Solubility of Erythromycin A Dihydrate in Different Pure Solvents and Acetone + Water Binary Mixtures between 293 K and 323 K

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The solubility of erythromycin A dihydrate in pure ethanol, propan-2-ol, methanol, acetone, chloroform, and acetone + water was measured by a synthetic method at temperature ranging from 293.20 K to 323.00 K at atmosphere pressure. The laser monitoring observation technique was used to determine the disappearance of the solid phase in a solid + liquid mixture. The results of these measurements were correlated by a semiempirical Apelblat equation.

Introduction

Erythromycin is a mixture of macrolide antibiotics produced by *Streptomyces erythreus*. The major component is erythromycin A, which is the most active antimicrobial agent in erythromycin mixtures.[1] Treatment with this antibiotic drug in human and veterinary practice is still very common because of the high activity against gram-positive and a few gram-negative strains. In addition, erythromycin is useful as an intermediate for the preparation of roxithromycin, azithromycin, and clarithromycin, and commercial erythromycin is usually available as the dihydrate.

Chemical solubility data are of great technical interest. Crystallization processes are the critical steps that determine the quality of final product, and crystallization in aqueous and organic solvents and solvent mixtures is often employed in the manufacturing of pharmaceuticals. The solubility of solid compounds in pure solvents and solvent mixtures plays a crucial role in the development and operation of crystallization processes. Therefore, knowing the solubility of the product is a necessary procedure in designing the crystallization process properly. In industrial manufacturing, erythromycin is crystallized from solution in the purification step. To determine the proper solvent and to design an optimized crystallizer, it is necessary to know its solubility in different solvent systems. The published works relating to erythromycin are mainly concerned with synthesis, degradation, and clinical study. Investigations of solubility are relatively rare. Huang and Wu studied the solubility of erythromycin in an aqueous acetone solution from 273.00 K to 293.00 K.[2] However, the solubility of erythromycin between 293.20 K and 323.00 K is needed in industrial crystallization processes. A systematic study of the solubility of this drug in different solvent systems between 293.20 K and 323.00 K has not been reported in the literature.

In the present study, the solubility of erythromycin A dihydrate in various organic solvents and acetone + water was measured in the temperature range from 293.20 K to 323.00 K at atmosphere pressure by a laser monitoring observation technique, and the modified Apelblat equation was used for the correlation of the solubility of erythromycin A dihydrate in different solvents and acetone + water binary mixtures.

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Experimental Section

Materials. Erythromycin A dihydrate (Figure 1, molecular weight 769.94) had a mass fraction purity of 99.4 %. It was obtained by purifying commercial erythromycin, which was obtained from Xi'an Rejoy Pharmaceutical Co. Ltd. of China. First, 20.0 g of erythromycin A dihydrate was dissolved in 80 mL of acetone at a temperature of 45 °C. Then, 160 mL of water was added to the mixture and stirred at 45 °C for 2 h. The wet crystals of erythromycin obtained by filtration were washed in 50 °C purified water for 30 min. The crystals were then filtered off and dried at 45 °C to obtain erythromycin A dihydrate. Acetone used for the experiments was of analytical reagent grade. Distilled deionized water of HPLC grade was used.

Method and Apparatus. The melting point of erythromycin A dihydrate was measured with a differential scanning calorimeter (Netzsch DSC-204) that was equipped with a data station (TA analysis) to analyze the result. The temperature axis and the cell constant of the DSC cell were calibrated with indium. A sample of 5 mg in a punctured aluminum pan was heated at a rate of 10 K/min under a nitrogen purge of 45 mL/min to 55 mL/min. The range of temperature was from 298 K to 573 K. A thermogravimetric analyzer (Netzsch TG 209) was employed to measure the water content. Measurements were carried out at a rate of 85 mL/min^{-1} under a dynamic atmosphere of dry nitrogen. The temperature range was ambient to 673 K at a heating rate of 10 K/min. The runs were performed using an alumina crucible containing 4.4 mg of sample, and the alumina crucible was used as a reference material. Three experiments were conducted, and nearly identical results were obtained.

Solubility was measured by the synthetic method.[3−5] The apparatus for the solubility measurement (Figure 2) is the same as that described in the literature.[6,7] The solubility of erythromycin A dihydrate 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 mixtures. The system consisted of a laser generator, a photoelectric transformer, and a light-intensity display. 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 the temperature was ± 0.05 K. Continuous stirring was achieved with a magnetic stir bar. A condenser was

10.1021/je0505265 CCC: $33.50
Published on Web 03/09/2006

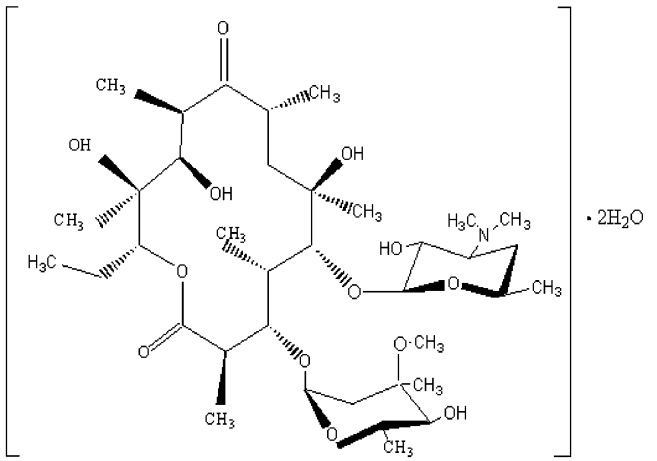

Figure 1. Structure of erythromycin A dihydrate.

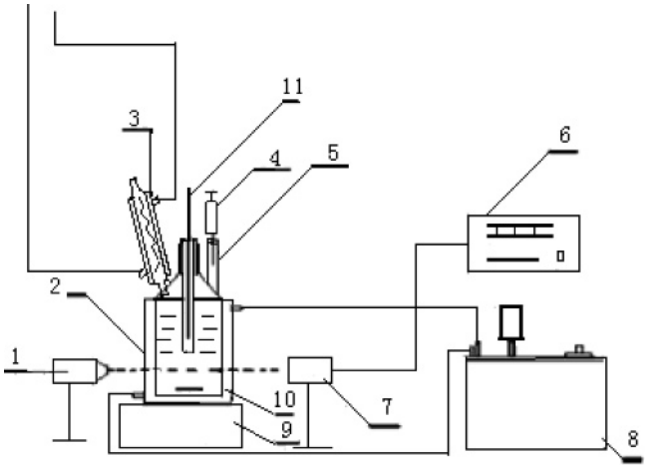

Figure 2. Schematic setup for the solubility determination: 1, laser generator; 2, dissolution kettle; 3, condenser; 4, injector; 5, inlet for solid; 6, digital display; 7, photoelectric switch; 8, superthermostatic bath; 9, magnetic stirrer; 10, stir bar; 11, thermometer.

connected to the vessel to prevent the solvent from evaporating. A mercury-in-glass thermometer was inserted into the inner chambers of the vessel for the measurement of the temperature. The temperature had an uncertainty of ± 0.05 K. The masses of the solvent and solute were weighed using an analytical balance (type TG 332A, China) with an accuracy of ± 0.0001 g.

During the measurement, predetermined excess amounts of solute and various solvents or binary solvents of known masses were transferred to the equilibrium vessel. The contents of the vessel were stirred continuously at an invariable, required temperature for 30 min. Then, additional solvent of known mass was introduced into the cell. When the last portion of solute just disappeared, the intensity of the laser beam penetrating the vessel reached the maximum, and the solvent mass consumed in the measurement was recorded. Together with the mass of solute, the solubility was obtained. The saturated mole fraction solubility of the solute (x_A) in different pure solvents and binary acetone + water solvent mixtures can be obtained as follows

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

in which m_A, m_B, and m_C represent the masses of solute, acetone, and water. M_A, M_B, and M_C are the molecular weights of solute, acetone, and water, respectively. With regard to pure solvents

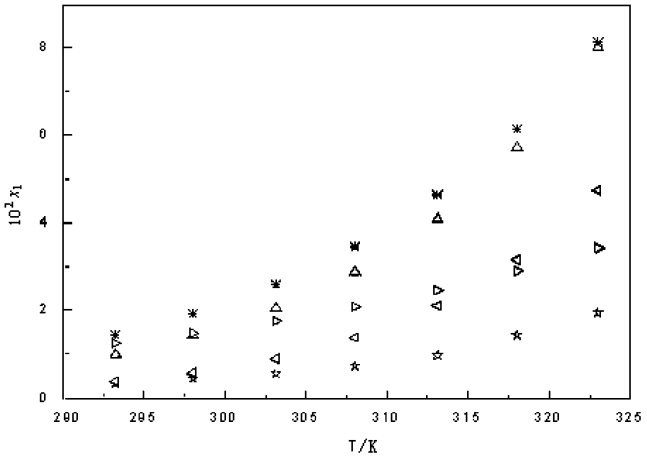

Figure 3. Mole fraction solubility of erythromycin A dihydrate (x_1) in different pure solvents: *, ethanol; △, acetone; open triangle with point facing left, chloroform; open triangle with point facing right, methanol; ☆, propan-2-ol.

Table 1. Mole Fraction Solubility of Erythromycin A Dihydrate (1) in Different Pure Solvents from 293.20 K to 323.00 K

		$100(x_1 - x_{1,calcd})$		$100(x_1 - x_{1,calcd})$		$100(x_1 - x_{1,calcd})$
T/K	10^2x_1	x_1	10^2x_1	x_1	10^2x_1	x_1
	Propan-2-ol		Methanol		Acetone	
293.20	0.3000	2.19	1.162	−0.81	0.9140	−9.39
298.00	0.4012	−0.29	1.432	0.89	1.310	−8.18
303.15	0.5560	−0.92	1.789	2.77	2.170	4.77
308.00	0.7542	−1.32	2.154	1.43	2.930	1.74
313.10	0.9953	−5.62	2.534	−0.95	4.330	3.16
318.00	1.430	0.63	3.050	−1.07	5.420	−3.37
323.00	1.940	0.86	3.730	0.26	8.040	6.23
	Chloroform		Ethanol		Water	
293.20	0.3914	5.67	1.483	4.19	0.0054	5.56
298.00	0.5399	−5.39	1.919	1.00	0.0047	−2.13
303.15	0.8749	−2.43	2.544	−1.59	0.0042	−7.14
308.00	1.341	−1.61	3.383	−1.62	0.0040	−5.00
313.10	2.159	2.81	4.600	−0.51	0.0038	0.00
318.00	3.129	−0.71	6.200	1.25	0.0035	0.00
323.00	4.734	0.00	8.100	−0.30	0.0034	8.82

system, m_A, m_B represent the masses of solute and solvents, M_A, M_B are the molecular weights of solute and solvents, and $m_C = 0$. The same solubility experiment was performed three times. The uncertainty in the solubility values is estimated to be 0.5 %.

Results and Discussion

The melting point of erythromycin A dihydrate measured by differential scanning calorimetry is 410.80 K, and the literature value is 407.00 K to 411.00 K.[8] The loss of 4.8 % of the sample weight by thermogravimetric analysis (4.7 % in theory) corresponds to two water molecule in an erythromycin A molecule.

The measured solubility of erythromycin A dihydrate in pure methanol, ethanol, acetone, propan-2-ol, and chloroform at different temperatures is listed in Table 1 and plotted in Figure 3. The temperature dependence of the erythromycin A dihydrate solubility in pure solvents is described by a modified Apelblat equation[9]

$$\ln x = A + \frac{B}{T} + C \ln T \quad (2)$$

where x is the mole fraction solubility of erythromycin A dihydrate, T is the absolute temperature, and A, B, and C are the model parameters. The calculated solubility values of erythromycin A dihydrate are also given in Table 1. The values

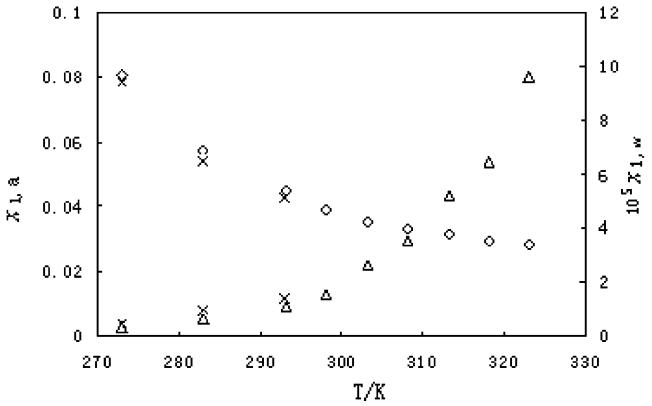

Figure 4. ◇, Solubility of erythromycin A dihydrate in water ($x_{1,w}$); △, solubility of erythromycin A dihydrate in pure acetone ($x_{1,a}$); ×, solubility in the literature.[2]

Table 2. Parameters of Equation 1 for Erythromycin A Dihydrate in Different Pure Solvents

solvents	*A*	*B*	*C*	10^2rmsd
acetone	−120.30	−76.628	21.222	0.11
ethanol	−121.41	887.84	20.900	0.05
propan-2-ol	−108.14	−157.08	18.914	0.02
methanol	−110.05	−1995.6	18.206	0.03
chloroform	−105.23	−2079.5	19.596	0.03

of parameters *A*, *B*, and *C* and the root deviation (rmsd) are listed in Table 2. The rmsd is defined as

$$\text{rmsd} = \left\{\frac{1}{N}\sum_{i=1}^{N}(x_i^{\text{calcd}} - x_i^{\text{exptl}})^2\right\}^{1/2} \quad (3)$$

where N is the number of experimental points, x_i^{calcd} represents the solubility calculated from eq 2, and x_i^{exptl} represents the experimental solubility values. The solubility in all five solvents increases with temperature. It can be seen from Table 1 that ethanol and acetone are relatively good solvents for the title compound. Because the throughput is a very important target for industrial interest, relatively high solubility of the compound is needed. By further comparison of the solubility of erythromycin A dihydrate in ethanol and acetone, it is found that acetone can be a more appropriate solvent because of its more obvious dependence on temperature. Because erythromycin A dihydrate in pure water is slightly soluble, acetone + water can be an ideal system for the dilution crystallization of erythromycin. The solubility of erythromycin A dihydrate in acetone + water was also experimentally measured.

Figure 4 is a plot of the solubility of erythromycin A dihydrate in pure acetone and distilled water between 293.20 K and 323.00 K. From Figure 4, it can be seen that the solubility of erythromycin A dihydrate decreases with increasing temperature in pure water, whereas solubility rapidly rises with increasing temperature in pure acetone. There is an inverse dependence of the solubility in pure water on temperature, which is in good agreement with the literature.[10]

On the basis of the above results, it can be expected that there should be two contrary tendencies for solubility in acetone + water, and it can be inferred that these two tendencies with respect to solubility will be equal at a certain acetone mole fraction.

The solubility data of erythromycin A dihydrate in acetone + water in the temperature range from 293.20 K to 323.00 K are listed in Table 3, confirming the above conclusions. X_3 refers to the initial mole fraction composition of water in the binary

Table 3. Solubility Data of Erythromycin A Dihydrate (1) in Acetone (2) + Water (3)

		$100(x_1 - x_{1,\text{calcd}})$		$100(x_1 - x_{1,\text{calcd}})$		$100(x_1 - x_{1,\text{calcd}})$
T/K	10^4x_1	x_1	10^4x_1	x_1	10^4x_1	x_1
	$x_3 = 0.2649$		$x_3 = 0.4465$		$x_3 = 0.5935$	
293.20	60.00	0.28	34.10	5.90	18.10	0.15
298.00	82.00	−3.35	47.10	5.87	23.89	−5.55
303.15	126.4	3.67	63.20	1.65	34.90	−1.10
308.00	170.0	0.23	82.80	−2.35	49.20	3.46
313.10	246.4	3.50	118.3	−1.57	63.80	0.14
318.00	309.7	−5.41	148.9	−5.33	82.70	−0.40
323.00	453.6	1.50	215.5	2.11	106.9	−0.11
	$x_3 = 0.6827$		$x_3 = 0.7636$		$x_3 = 0.8273$	
293.20	8.240	−5.91	3.621	−1.91	2.501	−3.89
298.00	11.77	−3.50	5.021	−1.59	3.312	−0.04
303.15	17.21	1.02	7.320	3.70	4.298	2.03
308.00	24.30	5.85	9.612	2.62	5.359	3.35
313.10	30.10	−1.56	11.90	−3.79	6.182	−2.25
318.00	38.90	−1.90	15.80	−0.10	7.386	−1.90
323.00	51.10	0.67	20.10	0.55	8.953	1.14
	$x_3 = 0.8826$		$x_3 = 0.9290$		$x_3 = 0.9668$	
293.20	1.914	2.46	1.434	3.35	0.5854	4.00
298.00	2.166	3.00	1.409	−0.65	0.5098	−2.51
303.15	2.323	−0.90	1.407	−1.91	0.4667	−2.49
308.00	2.483	−3.20	1.400	−2.23	0.4186	−4.15
313.10	2.718	−1.96	1.388	−1.70	0.3857	−1.63
318.00	2.899	−1.70	1.380	0.14	0.3623	3.12
323.00	3.205	3.25	1.376	3.26	0.3267	4.74

Table 4. Parameters of Equation 1 for Erythromycin A Dihydrate (1) in Acetone (2) + Water (3)

water mole fraction (x_3)	*A*	*B*	*C*	10^4rmsd
0.2649	−3.9815	−5024.2	4.4375	7.8
0.4465	148.597	−3448.9	−16.243	3.8
0.5935	251.89	−16 152	−34.133	0.84
0.6827	292.14	−17 979	−40.250	0.69
0.7636	311.85	−18 721	−43.426	0.23
0.8273	310.17	−17 421	−43.971	0.12
0.8826	307.47	−15 386	−44.776	0.06
0.9290	305.49	−13 840	−45.408	0.03
0.9668	303.04	−12 292	−46.065	0.01

solvents. The temperature dependence of erythromycin A dihydrate solubility in acetone + water is also described by the modified Apelblat equation. The calculated solubility is listed in Table 3. Values of parameters *A*, *B*, and *C* and the root deviations (rmsd values) are listed in Table 4. From the data listed in Table 3, it can be concluded that when $x_3 < 0.9290$, the solubility values of erythromycin A dihydrate increase with increasing temperature in acetone + water mixtures in the temperature range from 293.20 K to 323.00 K. When $x_3 > 0.9290$, the solubility values of erythromycin A dihydrate decrease slightly with increasing temperature in the temperature range from 293.20 K to 323.00 K. At a fixed temperature, the solubility data of erythromycin A dihydrate in acetone + water decreases with increasing water content.

Conclusions

From Tables 1 to 4 and Figure 3, we can draw the following conclusions: (1) For all pure solvent systems, solubility is a function of temperature, and solubility increases with increasing temperature. The best solubility of erythromycin A dihydrate is shown in acetone. (2) For acetone + water binary mixtures, $x_3 = 0.9290$ is the mole fraction where the solubility of erythromycin A dihydrate in acetone + water is essentially independent of temperature. When $x_3 < 0.9290$, the solubility of erythromycin A dihydrate increases with increasing temperature in the temperature range from 293.20 K to 323.00 K. When $x_3 > 0.9290$, the solubility values of erythromycin A dihydrate

decrease slightly with increasing temperature in the temperature range from 293.20 K to 323.00 K.

The calculated solubility shows good agreement with the experimental values. The experimental solubility and correlation equation presented can be used as essential data and models in the process of the resolution of erythromycin A dihydrate.

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Received for review December 16, 2005. Accepted February 14, 2006.

JE0505265