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Measurement and Correlation of the Solubility of Prednisone Acetate in Different Solvents

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ABSTRACT: The solubility of prednisone acetate in ethanol, ethyl acetate, 1,2-dichloroethane, methanol, and chloroform has been determined by a dynamic method. The experimental data were correlated with the Apelblat equation and an exponential function equation. The solubility correlated by the model showed good agreement with the experimental data.

INTRODUCTION

Prednisone acetate is an important glucocorticoid drug with anti-inflammatory and immunosuppressive properties.[1,2] Its chemical structure is shown in Figure 1. It is prepared by fermentation, extraction, concentration, crystallization, and recrystallization. The entire usage requires purified prednisone acetate products. Crystallization and recrystallization processes are the critical steps to determine the quality of the final product. The solubility of solid compounds in solvents plays a crucial role in the determination of proper solvents and the development and operation of crystallization processes. Therefore, it is very important to know the solubility of the product. Published works relating to prednisone acetate are mainly concerned with fermentation and synthesis.[3] The literature has few solubility data for prednisone acetate in ethanol, ethyl acetate, 1,2-dichloroethane, methanol, and chloroform.

In this study, the solubility of prednisone acetate in the solvents above was measured from (285.45 to 337.45) K. The experimental data were correlated with the modified Apelblat equation and an exponential function equation, and the solubility was correlated by the Apelblat model and the exponential function model showing good agreement with the experimental data.

EXPERIMENTAL SECTION

Chemicals. In all experiments, deionized water was used, and prednisone acetate was obtained from Anyang LiHua Pharmaceutical Co. Ltd. Sodium chloride, ethanol, ethyl acetate, and 1,2-dichloroethane were supplied by the Tianjin Kermel Chemical Reagent Co. Ltd., and methanol and chloroform were supplied by Tianjin Kaitong Chemical Reagent Co. Ltd. The purity of these chemicals was higher than 99.5 %.

Apparatus and Procedure. The solubility of prednisone acetate in different solvents was measured by the dynamic method using the apparatus previously described.[4] The laser monitoring observation technique was used to determine the dissolution temperature of the solid−liquid mixture of known composition. The laser monitoring system consists of a laser generator, a photoelectric transformer, and a light intensity display.

The experiments were carried out in a 50 mL jacketed glass vessel with a magnetic stirrer, and a constant temperature (± 0.02 K) was maintained at the required temperature by circulating water through the outer jacket from a thermoelectric controller. A glass bushing with a mercury glass microthermometer was inserted into the inner chamber of the vessels for the measurement of the temperature.

Predetermined amounts of prednisone acetate and the solvents for the solubility measurement were weighed by an electronic balance (Mettler Toledo AB204-N) with an accuracy of ± 0.0001 g and then transferred into the vessel. The contents of the vessel were heated very slowly at the rate of 1 K per hour until the system reached equilibrium. To prevent volatilization of the solvent, a cold-water condenser tube was also connected with the vessel, and all the opening connectors were sealed. In the early stage of the experiment, the laser beam was blocked by the particles of prednisone acetate in the solution, so the intensity of the laser beam penetrating the vessel was lower. The intensity of the laser beam increased gradually along with an increase of the amount of prednisone acetate dissolved. The intensity of the laser beam reached a maximum when the last portion of prednisone acetate just disappeared. The temperature was recorded. The solubility of prednisone acetate was expressed by mole fraction with the formula as follows[5]

$$x = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

where m_1 and m_2 represent the mass of solute and solvent. M_1 and M_2 are the molecular mass of the solute and solvent, respectively.

Each experiment was repeated three times, and the average of the measurements is considered to be the solubility. The uncertainty of the solubility values is less than 2 %.

Test of Apparatus. To ensure the reliability and the uncertainty of the measurement, the solubility of NaCl in water was measured and compared with the values reported in the literature.[6,7] The experimental measurements agreed with the

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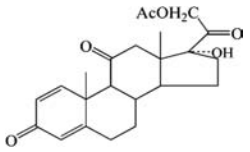

Figure 1. Chemical structure of prednisone acetate.

Table 1. Solubility of Sodium Chloride in Water

	NaCl + H_2O			
T/K	293.15	303.15	313.15	333.15
x	0.0998	0.1002	0.1011	0.1028
x(lit.)[6]	0.0996	0.1001	0.1009	0.1026
RD	0.0020	0.0010	0.0020	0.0019

reported values with a mean relative deviation of 0.20 %. The measured values are listed in Table 1.

RESULTS AND DISCUSSION

The solubility data of prednisone acetate in different solvents at different temperatures are presented in Table 2. The temperature dependence of prednisone acetate in different solvents (except chloroform) is described by the modified Apelblat equation

$$\ln x = A + \frac{B}{T} + C \ln T \tag{2}$$

Prednisone acetate in chloroform is described by the follow exponential function equation

$$x = A_0 + B_0 \exp^{(-T/C_0)} \tag{3}$$

where x is the mole fraction of solubility of prednisone acetate, and T is the absolute temperature. A, B, C, A_0, B_0, and C_0 are the model parameters.

The solubility curves by eq 2 and eq 3 are shown in Figure 2 and Figure 3. The root-mean-square deviation is defined as[6]

$$\text{rmsd} = \left[\frac{1}{N-1}\sum_{i=1}^{N}(x_{ci} - x_i)^2\right]^{1/2} \tag{4}$$

where N is the number of experimental points; x_{ci} represents the solubility calculated from eq 2 and eq 3; and x_i represents the experimental solubility values. The relative deviations between the experimental value and calculated value are also listed in Table 2. Relative deviations (RD) are calculated according to

$$\text{RD} = \frac{x - x_c}{x} \tag{5}$$

The relative average deviations (RAD) and the root-mean-square deviation (rmsd) from eq 2 and eq 3 are listed in Table 3 and Table 4. The RAD is defined as

$$\text{RAD} = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{x_i - x_{ci}}{x_i}\right| \tag{6}$$

From Table 3 and Table 4, it can be found that the calculated solubility data show good agreement with the experimental data,

Table 2. Solubility of Prednisone Acetate in Different Solvents

T/K	$x \cdot 10^2$	$x_c \cdot 10^2$	100RD
	Ethanol		
296.45	0.0762	0.0780	−2.28
298.55	0.0789	0.0839	−6.28
301.85	0.0928	0.0941	−1.36
305.05	0.106	0.105	0.93
310.65	0.132	0.127	3.35
315.95	0.159	0.152	3.94
319.65	0.174	0.172	0.91
324.55	0.203	0.203	0.23
330.25	0.242	0.245	−0.81
337.45	0.310	0.309	0.17
	Ethyl Acetate		
295.65	0.135	0.141	−4.51
305.05	0.180	0.182	−1.18
309.65	0.209	0.205	1.59
313.15	0.229	0.225	1.73
317.45	0.254	0.252	0.55
321.75	0.281	0.282	−0.67
327.25	0.325	0.326	−0.26
331.85	0.366	0.368	−0.50
337.45	0.424	0.425	−0.21
	1,2-Dichloroethane		
293.35	0.195	0.203	−8.04
298.15	0.262	0.245	−0.33
306.05	0.342	0.323	−0.01
311.25	0.412	0.386	1.39
315.45	0.476	0.445	2.05
318.65	0.522	0.495	1.02
321.95	0.576	0.553	0.053
325.75	0.645	0.626	−0.77
329.85	0.745	0.715	0.56
334.65	0.857	0.835	−0.67
	Methanol		
285.45	0.054	0.057	−6.42
292.95	0.081	0.079	1.81
298.25	0.102	0.099	2.89
302.55	0.124	0.118	5.36
306.85	0.145	0.140	3.38
310.75	0.170	0.164	3.76
314.95	0.197	0.193	2.07
319.05	0.231	0.226	2.04
325.15	0.286	0.286	0.01
	Chloroform		
287.05	1.075	1.085	−0.94
289.25	1.309	1.297	0.92
293.65	1.653	1.665	−0.73
299.45	2.100	2.053	2.23
313.15	2.628	2.660	−1.21
320.75	2.837	2.869	−1.11
323.95	2.936	2.938	−0.07
327.65	3.040	3.007	1.09

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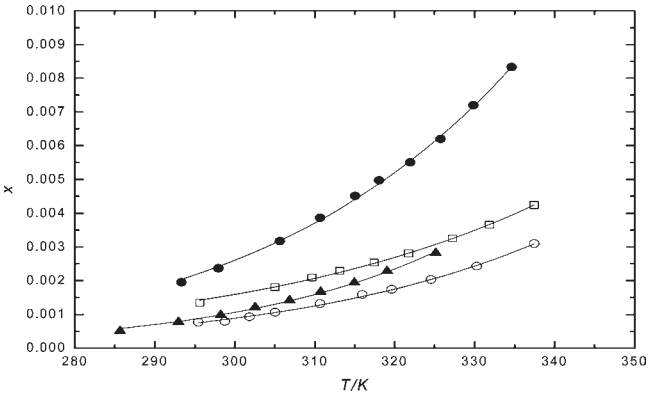

Figure 2. Solubility curves of prednisone acetate in different solvents: ●, 1,2-dichloroethane; □, ethyl acetate; ○, ethanol; ▲, methanol.

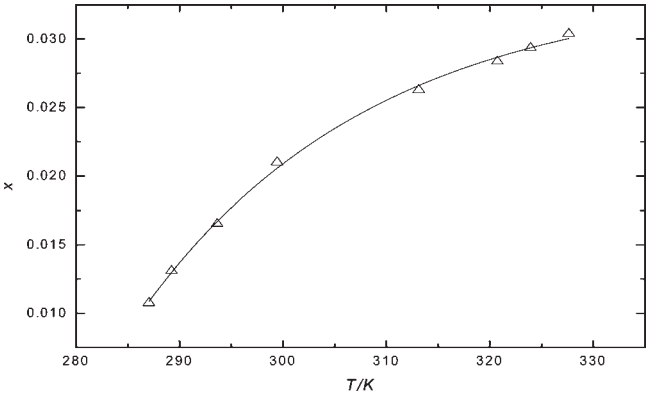

Figure 3. Solubility curves of prednisone acetate in chloroform.

Table 3. Parameters and Coefficient of Determination of Prednisone Acetate in Different Solvents by Equation 2

solvent	A	B	C	R^2	10^3 rmsd	10^2 RAD
ethanol	−92.47	1159.41	14.30	0.9980	0.033	2.03
ethyl acetate	−92.64	1807.22	14.06	0.9988	0.031	1.24
1,2-dichloroethane	−98.20	1569.72	15.27	0.9988	0.073	1.49
methanol	−94.18	786.33	14.85	0.9977	0.127	3.08

Table 4. Parameters and Correlation of Determination of Prednisone Acetate in Chloroform by Equation 3

solvent	A_0	B_0	C_0	R^2	10^3 rmsd	10^2 RAD
chloroform	0.034	−6449.93	22.90	0.9986	0.307	1.08

the overall rmsd of 46 data points for the prednisone acetate system in different solvents being $0.571 \cdot 10^{-3}$. The RD by eq 2 among all of these values does not exceed 8.04 %. The relative average deviations are 2.03 %, 1.24 %, 1.49 %, 3.08 %, and 1.08 % for ethanol, ethyl acetate, 1,2-dichloroethane, methanol, and chloroform, respectively, which indicates that the modified Apelblat equation is suitable to correlate the solubility data of prednisone acetate in ethanol, ethyl acetate, methanol, and 1, 2-dichloroethane, and the exponential function equation is suitable to correlate the solubility data of prednisone acetate in chloroform.

A graph of solubility of the prednisone acetate in the selected solvent systems is shown in Figure 2 and Figure 3. It can be observed from Figure 2 and Figure 3 that the solubility increases with an increase of temperature and follows the order: chloroform > 1,2-dichloroethane > ethyl acetate > ethanol > methanol. This is because the polarity of prednisone acetate is weak. The polarity of chloroform is weakest, so the solubility is greatest in this solvent, which agrees with the principle that like dissolves like.

CONCLUSION

The solubility of prednisone acetate in solvent systems has been measured from (285.45 to 337.45) K by a dependable experimental method and simple solubility apparatus.

The modified Apelblat equation based on solid−liquid phase equilibrium principles is used to correlate the solubility data of prednisone acetate in ethanol, ethyl acetate, 1,2-dichloroethane, and methanol; however, in chloroform an exponential equation $x = A_0 + B_0 \exp^{(-T/C_0)}$ was used, and the values of relative deviation do not exceed 2.23 %. The solubility calculated by the Apelblat and exponential function equations shows good agreement with the experimental data.

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