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Experimental Determination of Solubilities of Betulin in Acetone + Water and Ethanol + Water Mixed Solvents at $T = (278.2, 288.2, 298.2, 308.2, \text{and } 318.2)$ K

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The solubilities of betulin in acetone + water and ethanol + water were measured at $T = (278.2, 288.2, 298.2, 308.2, \text{and } 318.2)$ K. The solubilities of betulin in the two mixed solvent systems increase significantly with temperature and composition of acetone or ethanol. The Apelblat equation was used to correlate the experimental data.

Introduction

Crystallization is the preferred method of purification in the pharmaceutical industry for both the final drug substance and the isolated intermediates in the synthesis. Solubility is no doubt one of the most important physicochemical properties to design the process of crystallization.[1,2] Solid−liquid equilibrium data of organic substances in water and organic solvent are becoming increasingly important.

For extensive biological investigation, crude betulin has to be purified by crystallization. There are many cases where mixtures of multiple solvents lead to better separations than pure solvents, and the use of binary solvent mixtures is a highly versatile and very powerful means of altering (increasing or decreasing) the solubility of a solute. Betulin has a poor solubility in water, but it is easily dissolved in acetone or ethanol.[3] For this reason, crude betulin can be purified easily using antisolvent crystallization. But the solubility data of betulin in acetone + water and ethanol + water mixed solvents have not been found in the literature.

In continuation of our studies on the solubilities of betulin in pure solvents at different temperatures,[4] in this paper, betulin solubilities were determined in acetone + water and ethanol + water at $T = (278.2, 288.2, 298.2, 308.2, \text{and } 318.2)$ K. The Apelblat equation was used to correlate the experimental data.

Experimental Section

A white crystalline powder of betulin with a melting point of (256 ± 0.5) °C was used, and its purity was higher than 0.995 mass fractions (HPLC). The reference standard of betulin, whose purity was > 0.98 mass fractions, was purchased from Sigma-Aldrich Chemical Corporation (USA). HPLC grade acetonitrile (TEDIA COMPANY INC) was used for the HPLC analysis. Deionized water and analytical grade acetone and ethanol were obtained from Hangzhou Chemical Reagent Co.

The solubilities of betulin in acetone + water and ethanol + water at different temperatures were measured using the HPLC analysis method.[4−6] More details of the experimental setup have been described previously.[4] The temperature was controlled to be constant through a thermostat water bath with a temperature stability of ± 0.01 K and a temperature uncertainty of ± 0.25 K. The masses of saturated solutions were weighted using an analytical balance (Sartorius type 1712 analytical balance) with an uncertainty of ± 0.01 mg. Binary solvent mixtures were prepared by mass. The uncertainty of mole fraction of solvent mixtures on a solute-free basis was 0.0001. The relative uncertainty of the experimental solubility is within 2.6 %.

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Table 1. Solubilities of Betulin (m_3, x_3) in the Mixed Solvents Acetone (1) + Water (2) at $T = (278.2, 288.2, 298.2, 308.2, \text{and } 318.2)$ K[a]

T/K	$10^4 m_3$/mol·kg^{-1}	$10^5 x_3$	T/K	$10^4 m_3$/mol·kg^{-1}	$10^5 x_3$
	$x_1^b = 0.3111$			$x_1 = 0.4261$	
278.2	3.50 (0.04)	1.07 (0.01)	278.2	14.36 (0.11)	5.04 (0.04)
288.2	5.18 (0.08)	1.58 (0.03)	288.2	17.42 (0.13)	6.11 (0.04)
298.2	7.35 (0.08)	2.24 (0.03)	298.2	26.04 (0.16)	9.14 (0.06)
308.2	11.53 (0.04)	3.51 (0.01)	308.2	33.01 (0.09)	11.58 (0.03)
318.2	20.20 (0.09)	6.16 (0.03)	318.2	41.93 (0.13)	14.71 (0.04)
	$x_1 = 0.5107$			$x_1 = 0.5958$	
278.2	36.73 (0.12)	14.13 (0.05)	278.2	66.88 (0.19)	28.01 (0.08)
288.2	40.90 (0.25)	15.74 (0.10)	288.2	71.08 (0.17)	29.77 (0.07)
298.2	46.05 (0.23)	17.72 (0.09)	298.2	75.32 (0.21)	31.54 (0.09)
308.2	52.96 (0.23)	20.37 (0.09)	308.2	81.81 (0.23)	34.26 (0.09)
318.2	63.57 (0.11)	24.45 (0.04)	318.2	86.92 (0.28)	36.39 (0.12)
	$x_1 = 0.7207$			$x_1 = 0.8479$	
278.2	90.39 (0.30)	42.37 (0.13)	278.2	106.1 (0.38)	55.15 (0.19)
288.2	97.94 (0.24)	45.90 (0.11)	288.2	124.4 (0.41)	64.64 (0.21)
298.2	113.0 (0.28)	52.96 (0.13)	298.2	151.1 (0.38)	78.49 (0.20)
308.2	128.0 (0.31)	59.98 (0.15)	308.2	176.9 (0.46)	91.90 (0.24)
318.2	141.0 (0.39)	66.09 (0.18)	318.2	193.3 (0.45)	100.4 (0.23)
	$x_1 = 1.0000$				
278.2	118.8 (0.29)	68.94 (0.17)			
288.2	173.5 (0.28)	100.7 (0.16)			
298.2	258.7 (0.39)	150.0 (0.28)			
308.2	349.6 (0.48)	202.6 (0.28)			
318.2	420.2 (0.63)	243.4 (0.36)			

[a] m_3 is the molality of betulin; x_3 is the solubility of betulin in mole fraction; and values in parentheses are the mean standard deviation. [b] x_1 is the mole fraction of acetone in mixed solvents on a solute-free basis.

Results and Discussion

The solubility data of betulin in acetone + water and ethanol + water at different temperatures expressed in molalities m_3 (mol·kg^{-1}) and mole fraction solubility x_3 together with the mean standard deviation σ_n are presented in Tables 1 and 2. Molalities m_3 and mole fraction solubility x_3 in Tables 1 and 2 are the average values taken from two test tubes and two samples for each tube at the same composition of mixed solvents.

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Table 2. Solubilities of Betulin (m_3, x_3) in the Mixed Solvents Ethanol (1) + Water (2) at T = (278.2, 288.2, 298.2, 308.2, and 318.2) K[a]

T	$10^4 m_3$		T	$10^4 m_3$	
K	mol·kg^{-1}	$10^5 x_3$	K	mol·kg^{-1}	$10^5 x_3$
	x_1[b] = 0.3531			x_1 = 0.4907	
278.2	8.05 (0.04)	2.25 (0.01)	278.2	34.97 (0.11)	11.11 (0.04)
288.2	9.85 (0.08)	2.75 (0.03)	288.2	38.66 (0.13)	12.29 (0.04)
298.2	13.31 (0.08)	3.72 (0.02)	298.2	44.67 (0.16)	14.19 (0.06)
308.2	16.87 (0.04)	4.71 (0.01)	308.2	54.17 (0.09)	17.21 (0.03)
318.2	24.16 (0.29)	6.75 (0.08)	318.2	64.09 (0.13)	20.36 (0.04)
	x_1 = 0.5800			x_1 = 0.6499	
278.2	51.77 (0.12)	17.75 (0.04)	278.2	64.29 (0.39)	23.30 (0.14)
288.2	60.46 (0.26)	20.72 (0.09)	288.2	76.03 (0.17)	27.55 (0.06)
298.2	80.27 (0.23)	27.51 (0.08)	298.2	107.9 (0.21)	39.09 (0.08)
308.2	92.83 (0.28)	31.82 (0.10)	308.2	134.0 (0.23)	48.54 (0.08)
318.2	114.1 (0.26)	39.10 (0.09)	318.2	155.9 (0.28)	56.47 (0.10)
	x_1 = 0.7578			x_1 = 0.8685	
278.2	95.93 (0.30)	37.66 (0.11)	278.2	149.8 (0.38)	63.43 (0.17)
288.2	116.0 (0.34)	45.54 (0.13)	288.2	168.9 (0.41)	71.52 (0.18)
298.2	156.0 (0.28)	61.25 (0.11)	298.2	198.6 (0.38)	84.08 (0.16)
308.2	187.8 (0.36)	73.70 (0.14)	308.2	226.6 (0.46)	95.92 (0.20)
318.2	212.2 (0.39)	83.26 (0.16)	318.2	246.5 (0.45)	104.3 (0.19)
	x_1 = 1.0000				
278.2	182.9 (0.29)	84.17 (0.13)			
288.2	208.5 (0.28)	95.97 (0.13)			
298.2	232.1 (0.28)	106.8 (0.13)			
308.2	267.0 (0.38)	124.3 (0.18)			
318.2	293.9 (0.41)	135.2 (0.19)			

[a] m_3 is the molality of betulin; x_3 is the solubility of betulin in mole fraction; and values in parentheses are the mean standard deviation. [b] x_1 is the mole fraction of ethanol in mixed solvents on a solute-free basis.

Table 3. Parameters of the Apelblat Equation for Betulin in Different Solvent Compositions of the Acetone (1) + Water (2) System

x_1[a]	a	b/K	c	10^5rmsd
0.3111	−534.22	20010	80.105	0.06
0.4261	−59.688	139.71	8.753	0.31
0.5107	−201.87	7562.2	29.464	0.11
0.5958	−53.738	1528.4	7.118	0.17
0.7207	−67.094	1773.0	9.407	0.77
0.8479	81.118	−5088.7	−12.497	1.20
1.0000	280.78	−15189	−41.482	3.58

[a] x_1 is the mole fraction of acetone in mixed solvents on a solute-free basis.

According to the solid−liquid phase equilibrium theory, the relationship between solubility and temperature is described by the Apelblat equation.[7−9]

$$\ln x_3 = a + \frac{b}{T/\mathrm{K}} + c \ln T/\mathrm{K} \qquad (1)$$

where x_3 is the mole fraction solubility of betulin; T is the absolute temperature; and a, b, and c are empirical parameters. The experimental data of mole fraction solubility in Tables 1 and 2 were correlated with eq 1. The values of the three parameters a, b, and c together with the root-mean-square deviations (rmsd's) are also listed in Tables 3 and 4. The rmsd's are defined as

$$\mathrm{rmsd} = \left[\frac{1}{n}\sum_{i=1}^{n}(x_{3,i}^{\mathrm{calcd}} - x_{3,i}^{\mathrm{exptl}})^2\right]^{1/2} \qquad (2)$$

where $x_{3,i}^{\mathrm{calcd}}$ is mole fraction solubility calculated by eq 1 using the parameters in Tables 3 and 4; $x_{3,i}^{\mathrm{exptl}}$ is the experimental value of mole fraction solubility of betulin; and n is the number of experimental points at the same composition of mixed solvents (n = 5).

Table 4. Parameters of the Apelblat Equation for Betulin in Different Solvent Compositions of the Ethanol (1) + Water (2) System

x_1[a]	a	b/K	c	10^5rmsd
0.3531	−323.47	11852	48.001	0.07
0.4907	−224.61	8416.7	32.913	0.15
0.5800	−55.027	564.45	7.880	0.67
0.6499	34.669	−3651.3	−5.319	1.31
0.7578	117.63	−7113.4	−17.761	1.48
0.8685	27.458	−2505.8	−4.588	1.23
1.0000	−8.448	−834.96	0.776	1.31

[a] x_1 is the mole fraction of ethanol in mixed solvents on a solute-free basis.

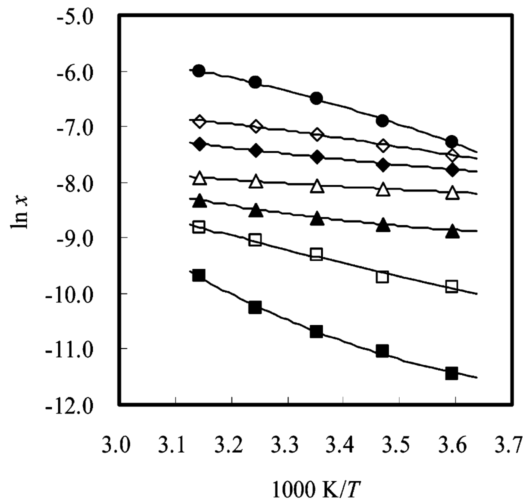

Figure 1. Solubilities of betulin in the binary system of an acetone + water mixture at T = (278.2, 288.2, 298.2, 308.2, and 318.2) K: ■, x_1 = 0.3111; □, x_1 = 0.4261; ▲, x_1 = 0.5107; Δ, x_1 = 0.5958; ◆, x_1 = 0.7207; ◇, x_1= 0.8479; ●, x_1= 1.000; line, calculated by eq 1 (parameters taken from Table 3).

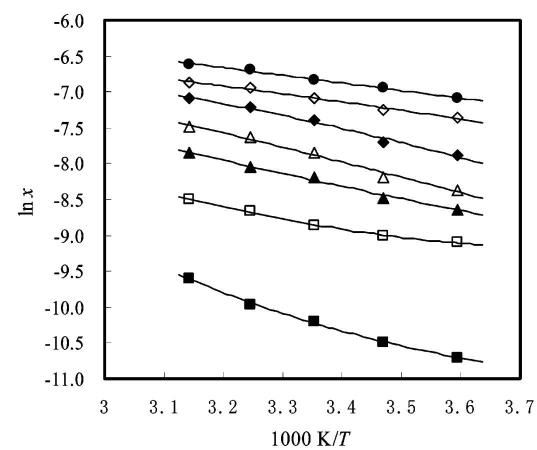

Figure 2. Solubilities of betulin in the binary system of an ethanol + water mixture at T = (278.2, 288.2, 298.2, 308.2, and 318.2) K: ■, x_1 = 0.3531; □, x_1 = 0.4907; ▲, x_1 = 0.5800; Δ, x_1 = 0.6499; ◆, x_1 = 0.7578; ◇, x_1= 0.8685; ●, x_1= 1.000; line, calculated by eq 1 (parameters taken from Table 4).

The data for the solubilities of betulin in acetone + water and ethanol + water at different temperatures were also plotted as Figures 1 and 2, respectively. It can be seen that the solubilities of betulin in acetone + water and ethanol + water increase with increasing temperature and the content of acetone (ethanol).

Conclusions

The solubilities of betulin in acetone + water and ethanol + water at different temperatures have been studied. The Apelblat equation has been used to correlate the experimental data. From Tables 1 and 2 and Figures 1 and 2, we can draw the following conclusions: (1) The solubilities of betulin in acetone + water and ethanol + water increase significantly with increasing temperature. (2) The solubilities of betulin increase with the content of acetone (ethanol) in the mixed solvents. (3) The calculated solubilities of betulin are in good agreement with the experimental values except the molar fraction of acetone, ≥ 0.8.

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