone, *n*-hexane + ethyl acetate, *n*-hexane + ethanol, and *n*-hexane + 2-propanol solvent mixtures at 303.15 K and atmospheric pressure by laser monitoring technique.

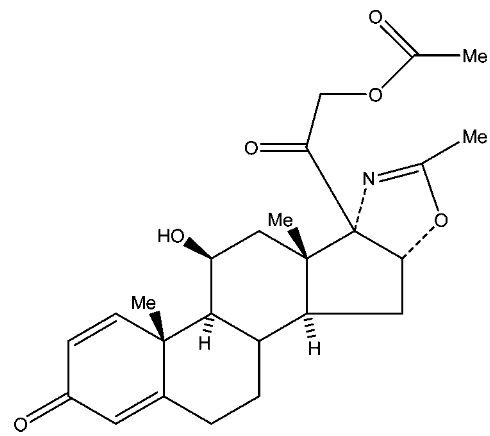

Figure 1. Chemical structure of deflazacort.

Experimental Section

Materials. Deflazacort supplied by Tianjin Tianyao Pharmaceutical (China) was recrystallized to yield product with a mass fraction purity of greater than 99.0 %. *n*-Hexane, acetone, ethyl acetate, ethanol, and 2-propanol (Tianjin Chemical Reagent, China) used for experiments were of analytical reagent grade, and the mass fractions were 98.0 %, 99.5 %, 99.5 %, 99.7 %, and 99.7 %, respectively.

Apparatus and Procedures. The solubility data were measured by a synthetic method.[3,5] The apparatus for the solubility measurement was the same as that described in the literature.[3] Experiments were performed in a cylindrical double-jacketed glass vessel that had a working volume of 50 mL. A magnetic stir bar was used for turbulent mixing of the suspension. The temperature was kept at (303.15 ± 0.1) K by a constant temperature water bath (Wanda/sida instrument HC2010, China). A total reflux condenser was connected to the vessel to prevent the solvents from evaporating. The dissolution of the solute was examined by the intensity change of the laser that penetrated through the suspension. The detailed introduction to the method was published in the literature.[3]

Binary solvent mixtures were prepared by mixing a certain quantity of two solvents measured by an analytical balance (Metler Toledo AB204-N, Switzerland) with an uncertainty of ± 0.1 mg. In the experiments, excess solvent and solute were placed in the jacketed vessel and allowed to mix completely at (303.15 ± 0.1) K for 1 h. Then, an additional solute of known mass (about (1 to 5) mg) determined by the above analytical balance was introduced to the vessel. This procedure was repeated until the last addition of solute could not completely dissolve. The interval of addition was 20 min. The laser intensity that penetrated the solution attained its maximum when the solute completely dissolved. When the laser intensity did not exceed 90 % of the maximum, the solute was believed to be not completely dissolved. The amount of solute leading to the laser intensity decrease of 10 % from the maximum was less than 1.0 mg. The uncertainty of the solubility values was estimated to be 1.0 %. The mean values representing the average of more than two independent determinations were used to calculate the mole fraction solubility. The solubility of the solute in mole fraction (x_A) in different binary solvent mixtures could be obtained as follows

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_1/M_1 + m_2/M_2} \tag{1}$$

where m_A, m_1, and m_2 represent the mass of the solute (deflazacort), *n*-hexane, and solvent (2 = acetone, ethyl acetate, ethanol, or 2-propanol), respectively. M_A, M_1, M_2 are the respective molecular masses.

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Table 1. Experimental Solubility (x_A) of Deflazacort in Binary *n*-Hexane (1) + the Other Solvent (2) Mixtures at 303.15 K

x_1^0	$10^4 x_A^{exptl}$	$10^4 x_A^{calcd}$	$(x_A^{exptl} - x_A^{calcd})/x_A^{exptl}$
n-Hexane (1) + Acetone (2)			
0.0000	72.1402	72.7654	− 0.0087
0.0961	63.9623	62.6600	0.0204
0.1721	53.0990	53.0719	0.0005
0.2792	38.1177	38.9661	− 0.0223
0.3750	27.2445	27.2666	− 0.0008
0.5019	14.6141	14.8782	− 0.0181
0.5622	11.1608	10.5027	0.0590
0.7081	3.4338	3.7363	− 0.0881
0.7537	2.6777	2.5397	0.0515
0.8916	0.6351	0.6358	− 0.0010
n-Hexane (1) + Ethyl Acetate (2)			
0.0000	39.9483	38.7915	0.0290
0.0931	28.0728	30.2925	− 0.0791
0.1976	22.6002	21.6821	0.0406
0.2968	15.4265	15.0807	0.0224
0.3985	10.0227	9.9245	0.0098
0.4995	6.0541	6.1685	− 0.0189
0.5930	3.5827	3.6885	− 0.0295
0.6919	1.9018	1.9162	− 0.0076
0.7818	0.9654	0.9233	0.0437
0.8958	0.2796	0.2843	− 0.0167
n-Hexane (1) + Ethanol (2)			
0.0000	24.0159	24.0809	− 0.0027
0.0613	26.0121	25.8863	0.0048
0.0796	26.1132	26.0720	0.0016
0.0950	26.1515	26.1140	0.0014
0.1150	26.0898	26.0260	0.0024
0.1528	25.4337	25.4798	− 0.0018
0.1988	23.9309	24.2958	− 0.0152
0.2417	23.0074	22.8588	0.0065
0.2745	21.5129	21.6305	− 0.0055
0.3934	17.2123	16.9333	0.0162
0.5044	12.7621	12.7744	− 0.0010
0.6053	9.1563	9.2729	− 0.0127
0.7057	6.0449	6.0395	0.0009
0.8095	3.2066	3.1818	0.0077
0.9134	1.2184	1.2221	− 0.0031
n-Hexane (1) + 2-Propanol (2)			
0.0000	20.3793	20.2858	0.0046
0.0483	21.2905	21.3558	− 0.0031
0.0978	21.7756	21.8091	− 0.0015
0.1302	21.6659	21.7793	− 0.0052
0.1965	21.0811	21.0382	0.0020
0.3027	18.4991	18.4855	0.0007
0.4031	15.3655	15.2391	0.0082
0.5161	11.2743	11.2880	− 0.0012
0.6060	8.2740	8.2419	0.0039
0.7055	5.0741	5.2378	− 0.0323
0.8052	2.9537	2.8566	0.0329
0.9056	1.2433	1.2560	− 0.0102

Results and Discussion

The solubility data of deflazacort in all four binary solvent mixtures with the mole fraction of *n*-hexane ranging from 0.000 to about 0.900 at 303.15 K are listed in Table 1. Acree and his coworkers[7−9] developed the combined nearly ideal binary solvent (NIBS)/Redlich−Kister model

$$\ln x_A = x_2^0 \ln(x_A)_2 + x_1^0 \ln(x_A)_1 + x_2^0 x_1^0 \sum_{i=0}^{N} S_i (x_2^0 - x_1^0)^i \quad (2)$$

as a possible mathematical representation for describing how isothermal solubility of a crystalline solute dissolved in a binary solvent mixture varies with the binary solvent composition. In eq 2, S_i is the model parameter. N can be equal to 0, 1, 2, or 3. Depending on the value of N, four equations can be obtained from eq 2. x_1^0 and x_2^0 refer to the initial mole fraction of the binary solvent as if solute (A) was not present. $(x_A)_i$ represents the saturate mole fraction solubility of the solute in pure solvent i. Substitution of $(1 - x_1^0)$ for x_2^0 in eq 2 with $N = 2$ and subsequent rearrangements result in eq 3

$$\ln x_A = \ln(x_A)_2 + [\ln(x_A)_1 - \ln(x_A)_2 + S_0 + S_1 + S_2]x_1^0 + [-S_0 - 3S_1 - 5S_2]x_1^{0^2} + [2S_1 + 8S_2]x_1^{0^3} + [-4S_2]x_1^{0^4} \quad (3)$$

which can be rewritten in simple form as

$$\ln x_A = B_0 + B_1 x_1^0 + B_2 x_1^{0^2} + B_3 x_1^{0^3} + B_4 x_1^{0^4} \quad (4)$$

The calculated solubility values of deflazacort from eq 4 are also given in Table 1. For comparison with each of the experimental points, the solubility of deflazacort in all four binary solvent mixtures with the mole fraction of *n*-hexane ranging from 0.000 to about 0.900 at 303.15 K are plotted in Figure 2. The values of the five parameters B_0, B_1, B_2, B_3, and B_4 together with the root-mean-square deviation (rmsd) defined by eq 5 are listed in Table 2.

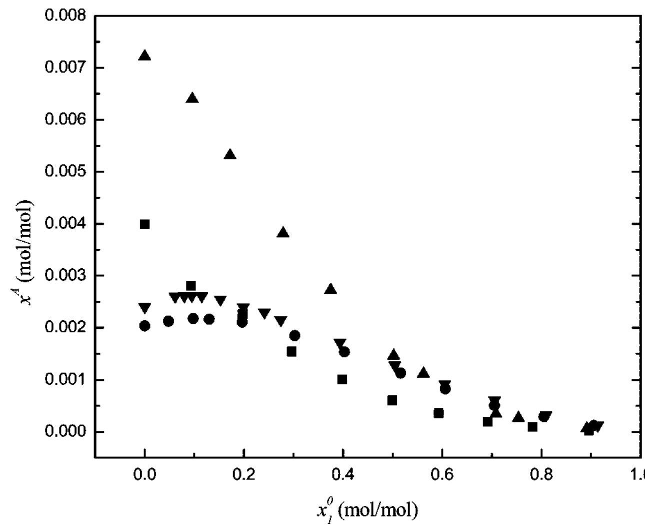

Figure 2. Mole fraction solubility of deflazacort in four binary solvent mixtures at 303.15 K: ■, *n*-hexane + ethyl acetate; ▲, *n*-hexane + acetone; ▼, *n*-hexane + ethanol; ●, *n*-hexane + 2-propanol.

Table 2. Curve-Fitting Parameters of Deflazacort in Binary *n*-Hexane (1) + the Other Solvent (2) Mixtures at 303.15 K

	binary solvent mixtures			
	n-hexane (1) + acetone (2)	*n*-hexane (1) + ethyl acetate (2)	*n*-hexane (1) + ethanol (2)	*n*-hexane (1) + 2-propanol (2)
B_0	− 4.92310	− 5.55214	− 6.02892	− 6.20042
B_1	− 1.20755	− 2.34085	1.86646	1.41669
B_2	− 3.63218	− 3.76871	− 12.26170	− 7.67253
B_3	0.21258	4.55081	17.89917	8.31150
B_4	− 1.46564	− 4.76119	− 11.63074	− 5.86611
10^4 rmsd	0.5849	0.8523	0.1392	0.0830

$$\text{rmsd} = \left\{ \frac{1}{N} \sum_{i=1}^{N} \left(x_i^{calcd} - x_i^{exptl} \right)^2 \right\}^{1/2} \quad (5)$$

where N is the number of experimental points, x_i^{calcd} represents the solubility calculated from eq 4; and x_i^{exptl} represents the experimental solubility values.

Results showed that: (1) The solubility of deflazacort decreases as the fraction of *n*-hexane in *n*-hexane + ethyl acetate and *n*-hexane + acetone systems increases. Solubility of deflazacort in the *n*-hexane + acetone system is higher than that in the *n*-hexane + ethyl acetate system at the same x_1^0 value. (2) At 303.15 K, the solubility of deflazacort in the *n*-hexane + ethanol and *n*-hexane + 2-propanol systems has a maximum when $x_1^0 \approx 0.09$. The reason is unknown and will be studied further. The solubility of deflazacort in the *n*-hexane + ethanol system is higher than that in the *n*-hexane + 2-propanol system at the same x_1^0 value. (3) At 303.15 K, the solubility of deflazacort in a single solvent increases in the order 2-propanol < ethanol < ethyl acetate < acetone. Deflazacort dissolves in *n*-hexane very little. (4) The calculated solubility data showed good agreement with the experimental solubility data, so the mathematical correlation equation can be used as a predictive model.

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