Solubility of Tiamulin Hydrogen Fumarate in Acetone, Acetonitrile, Ethyl Acetate, Ethyl Formate, and Butyl Acetate from (288.2 to 318.2) K

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Despite its biological importance, little is known about the solubility properties of tiamulin hydrogen fumarate in different solvents. This work presents solubility of tiamulin hydrogen fumarate in acetone, acetonitrile, ethyl acetate, ethyl formate, and butyl acetate from (288.2 to 318.2) K at atmospheric pressure. The solubility data have been correlated by the Apelblat equation.

Introduction

Tiamulin hydrogen fumarate (CAS no. 55297-96-6) is a semisynthetic antibiotic of the diterpene group active against Gram-positive and Gram-negative microorganisms. In veterinary medicine, it is widely used for the treatment, control, and prophylaxis of dysentery, pneumoniae, and mycoplasma diseases in swine and poultry.[1−6] The chemical name of this compound is (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl[[2-(diethylamino)ethyl]sulfanyl]acetate hydrogen (*E*)-but-2-enedioate. Figure 1 shows the chemical structure of tiamulin hydrogen fumarate. In the production and purification process of tiamulin hydrogen fumarate, the crystallization step plays an important role,[7] and the determination of its solubility in different solvents will be beneficial for the selection of the proper solvent and to optimize the crystallization process. Despite its biological importance, no measurements have been reported on the solubility properties of tiamulin hydrogen fumarate in different solvents.

In the present article, we report the solubility data of tiamulin hydrogen fumarate in acetone, acetonitrile, ethyl acetate, ethyl formate, and butyl acetate from (288.2 to 318.2) K at atmospheric pressure. Methods of measuring the solubility of a solid in liquid mixture can be classified as analytical[8−10] and synthetic.[11,12] Despite its disadvantages such as being time-consuming, the analytical method is widely used because it allows measuring a large number of samples simultaneously. In this work, the analytical method has been used for the measurement. The experimental solubility data have been correlated by the Apelblat equation.

Experimental Section

Reagents and Apparatus. Tiamulin hydrogen fumarate was supplied by Zhejiang Shenghua BIOK Biology Co. Ltd. (Huzhou, China) with a minimum purity of 99.5 %, determined by HPLC. Ethyl acetate (99.9 %, HPLC purity grade, Sk Chemicals, Korea); acetonitrile (99.9 %, HPLC/Spectro purity grade, Tedia Company, USA); acetone (99.05 %, analytical purity grade, Quzhou Juhua Chemical Reagent Factory, China); *n*-butyl acetate (99.0 %, analytical purity grade, Shanghai Shengxiang Chemical Reagent Co. Ltd., China); ethyl formate (97.0 %, Chemical purity grade, Shanghai Lingfeng Chemical Reagent Co., Ltd., China). All the solvents were dried and stored over 4 Å molecular sieves (Sinopharm. Group Chemical Regent Co. Ltd., China) and were filtered through a 0.45 μm membrane before use. Redistilled deionized water was used throughout.

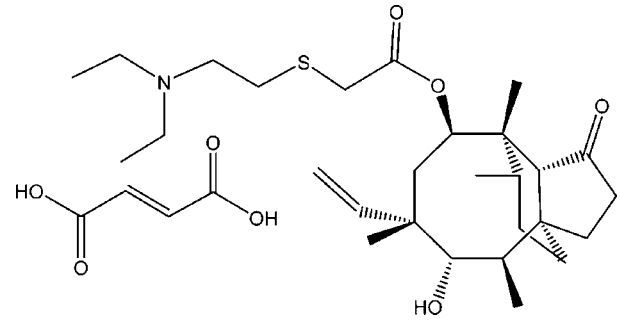

Figure 1. Molecular structure of tiamulin hydrogen fumarate.

A ZHWY-200B incubator shaker was supplied by Shanghai ZHICHENG Analytical Instrument Manufactory Co., Ltd. (Shanghai, China). An Auhaus (New Jersey, USA) analytical balance with sensitivity of 0.01 mg was used. Analytical experiments were performed using a Waters 2695 HPLC system composed of a quaternary pump, column and autosampler thermostat, and variable wavelength detector with detection monitored at 212 nm. A set of seven standard tiamulin hydrogen fumarate stock solutions were prepared by appropriate dilution of a stock solution, then used to generate a calibration curve (with regression coefficient better than 0.999). The solvent used to prepare the above stock and standard solution was pure ethanol. The calibration curve was used to determine the equilibrium concentrations of tiamulin hydrogen fumarate upon sampling and analysis.

Sample Preparation. Excess amounts of tiamulin hydrogen fumarate crystals were added to 30 mL of five organic solvents (acetone, acetonitrile, ethyl acetate, ethyl formate, and butyl acetate) with their temperatures ranging from (288.2 to 318.2) K. The temperature was controlled by a thermostat (uncertainty of ± 0.1 K) in the shaker. The suspended solution was kept shaken for 12 h in the shaker. After attaining equilibrium, the solution was allowed to settle for 2 h. Then the supernatant liquid was withdrawn and filtered through a 0.45 μm membrane.

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Table 1. Molar Concentration of Tiamulin Hydrogen Fumarate (c_i) in Different Organic Solvents at T = (288.2 to 318.2) K

	acetone		acetonitrile		ethyl acetate		ethyl formate		butyl acetate	
T/K	$10^3 c_i$	10^3 ($c_i - c_{i,cal}$)	$10^3 c_i$	10^3 ($c_i - c_{i,cal}$)	$10^3 c_i$	10^3 ($c_i - c_{i,cal}$)	$10^3 c_i$	10^3 ($c_i - c_{i,cal}$)	$10^3 c_i$	10^3 ($c_i - c_{i,cal}$)
288.2	17.90	0.38	2.13	0.10	5.73	0.02	5.61	−0.19	3.94	−0.01
293.2	19.23	−0.71	2.59	−0.23	6.47	0.17	7.12	0.21	4.57	−0.02
298.2	23.80	−0.24	3.94	0.04	6.79	−0.40	8.46	0.12	5.40	0.02
303.2	30.75	0.17	5.36	−0.03	8.45	−0.02	10.04	−0.14	6.45	0.07
308.2	42.40	1.50	7.90	0.46	10.82	0.55	12.56	0.00	7.64	0.01
313.2	55.85	−1.48	9.77	−0.47	12.39	−0.40	15.59	−0.06	9.10	−0.10
318.2	84.33	0.38	14.20	0.13	16.43	0.09	19.72	0.04	11.23	0.04

The filtered samples were poured into a volumetric flask and diluted to a fixed volume for HPLC analysis. Each measurement was repeated two to three times.

Sample Analysis. The solubility of tiamulin hydrogen fumarate was determined using the HPLC system mentioned above. The column (Agilent ZORBAX 80 A Extend-C18, 250 × 4.60 mm, 5 μm particle diameter) used for the reversed phase analysis was obtained from Agilent Technologies, and the mobile phase was composed of methanol (1), ammonium carbonate buffer (2), and acetonitrile (3) with a volume fraction ratio of 49 to 30 to 21. The buffer of ammonium carbonate was prepared as follows: 10.0 g of ammonium carbonate was dissolved in water, and 22 mL of perchloric acid (w = 0.06) was added. Then this mixture was diluted to 1000 mL. The pH value was adjusted to 8.9 by adding an appropriate amount of ammonia solution (w = 0.25) with the help of a digital pH meter. The calibration curve for estimation of tiamulin hydrogen fumarate was established by using the standard solutions in the appropriate concentration range. The analysis was performed at 303 K with a flow rate at 1.0 mL·min^{-1}. The injected volumes of the sample were 20 μL.

Results and Discussion

The solubility data of tiamulin hydrogen fumarate in acetone, acetonitrile, ethyl acetate, ethyl formate, and butyl acetate at different temperatures are presented in Table 1. It can be seen that the solubilities of tiamulin hydrogen fumarate in five solvents increase with the increase of temperature. The solubility of tiamulin hydrogen fumarate in acetone is higher than that in acetonitrile, ethyl acetate, ethyl formate, and butyl acetate. The solubility of tiamulin hydrogen fumarate in acetonitrile is the lowest. The solubility data reported in this work will be beneficial for the separation and purification process of tiamulin hydrogen fumarate in the pharmaceutical industry.

The temperature dependence of tiamulin hydrogen fumarate solubility in five pure solvents can be described by the modified Apelblat equation.[13−16] The modified Apelblat equation can be written as

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

where c is the solubility of tiamulin hydrogen fumarate; T is the absolute temperature; and A, B, and C are the parameters obtained by regression of the experimental data.

The values of parameters A, B, and C in eq 1 are obtained by regression of the experimental solubility data by minimizing the average relative deviation (ARD) as

$$\text{ARD} = \frac{1}{N}\sum_{i=1}^{N}\frac{|c_{i,\text{cal}} - c_i|}{c_i} \quad (2)$$

where N is the number of experimental points; c_i represents the experimental solubility values; and $c_{i,\text{cal}}$ represents the calculated solubility. The difference between experimental and calculated results is presented in Table 1. The parameters A, B, and C and root-mean-square deviations (rmsd) defined below are listed in Table 2.

Table 2. Parameters of Equation 1 for Tiamulin Hydrogen Fumarate in Different Organic Solvents at T = (288.2 to 318.2) K

solvent	A	B	C	10^3rmsd
acetone	−1436.07	60835.4	216.79	0.87
acetonitrile	−195.31	3848.4	32.25	0.27
ethyl acetate	−852.23	35790.1	128.85	0.30
ethyl formate	−415.42	15657.0	64.07	0.13
butyl acetate	−355.84	13422.2	54.85	0.05

$$\text{rmsd} = \left[\frac{1}{N}\sum_{i=1}^{N}(c_{i,\text{cal}} - c_i)^2\right]^{1/2} \quad (3)$$

From the data listed in Tables 1 and 2, it can be seen that the calculated solubility shows good agreement with the experimental values, which indicates that the modified Apelblat equation can be applied to represent the solubility of tiamulin hydrogen fumarate in the five solvents within the temperature range. Overall, the experimental solubility data and the modified Apelblat equation with the parameters can be used as essential physical data for the study of tiamulin hydrogen fumarate.

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