Short Articles

Solubility of Indinavir Sulfate in Different Solvents from (278.35 to 314.15) K

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The solubility of indinavir sulfate in ethanol, 1-propanol, 2-propanol, 1-butanol, and 2-methyl-1-propanol was measured over the temperature range of (278.35 to 314.15) K under atmospheric pressure. The experimental data were correlated by the modified Apelblat model. The results show that the solubility of indinavir sulfate in the selected solvents increased with increasing temperature.

Introduction

Indinavir sulfate (CAS registry no. 157810-81-6) is the popular name of D-erythro-pentonamide-2,3,5-trideoxy-*N*-(2,3-dihydro-2-hydroxy-1*H*-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-[1(1*S*,2*R*),5(*S*)]-sulfate(1:1) salt (Figure 1). It is a potent inhibitor of HIV protease widely used in the treatment of AIDS and prescribed in combination with other protease inhibitors, nucleoside analogues, or reverse transcriptase inhibitors.[1−3] Indinavir sulfate is usually prepared by reaction crystallization from an organic solvent. It is well-known that the solvent can influence the separation efficiency through its effect on crystallization kinetics, solution thermodynamics, and crystal interface structure.[4] Therefore, a poor initial choice of solvent can thermodynamically and kinetically limit the effectiveness of the separation. To select the proper solvent and to design an optimized crystallization process, it is necessary to know the solubility of indinavir sulfate in different solvents. However, no experimental solubility data of indinavir sulfate in any solvent had been reported. In this study, the solubility of indinavir sulfate in ethanol, 1-propanol, 2-propanol, 1-butanol, and 2-methyl-1-propanol was measured by ultraviolet visible spectrophotometry over the temperature range of (278.35 to 314.15) K under atmospheric pressure. The results were fitted with the modified Apelblat equation.

Experimental Section

Materials. A white crystalline powder of indinavir sulfate was prepared by crystallization from ethanol in the laboratory. Its mass fraction, determined by HPLC (Agilent 1100, purchased from Agilent Technologies) according to USP30, is greater than 0.99. It was dried under vacuum at 55 °C for 24 h and stored in a desiccator. No polymorphic transition was found in the treatment of the material. Ethanol, 1-propanol, 2-propanol, 1-butanol, and 2-methyl-1-propanol (purchased from the Tianjin Chemical Reagent Co., China) used for the experiments were of analytical reagent grade with a purity of greater than 0.995 in mass fraction.

Apparatus and Procedures. The setup for the solubility measurement)is similar to that described in the literature.[5]

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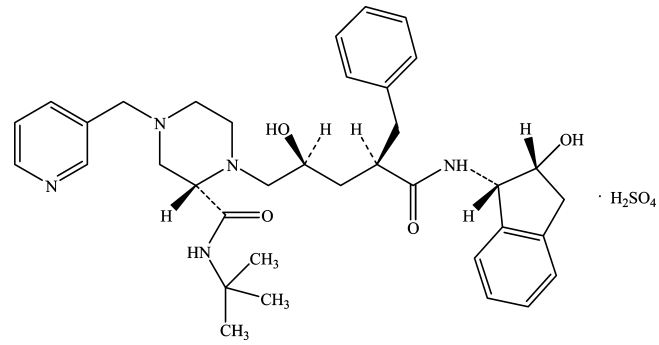

Figure 1. Chemical structure of indinavir sulfate.

Table 1. Verification of the Reliability of the Experimental Method

known concentration/ mg·mL^{-1}	measured concentration by UV/ mg·mL^{-1}	(known concentration − measured concentration)/ known concentration
0.034	0.034	0.000
0.045	0.044	0.022
0.056	0.055	0.017
0.078	0.077	0.013
0.112	0.113	−0.009
0.134	0.137	−0.022

Excess solute and solvent were placed in a cylindrical double-jacketed glass vessel with water circulated from a water bath. The temperature of the circulating water was controlled at the desired value by a thermostat (Wanda/sida instrument HC2010, China) within (± 0.05 K). A mercury-in-glass thermometer with an uncertainty of 0.05 K was inserted into the inner chamber of the vessel for the measurement of temperature. A magnetic stir bar was used for turbulent mixing of the suspension. We verified attainment of equilibrium by repetitively measuring the concentration of the solution at different stirring times until the value was almost constant. It was found that at least 10 h was needed for the attainment of solid−liquid equilibrium. The stirrer was then turned off to let the suspension settle for 2 h.[6] The upper portion was transferred, filtered with a 0.22 μm organic membrane filter, and then diluted appropriately for spectrophometric analysis on a U-3010 UV spectrophotometer (purchased from Hitachi High-Technology Corporation, Japan). All of the measurements are repeated three times,

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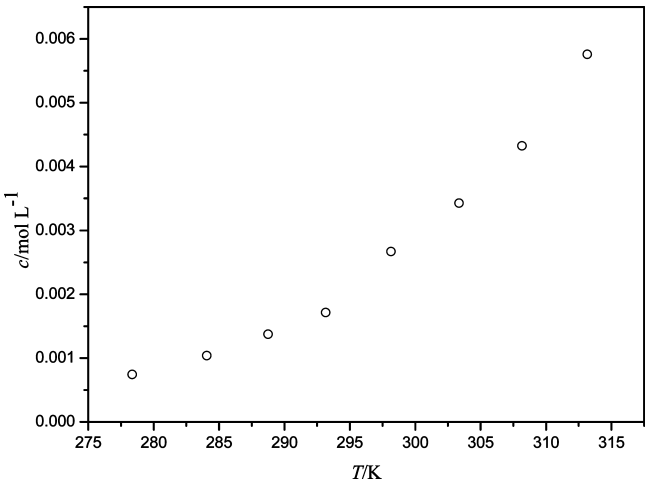

Figure 2. Solubility of indinavir sulfate in ethanol.

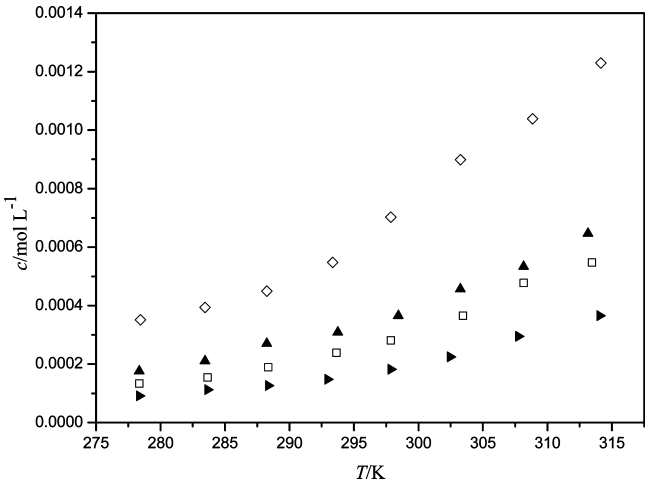

Figure 3. Solubility of indinavir sulfate in: ◇, 1-propanol; ▲, 2-propanol; □, 1-butanol; solid tilted triangle, 2-methyl-1-propanol.

and the average of the three measurements is considered to be the solubility.

Sample Analysis. To determine the concentration of indinavir sulfate in the solution, the absorbance of standard solution and the sample was measured at 259 nm, which was the maximum absorption wavelength predetermined by the authors. We obtained the standard curve by using standard solutions, and the calibration equation was set as $Y = 6.0949X - 0.0109$ and $R^2 = 0.9992$ in the appropriate concentration range from (0.022 to 0.157) mg·mL^{-1} at room temperature, where Y is UV absorbance and X is concentration of the standard solution. On the basis of the standard curve and diluted multiple, the real concentration of samples at different temperatures can be determined. To check the reliability of the experimental method, known masses of indinavir sulfate were completely dissolved in ethanol, and the concentrations of solution were measured by the UV spectrophotometer. The relative error was less than ± 2.2 % (shown in Table .

Results and Discussion

The solubilities of indinavir sulfate in ethanol, 1-propanol, 2-propanol, 1-butanol and 2-methyl-1-propanol from (278.35 to 314.15) K are listed in Table 2 and visually shown by Figure 2 and 3. Modeling of experimental solubility data is beneficial to represent mathematical aspects of solubility, and the unmeasured solubility could be predicted in terms of these models. The solubility of indinavir sulfate as a function of temperature is fitted by the modified Apelblat equation.[7,8]

$$\ln(c/\text{mol·L}^{-1}) = A + \frac{B}{T/\text{K}} + C\ln(T/\text{K}) \qquad (1)$$

where c is the solubility of indinavir sulfate; T is the absolute temperature; and A, B, C are model parameters. The calculated solubility values of indinavir sulfate from eq 1 and the relative error between experimental solubilities and calculated values are also given in Table 2. The values of the model parameters A, B, and C together with the root-mean-square deviation (rmsd) defined by eq 2 are listed in Table 3.

Table 2. Solubility of Indinavir Sulfate in Different Solvents

T/K	$10^3 c^{\text{exptl}}$ mol·L^{-1}	$10^3 c^{\text{calcd}}$ mol·L^{-1}	$(c^{\text{exptl}} - c^{\text{calcd}})/c^{\text{exptl}}$
	Ethanol		
278.35	0.745	0.741	0.005
284.05	1.040	1.064	−0.023
288.75	1.377	1.423	−0.033
293.15	1.714	1.855	−0.082
298.15	2.670	2.490	0.067
303.35	3.428	3.355	0.021
308.15	4.327	4.390	−0.015
313.15	5.760	5.770	−0.002
	1-Propanol		
278.45	0.351	0.325	0.074
283.45	0.393	0.398	−0.013
288.25	0.450	0.481	−0.069
293.35	0.548	0.585	−0.068
297.85	0.702	0.693	0.013
303.25	0.900	0.846	0.06
308.85	1.034	1.036	−0.002
314.15	1.230	1.248	−0.015
	2-Propanol		
278.35	0.176	0.174	0.011
283.45	0.211	0.213	−0.009
288.25	0.270	0.256	0.052
293.75	0.309	0.316	−0.023
298.45	0.365	0.377	−0.033
303.25	0.457	0.450	0.015
308.15	0.534	0.538	−0.007
313.15	0.646	0.643	0.005
	1-Butanol		
278.35	0.133	0.123	0.075
283.65	0.155	0.156	−0.006
288.35	0.190	0.193	−0.016
293.65	0.239	0.243	−0.017
297.85	0.281	0.291	−0.035
303.45	0.365	0.370	−0.014
308.15	0.478	0.450	0.059
313.45	0.548	0.560	−0.022
	2-Methyl-1-propanol		
278.35	0.091	0.0837	0.080
283.62	0.112	0.105	0.063
288.35	0.126	0.128	−0.016
292.95	0.147	0.155	−0.054
297.85	0.183	0.190	−0.038
302.45	0.225	0.230	−0.022
307.75	0.295	0.285	0.034
314.05	0.365	0.366	−0.003

Table 3. Parameters of Equation 1 for Indinavir Sulfate in Different Solvents

	solvents				
	ethanol	1-propanol	2-propanol	1-butanol	2-methyl-1-propanol
A	−46.760	−48.423	−74.842	−88.136	−107.528
B	−2580.981	−988.526	165.968	323.045	1292.566
C	8.674	7.806	11.652	13.852	16.610
10^5rmsd	8.951	2.806	0.751	1.212	0.674

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

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

From Figures 2 and 3 and Tables 2 and 3, the following conclusions can be drawn: (1) In all solvents under consideration, the solubility of indinavir sulfate is a function of temperature, and solubility increases with an increase in temperature. (2) The solubility of indinavir sulfate in the solvents increased in the order: 2-methyl-1-propanol < 1-butanol < 2-propanol < 1-propanol < ethanol. (3) The calculated solubility data show good agreement with the experimental values, which indicated that the modified Apelbat equation could be employed to fit the measured solubility of indinavir sulfate in the selected five solvents over the temperature range studied. Therefore, the experimental solubility and correlation equation presented can be used as essential data for the design and operation of the crystallization process of indinavir sulfate.

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