Solubility of Dexamethasone Sodium Phosphate in Different Solvents

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The solubilities of dexamethasone sodium phosphate in different solvents were measured using a synthetic method. The laser monitoring observation technique was used to determine the disappearance of the solid phase in a solid + liquid mixture. The solubility data were correlated with Apelblat equation.

Introduction

Dexamethasone sodium phosphate is pregna-1,4-diene-3,20-dione,9-fluoro-11β,17α,21-trihydroxy-16α-methyl-21-(dihydrogen phosphate) disodium salt. It is a white or almost white powdered crystal. As an antiinflammatory drug of the adrenal cortex hormone, dexamethasone sodium phosphate is widely used in clinical applications. In industrial manufacture, dexamethasone sodium phosphate is crystallized from solution in the purification step.[1] To determine the proper solvent and to design an optimized crystallizer, it is necessary to know its solubility in different solvents.[2] However, from a review of the literature on dexamethasone sodium phosphate, it was found that no experimental solubility data in aqueous + organic solvents have been reported. The scarcity of basic solubility data hinders progress in the design of production flow processes or expanding production capacity. In this work, the solubilities of dexamethasone sodium phosphate in different solvent systems were experimentally determined using a synthetic method. The solubilities of dexamethasone sodium phosphate in various organic solvents and organic solvents + water mixed solvents were studied. The experimental data were correlated with the modified Apelblat equation.

Methods of measuring the solubility of a solid-in-liquid mixture can be classified as analytical and synthetic.[3,4] The advantage of the analytical method lies in the possibility of measuring a large number of samples simultaneously with a reliable method. Its disadvantage is that it is tedious and time-consuming. With a synthetic method, solubility data can be obtained much faster and more readily.[5,6] In this work, the last crystal disappearance method, a synthetic method, was used to determine the solubility data of dexamethasone sodium phosphate.

Experimental Section

Materials. A white crystalline powder of dexamethasone sodium phosphate, with a melting/decomposition point of (234.6 ± 0.5) °C, was prepared by recrystallization from a methanol + ethanol solution. Its purity, determined by HPLC according to BP2000, is higher than 99.5 mass %. It was dried in vacuo at 50 °C for 48 h and stored in a desiccator. The methanol and ethanol used for the experiments were of analytical reagent grade. Methanol and ethanol were dehydrated with molecular sieves, and their purity was higher than 99.8 mass %, as verified by gas chromatography. Distilled deionized water of HPLC grade was used.

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Table 1. Mole Fraction Solubility *x* of Dexamethasone Sodium Phosphate in Pure Solvents

	water		methanol		ethanol	
T/K	10^2x^{exptl}	10^2x^{calcd}	10^2x^{exptl}	10^2x^{calcd}	10^4x^{exptl}	10^4x^{calcd}
278.15	1.404	1.455	1.105	1.081	1.316	1.241
283.15	1.611	1.674	1.072	1.047	1.368	1.339
288.15	1.927	1.921	1.049	1.012	1.548	1.459
293.15	2.168	2.200	0.9823	0.9748	1.605	1.604
298.15	2.526	2.512	0.9523	0.9370	1.751	1.778
303.15	2.815	2.863	0.9036	0.8986	2.032	1.986
308.15	3.161	3.256	0.8862	0.8599	2.373	2.235
313.15	3.562	3.696	0.8301	0.8214	2.563	2.532
318.15	4.128	4.186	0.7817	0.7832	2.849	2.886

Table 2. Parameters of Equation 1 for Dexamethasone Sodium Phosphate in Pure Solvents

solvent	*A*	*B*	*C*	10^2 rmsd
water	−48.48	0.182	7.862	6.71
methanol	79.30	−3122	−12.90	2.02
ethanol	−272.1	10110	40.29	6.54

Apparatus and Procedure. The solubility of dexamethasone sodium phosphate was measured by the last crystal disappearance method. The laser monitoring observation technique was used to determine the disappearance of the last crystal in the solid + liquid mixture. The laser monitoring system consists of a laser generator, a photoelectric transformer, and a recorder. The equilibrium cell is a cylindrical double-jacketed glass vessel. A constant desired temperature was maintained by circulating water through the outer jacket from a thermostat. The uncertainty in temperature was ±0.05 K. The cell has a perforated rubber cover plate to prevent the solvent from evaporating, through which a mercury thermometer with an uncertainty of ±0.05 K was inserted into the inner chamber of the vessel. The mixtures of solute and solvent in the vessel were stirred with a magnetic stirrer. The masses of the solvent and solute were weighed using an analytical balance with an accuracy of ±0.0001 g.

In the experiments, excess dexamethasone sodium phosphate solid and solvent of known masses were transferred to the equilibrium vessel. The solid + liquid mixture was maintained at a fixed temperature for 1 h. Then, additional solvent of known mass was introduced into the cell with

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Table 3. Solubility of Dexamethasone Sodium Phosphate in Methanol (1) + Water (2) at 298.15 K

$100w_1$	0	12.25	25.32	42.22	58.46	80.60	85.85	92.23	94.06	95.96	97.91	100
10^3x	25.26	18.67	12.57	7.871	5.351	3.746	3.621	3.790	4.077	4.964	6.681	9.523

Table 4. Solubility of Dexamethasone Sodium Phosphate in Ethanol (1) + Water (2) at 298.15 K

$100w_1$	0	7.421	12.75	26.40	44.11	52.15	59.45	75.95	90.85	100
10^3x	25.26	18.27	13.99	9.325	6.081	4.538	3.409	1.782	0.6069	0.1751

continuous stirring. This procedure was repeated until the last crystal disappeared completely. The mass of the solvent added was gradually decreased when the saturation solution was approached. This process lasts more than 6 h. In the early stage of the experiment, the laser beam was blocked by the undissolved particles of dexamethasone sodium phosphate in the solution, so the intensity of the laser beam penetrating the vessel was low. The intensity increased gradually along with the increase in the amount of dexamethasone sodium phosphate dissolved. When the last particle of dexamethasone sodium phosphate disappeared, the intensity of the laser beam penetrating the vessel reached a maximum. The total amount of solvent used was recorded, and the solubility expressed in mole fraction was calculated. The same solubility experiment was conducted three times. The confidence of the experimental solubility values is about 95%.

Results and Discussion

The solubility data of dexamethasone sodium phosphate in pure water, methanol, and ethanol at different temperature are presented in Table 1. The temperature dependence of dexamethasone sodium phosphate solubility in pure solvents is described by the modified Apelblat equation[7]

$$\ln x = A + \frac{B}{T/\mathrm{K}} + C \ln(T/\mathrm{K}) \qquad (1)$$

where x is the mole fraction solubility of dexamethasone sodium phosphate, T is the absolute temperature, and A, B, and C are the parameters. The calculated solubility values of dexamethasone sodium phosphate are also given in Table 1. The values of parameters A, B, and C and the root-mean-square deviations (rmsd's) are listed in Table 2. The rmsd is defined as

$$\mathrm{rmsd} = \left\{ \frac{\sum_{i=1}^{N} [(x_i^{\mathrm{calcd}} - x_i^{\mathrm{exptl}})]^2}{N} \right\}^{1/2} \qquad (2)$$

where N is the number of experimental points, x_i^{calcd} represents the solubilities calculated from eq 1, and x_i^{exptl} represents the experimental solubility values.

From data listed in Table 1, it can be seen that the calculated solubilities show good agreement with the experimental values. The solubility of dexamethasone sodium phosphate in water is higher than in methanol and ethanol. The solubility in ethanol is the lowest. The solubility of dexamethasone sodium phosphate in pure water and ethanol increases with increasing temperature; however, its solubility in methanol decreases with increasing temperature. The reason for this phenomenon needs to be studied further.

The solubility data of dexamethasone sodium phosphate in methanol + water and ethanol + water mixed solvents at 298.15 K are presented in Tables 3 and 4, respectively.

From the data listed in Tables 3 and 4, the solubility of dexamethasone sodium phosphate in ethanol + water mixtures decreases with increasing ethanol content at constant temperature. However, its solubility in methanol + water mixed solvents is different from this. The solubility data reaches a minimum when $w_1 = 0.85$. If $w_1 < 0.85$, then the solubility decreases with increasing methanol content; hereafter, the solubility increases with increasing methanol content. The reason for this phenomenon needs to be studied further.

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