Solubilities of Adefovir Dipivoxil in Different Binary Solvents at 298.15 K

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The solubility data of adefovir dipivoxil in five different binary mixed solvents formed by isopropyl ether with ethanol, 2-propanol, dichloromethane, ethyl acetate, and acetone at 298.15 K were measured with the mole fraction of isopropyl ether ranging from 0.000 to 1.000. A laser monitoring observation technique was used to determine the dissolution of the solid phase in a solid + liquid mixture. The solubility data were correlated with a function of the binary solvent mole fractions by the combined nearly ideal binary solvent (NIBS)/Redlich–Kister equation.

Introduction

Adefovir dipivoxil is the popular name of 9-[2-bis(pivaloyloxymethyl)phosphonmethoxyethyl]adenine (CAS Registry No. 142340-99-6), whose chemical structure is shown in Figure 1. It is an orally bioavailable prodrug of 9-[2-(phosphonylmethoxy)ethyl]adenine, which acts as a chain terminator nucleotide analogue and is effective against the human immunodeficiency virus, herpesviruses, Epstein–Barr virus, retroviruses, cytomegalovirus, and other DNA viruses.[1–3] As a white or almost white powdered crystal product, adefovir dipivoxil is usually purified by crystallization in its manufacturing process. It is well-known that solvent has a significant effect on crystal size, morphology, and purity, and a poor initial choice of solvent may thermodynamically limit the effectiveness of the separation.[4] To select the proper solvents and to design an optimized crystallization processes, it is necessary to know the solubility data of adefovir dipivoxil in different solvents. However, research works concerned with adefovir dipivoxil published in the literature were mainly focused on the clinical pharmacology, clinical use, and chemical synthesis, while rarely work had been carried out on determination of the solubility data.

In this work, the solubilities of adefovir dipivoxil in commonly used solvents formed by isopropyl ether with ethanol, 2-propanol, dichloromethane, ethyl acetate, and acetone at 298.15 K with the mole fraction of isopropyl ether ranging from 0.000 to 1.000 at atmospheric pressure were measured using a synthetic method.[5–9] A laser monitoring observation technique was used to determine the dissolution of the solute at constant temperature.

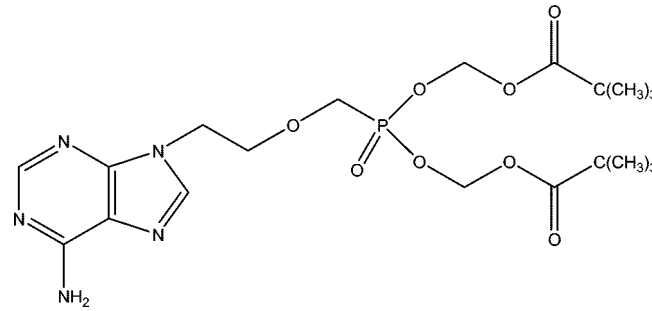

Figure 1. Chemical structure of adefovir dipivoxil.

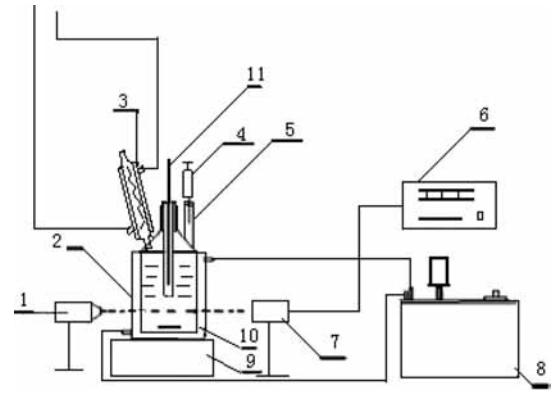

Figure 2. Schematic setup for the solubility determination: 1, laser generator; 2, equilibrium vessel; 3, condenser; 4, burette; 5, inlet for solid; 6, digital display; 7, photoelectric switch; 8, thermostat; 9, magnetic stirrer; 10, stir bar; 11, thermometer.

Experimental Section

Materials. Adefovir dipivoxil with a purity of higher than 99.0 % in mass fraction obtained from Taizhou Kangduoli Pharmaceutical Co., Ltd., China, was used as received without further purification. Isopropyl ether, ethanol, 2-propanol, dichloromethane, ethyl acetate, and acetone (purchased from Tianjin Chemical Regent Co., China) used for experiments were of analytical reagent grade.

Apparatus and Procedures. Determination of solubilities of adefovir dipivoxil in different binary solvents was carried out by a synthetic method. The setup for the solubility measurement is shown in Figure 2, which is the same as that described in the literature.[6] The experiment was performed in a cylindrical double-jacketed glass vessel having a working volume of 100 mL. A magnetic stir bar was used for turbulent mixing of suspension. The temperature with an uncertainty of ± 0.05 K was controlled at (298.15 ± 0.1) K by the circulating water through the outer jacket from a thermostat (Wanda/sida instrument HC2010, China). A condenser was connected with the vessel to prevent the solvents from evaporating. The dissolution of the solute was examined by the intensity of the laser beam that penetrated through the suspension. The laser monitoring system (purchased from Physical Department of Peking university) consisted of a laser generator (type JD-3, China), a

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Table 1. Experimental Solubilities (x_A) of Adefovir Dipivoxil in Binary Isopropyl Ether (1) + the Other Solvent (2) Mixtures at 298.15 K

x_1^0	$10^4 x_A^{exptl}$	$10^4 x_A^{calcd}$	$(x_A^{exptl} - x_A^{calcd})/x_A^{exptl}$
isopropyl ether (1) + ethanol (2)			
0.0000	340.5485	344.1000	−0.0104
0.0520	335.7054	326.2000	0.0283
0.1026	312.3090	315.9000	−0.0115
0.1631	300.1849	305.6000	−0.0180
0.2295	289.2413	290.0000	−0.0026
0.3087	265.0802	258.6000	0.0244
0.3986	204.8505	204.9000	−0.0002
0.5068	123.3157	129.9000	−0.0534
0.6359	63.7139	58.1000	0.0881
0.7944	15.4275	16.0000	0.0003
1.0000	0.3708	2.8000	−6.5512
isopropyl ether (1) + 2-propanol (2)			
0.0000	252.0234	250.7000	0.0053
0.0652	241.8899	245.2000	−0.0137
0.1346	235.3204	233.6000	0.0073
0.2113	217.0099	215.4000	0.0074
0.2882	190.0841	192.7000	−0.0138
0.3695	168.6535	165.1000	0.0210
0.4665	125.5079	129.4000	−0.0310
0.5756	90.2513	89.1000	0.0128
0.6982	50.3856	49.3000	0.0215
0.8360	19.0104	18.8000	0.0111
1.0000	0.37085	3.3000	−7.8985
isopropyl ether (1) + dichloromethane (2)			
0.0000	1751.3285	1751.5000	−0.0001
0.1002	1598.0221	1597.3000	0.0005
0.1987	1180.5637	1182.2000	−0.0014
0.2993	742.1754	740.5000	0.0023
0.3888	400.4103	399.9000	0.0013
0.4793	147.9008	151.2000	−0.0223
0.5773	30.6514	26.4000	0.1387
0.6768	11.1788	1.4000	0.8748
0.7803	4.7263	0.0097	0.9979
0.8675	1.3563	0.0000182	0.9999
1.0000	0.37085	0.00000000000822	1.0000
isopropyl ether (1) + ethyl acetate (2)			
0.0000	262.6739	262.9000	−0.0009
0.0896	195.5761	194.7000	0.0045
0.1800	128.5934	129.6000	−0.0078
0.2736	80.7735	81.7000	−0.0115
0.3652	53.7763	51.8000	0.0368
0.4622	32.8754	31.8000	0.0327
0.5627	15.4473	18.4000	−0.1911
0.6658	9.3688	9.0000	0.0394
0.7714	4.4789	3.2000	0.2855
0.8792	1.7153	0.6000	0.6502
1.0000	0.3708	0.0590	0.8409
isopropyl ether (1) + acetone (2)			
0.0000	661.5383	659.8000	0.0026
0.0690	489.4963	497.7000	−0.0168
0.1268	399.9986	389.8000	0.0255
0.1998	276.3636	279.6000	−0.0117
0.2742	193.5159	192.0000	0.0078
0.3603	113.2533	117.7000	−0.0393
0.4564	63.5918	63.8000	−0.0033
0.5634	34.5925	30.4000	0.1212
0.6827	14.9123	13.000	0.1282
0.8180	5.0391	5.6000	−0.1113
1.0000	0.3708	3.1000	−7.3603

photoelectric switch (type model 271, China), and a light intensity display.

Binary solvents were prepared by mixing a certain quantity of two solvents measured by an analytical balance (Metler Toledo AB204-N, Switzerland) with an uncertainty of ± 0.1 mg. At the beginning of the measurement, a certain amount of solid adefovir dipivoxil was added to a predetermined excess amount of binary solvents preloaded in the jacketed vessel. The suspension in the vessel was stirred continuously at 298.15 K for 1 h. The solute was dissolved completely, and an unsaturated solution was obtained. Here the light intensity penetrating through the solution would reach its maximum value. Then, additional solute of known mass was batch-type added into the vessel with intervals of 30 min until the last increment remained partially undissolved within 30 min. The dissolution of the solute was monitored by the light intensity penetrated through the suspension. When the solution was unsaturated, the suspension became clear after each batch addition of solute, and the intensity of the laser beam penetrating through the solution attained its maximum value within 30 min. When the laser intensity did not exceed 90 % of its maximum value, the solution was believed to be approaching its saturated state. The amount of solute leading to the laser intensity decrease of 10 % from its maximum value is less than 1 mg, and the uncertainty of the solubility data is estimated to be less than ± 1.0 %. The same solubility experiment was performed two more times, and the mean values were used to calculate the mole fraction solubility. Here, the solute mass having been added in the measurement was recorded. Together, with the mass of the solvents, the solubility of the solute in mole fraction (x_A) in different binary solvents could be obtained as follows

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

where m_A, m_1, and m_2 represent the mass of the solute, isopropyl ether, and another solvent, respectively, and M_A, M_1, and M_2 are the molecular weight of the solute, isopropyl ether, and another solvent, respectively.

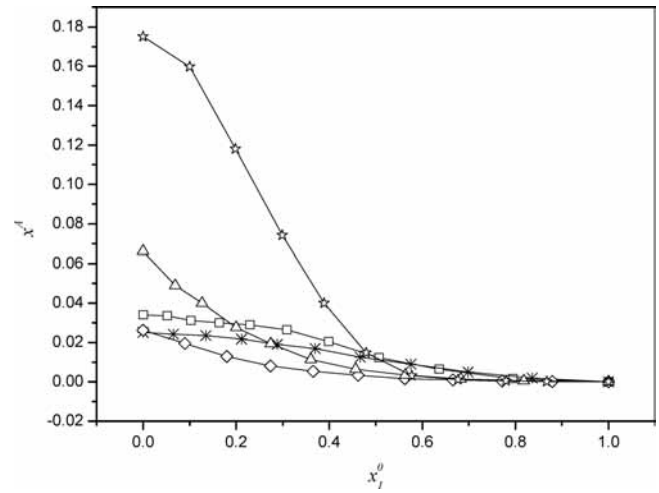

Figure 3. Mole fraction solubility of adefovir dipivoxil in five different binary mixed solvents at 298.15 K: ☆, isopropyl ether + dichloromethane; △, isopropyl ether + acetone; □, isopropyl ether + ethanol; ∗, isopropylether + 2-propanol; ◇, isopropyl ether + ethyl acetate.

Results and Discussion

The solubilities of adefovir dipivoxil in all five binary mixed solvents with the mole fraction of isopropyl ether ranging from 0.000 to 1.000 at 298.15 K are listed in Table 1. 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. Acree and his

Table 2. Curve-Fitting Parameters of Adefovir Dipivoxil in Binary Isopropyl Ether (1) + the Other Solvent (2) Mixtures at 298.15 K

	solvents				
	isopropyl ether (1) + ethanol (2)	isopropyl ether (1) + 2-propanol (2)	isopropyl ether (1) + dichloromethane (2)	isopropyl ether (1) + ethyl acetate (2)	isopropyl ether (1) + acetone (2)
B_0	−3.3695	−3.6860	−1.7421	−3.6387	−2.7184
B_1	−1.3295	−0.1596	−0.6890	−2.4447	−4.0814
B_2	6.9398	−2.9227	−19.8724	−12.2367	0.5956
B_3	−21.7321	1.9964	43.8461	25.7802	−9.9846
B_4	11.3051	−3.2361	−57.6551	−19.9975	8.1117
10^3 rmsd	1.6397	0.8000	0.3755	0.4427	1.5360

co-workers[10–12] proposed the following combined nearly ideal binary solvent (NIBS)/Redlich–Kister model

$$\ln x_A = x_2^0 \ln(x_A)_2 + x_1^0 \ln(x_A)_1 + x_2^0 x_1^0 \sum_{i=0}^{N} S_i (x_2^0 - x_1^0)^i \quad (2)$$

as a possible mathematical representation for describing how isothermal solubility of a crystalline solute dissolved in a binary solvent mixture varies with the binary solvent composition. In eq 2, x_1^0 and x_2^0 refer to the initial mole fraction of the binary solvent as if solute (A) was not present. $(x_A)_i$ stands for the saturate mole fraction solubility of the solute in pure solvent i. S_i is the model parameter. N can be equal to 0, 1, 2, and 3, respectively. Depending on the value of N, four equations can be obtained from eq 2. Substitution of $(1 - x_1^0)$ for x_2^0 in eq 2 with $N = 2$ and subsequent rearrangements results in eq 3

$$\ln x_A = \ln(x_A)_2 + [\ln(x_A)_1 - \ln(x_A)_2 + S_0 + S_1 + S_2]x_1^0 + [-S_0 + 3S_1 + 5S_2]x_1^{0^2} + [-2S_1 - 8S_2]x_1^{0^3} + [-4S_2]x_1^{0^4} \quad (3)$$

which can be rewritten in simple form as

$$\ln x_A = B_0 + B_1 x_1^0 + B_2 x_1^{0^2} + B_3 x_1^{0^3} + B_4 x_1^{0^4} \quad (4)$$

The calculated solubility values of adefovir dipivoxil from eq 4 are also given in Table 1. For comparison with each of the experimental points, the solubilities of adefovir dipivoxil in all five binary mixed solvents with the mole fraction of isopropyl ether ranging from 0.000 to 1.000 at 298.15 K are illustrated graphically in Figure 3. The values of the five parameters B_0, B_1, B_2, B_3, and B_4 together with the root-mean-square deviation (rmsd) defined by eq 5 are listed in Table 2.

$$\text{rmsd} = \left\{ \frac{1}{N} \sum_{i=1}^{N} (x_i^{\text{calcd}} - x_i^{\text{exptl}})^2 \right\}^{1/2} \quad (5)$$

where N is the number of experimental points; x_i^{calcd} represents the solubility calculated from eq 4; and x_i^{exptl} represents the experimental solubility values.

From Tables 1 and 2 and Figure 3, the following conclusions can be drawn:

(1) In all systems under consideration, the solubility of adefovir dipivoxil decreases with an increase of the fraction of isopropyl ether in the binary mixtures. Especially for the isopropyl ether and dichloromethane solvent mixture, as the concentration of isopropyl ether increases, the solubility of adefovir dipivoxil decreases sharply.

(2) At 298.15 K, the solubilities of adefovir dipivoxil in pure solvents increase in the order: isopropyl ether < 2-propanol < ethyl acetate < ethanol < acetone < dichloromethane.

(3) The calculated solubility data show good agreement with the experimental values, and the mathematical correlation describes correctly how the solubility of adefovir dipivoxil varies with solvent composition. So, the experimental solubility and correlation equation presented can be used as essential data for the design and operation of the crystallization process of adefovir dipivoxil.

Note Added after ASAP Publication: The paper was posted ASAP on March 4, 2008. Equations 3 and 4 were modified. The revised paper was reposted March 13, 2008.

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