Solubility of Clindamycin Phosphate in Methanol, Ethanol, and Dimethyl Sulfoxide

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The solubilities of clindamycin phosphate in different solvents (methanol, ethanol, and dimethyl sulfoxide) were measured at temperatures from (283.15 to 333.15) K by a synthetic method at atmospheric pressure. The experimental data were correlated with the modified Apelblat equation. The equation was found to provide an accurate representation of the experimental data. The dissolution enthalpy determined from the experimental solubility data was also presented.

Introduction

Clindamycin phosphate, (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), is shown in Figure 1. Clindamycin phosphate is the third generation product of Lincomycin and widely used in treatment of Gram-positive and Gram-negative bacteria. The crystallization step plays an important role in the production process of clindamycin phosphate, and the determination of its solubility in different solvents is crucial to determine the proper solvent and to optimize the crystallization process.[1] However, to the best of our knowledge, the solubilities of clindamycin phosphate in pure organic solvent have not been systematically studied, and only the solubilities of clindamycin phosphate in ethanol have been measured by an analytical method.[2]

Methods of measuring the solubility of a solid-in-liquid mixture can be classified as analytical and synthetic.[3,4] Solubilities of clindamycin phosphate in pure organic solvent over a temperature range have been measured by synthetic methods in this work. At the same time, the enthalpy of dissolution for the clindamycin phosphate−organic solvent system was determined from the experimental solubility data. The results can be used in the purification process of clindamycin phosphate.

Experimental Section

Materials. All the chemicals were of analytical reagent grade. Clindamycin phosphate, with a purity of 99.0 %, was obtained from North China Pharmaceutical Co., Ltd. The clindamycin phosphate solid was dried to constant mass in an air oven at 353 K before use and stored in a desiccator. Methanol, ethanol, and dimethyl sulfoxide were obtained from Tianjin Chemical Reagent Co., Ltd. (Tianjin, China).

Procedure. The solubility of a solid in a solvent was measured by a synthetic method. At the beginning of the experiment, the mass of the solute and the solvent was determined with an electronic analytical balance (type AL204, Mettler Toledo) with an uncertainty of ± 0.1 mg. The solvent was loaded into the jacketed vessel which was kept at the desired temperature by circulating water from a constant-temperature bath (type 501A, China). The solution was stirred by an electric magnetic stirrer, and a microthermometer was used to determine the temperature of the system. The uncertainty in the temperature was ± 0.01 K. Some of the solubility experiments were conducted two or three times to check the repeatability in this work, and the repeatability evaluated by mean relative deviation was less than 3 %.

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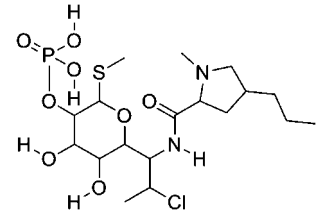

Figure 1. Chemical structure of clindamycin phosphate.

Table 1. Experimental Solubilities (x^{exptl}) and Calculated Solubilities (x^{calcd}) of Clindamycin Phosphate in Different Organic Solvents

T	$10^3 x^{exptl}$	100 δ	T	$10^3 x^{exptl}$	100 δ
		Methanol			
286.15	0.337	2.94	306.15	0.491	0.38
291.15	0.359	1.05	311.15	0.541	0.54
296.15	0.394	2.04	316.15	0.591	0.05
301.15	0.441	0.62	321.15	0.648	0.03
		Ethanol			
283.15	0.00759	0.59	303.15	0.0139	0.47
288.15	0.00843	3.13	308.15	0.0156	0.23
293.15	0.0101	2.45	313.15	0.0176	1.35
298.15	0.0126	0.51	318.15	0.0190	1.02
		Dimethyl Sulfoxide			
298.15	0.422	11.79	318.15	1.197	0.56
303.15	0.519	3.50	323.15	1.506	6.63
308.15	0.702	4.24	328.15	2.169	1.46
313.15	0.893	0.81	333.15	2.859	0.71

Results and Discussion

The solubility data of clindamycin phosphate in pure methanol, ethanol and dimethyl sulfoxide at different temperatures are presented in Table 1 and visually shown by Figure 2. The temperature dependence of clindamycin phosphate solubility in pure solvents is described by the modified Apelblat equation[5]

10.1021/je800291t CCC: $40.75
Published on Web 07/23/2008

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

where x is the mole fraction solubility of clindamycin phosphate; T is the absolute temperature;and A, B, and C are the parameters of the equation. The calculated relative deviation of clindamycin phosphate and the solubility data of previous work are also given in Table 1. The relative deviation is defined as

$$\delta = \left| \frac{x_i^{\mathrm{exptl}} - x_i^{\mathrm{calcd}}}{x_i^{\mathrm{exptl}}} \right| \quad (2)$$

where x_i^{calcd} represents the solubility calculated from eq 1 and x_i^{exptl} represents the experimental solubility. The parameters A, B, and C were obtained by fitting the experimental solubility data and are presented in Table 2 together with the average relative deviation. The average relative deviation is defined as

$$\bar{\delta} = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{|x_i^{\mathrm{exptl}} - x_i^{\mathrm{calcd}}|}{x_i^{\mathrm{exptl}}} \right] \quad (3)$$

where n is the number of experimental points; x_i^{calcd} represents the solubility calculated from eq 1; and x_i^{exptl} represents the experimental solubility.

The enthalpies of dissolution for the clindamycin phosphate in organic solvent were determined from the experimental solubility data by implementing the following basic thermodynamic relationship[6]

$$\ln(x_{\mathrm{eq}}) = \frac{-\Delta_{\mathrm{diss}}H}{RT} + C \quad (4)$$

where C is a constant; x_{eq} is mole fraction solubility; $-\Delta_{\mathrm{diss}}H$ is enthalpy of dissolution; R is air constant; and T is absolute temperature. Thus, fitting the solubility data of clindamycin phosphate in organic solvent to eq 4 ($\ln(x_{\mathrm{eq}})$ against $1/RT$) will result in a straight line approximation, as shown in Figure 3. The enthalpy of dissolution ($\Delta_{\mathrm{diss}}H$) shown in Table 3 can then be calculated from the slope.

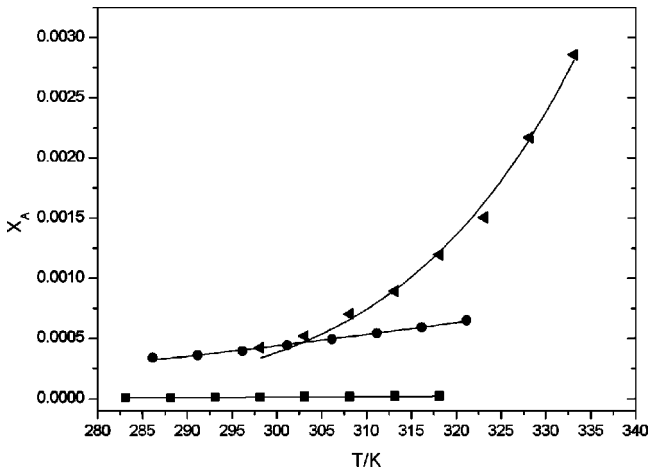

Figure 2. Solubility of clindamycin phosphate solubilities in different organic solvents at different temperatures: ■, ethanol; ●, methanol; ▼, dimethyl sulfoxide.

Table 2. Parameters of the Apelblat Equation for Clindamycin Phosphate in Different Solvents

solvent	A	B	C	$\bar{\delta}$
methanol	−29.49408	−546.64232	4.13292	0.9549
ethanol	0.98598	−2349.11255	−0.79224	1.2190
dimethyl sulfoxide	−180.20451	3172.31016	28.37487	3.7120

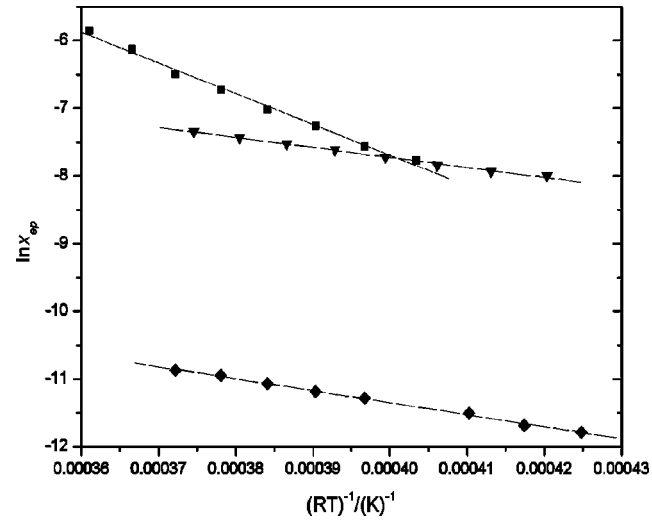

Figure 3. Fitting of the experimental solubility data to eq 4: ◆, ethanol; ▼, methanol; ■, dimethyl sulfoxide.

Table 3. Enthalpy of Dissolution for Clindamycin Phosphate in Different Solvent with Corresponding Correlation Coefficient

solvent	$\Delta_{\mathrm{diss}}H/(\mathrm{kJ\cdot mol^{-1}})$	R^2
ethanol	17.702	0.9976
methanol	14.811	0.9954
dimethyl sulfoxide	45.405	0.9936

From data listed in Table 1, it can be seen that the calculated solubilities show good agreement with the experimental values. The solubility of clindamycin phosphate in dimethyl sulfoxide is higher than in methanol and ethanol, and the solubility in ethanol is the lowest. The experimental data show that the solubility of clindamycin phosphate in pure methanol, ethanol, and dimethyl sulfoxide increases with increasing temperature.

Conclusions

The solubilities of clindamycin phosphate in methanol and dimethyl sulfoxide were measured over a temperature range. To keep the consistency of the experimental method, the methanol of clindamycin phosphate in pure solvent over a temperature range was also measured by a synthetic method. Raising the temperature increased the solubility of clindamycin phosphate regardless of the solvent used. The solubility data show that the trend of solubility in different solvent is: $w_{\mathrm{dimethyl\ sulfoxide}} > w_{\mathrm{methanol}} > w_{\mathrm{ethanol}}$. The temperature dependence of clindamycin phosphate solubility in different solvents can be well correlated by the modified Apelblat equations, and the calculated solubilities show good agreement with the experimental values. In this work, the dissolution enthalpy of clindamycin phosphate was also presented.

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Received for review April 25, 2008. Accepted June 3, 2008.

JE800291T