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SHORT ARTICLE

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Solubility of Minoxidil in Methanol, Ethanol, 1-Propanol, 2-Propanol, 1-Butanol, and Water from (278.15 to 333.15) K

Hao Yan, Runyan Li, Qiang Li, Jingkang Wang, and Junbo Gong*

School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, People's Republic of China

ABSTRACT: The solubility of minoxidil in pure methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, and water was measured at temperatures ranging from (278.15 to 333.15) K by a gravimetrical method. The experimental data were well-correlated as a function of temperature using the Apelblat equation. At the same temperature, the mole fraction solubility decreases in the order: methanol > 1-propanol > 1-butanol > ethanol > 2-propanol > water.

INTRODUCTION

Minoxidil (6-(1-piperidinyl)-2,4-pyrimidinediamine 3-oxide) is an important drug that is efficacious in patients with the drug-resistant forms of hypertension and androgenetic alopecia. Minoxidil relaxes the vascular smooth musculature mainly at an arteriolar level and enhances the follicular size.[1−4] The mole mass of minoxidil is 209.25, and the CAS Registry number is 38304-91-5. Minoxidil is one of the most popular medicaments in the world with a market of more than 100 million dollars per year in the United States alone.[5] The chemical structure of minoxidil is shown in Figure 1.

The solubility of minoxidil is associated with the bioavailability, which plays an important role in the drug discovery and preparation stages in the pharmaceutical industry.[6] Also, it is necessary to know the solubility of minoxidil in the screening of solvents for the design of an optimized crystallization process. Actually, in the open literature, the data of minoxidil solubility are quite scarce. In this contribution, the solubility of minoxidil in pure methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, and water was investigated in the temperature range from (278.15 to 333.15) K by a gravimetrical method under atmospheric pressure.

EXPERIMENTAL SECTION

Reagents. Minoxidil with a mass fraction purity of 0.995 analyzed by high-performance liquid chromatography (HPLC; type Agilent 1100, Agilent Technologies, USA) was supplied by Zhejiang Xingcheng Chemphar Co., Ltd. of China. All of the organic solvents, methanol, ethanol, 1-propanol, 2-propanol, and 1-butanol for experiments were analytical grade reagents (volume fractions were higher than 0.995) from Tianjin Kewei Chemical Co. in China and used without any treatment. Distilled−deionized water was used.

Apparatus and Procedure. The solubility of Minoxidil was measured by a gravimetric method that was described in detail in the literature.[7] For each measurement, an excess mass of Minoxidil was added to 50 mL of solvent in a cylindrical double-jacketed glass vessel having a working volume of 100 mL, in which the temperature was controlled to be constant by a thermostatted bath (type 501A, Shanghai Laboratory Instrument Works Co., Ltd., China) with an uncertainty of ± 0.05 K. After the solution was kept under agitation by a magnetic stir bar for more than 4 h to ensure that equilibrium was reached, the stirring was stopped, and the solution was kept still for 2 h. Ten mL of the upper clear solution was filtered and taken in a weighted measuring Petri dish (m_0) by a preheated injector and a filter (PTFE 0.2 μm). All of the masses were taken using a balance (type AB204, Metler Toledo, Switzerland) with an uncertainty of ± 0.0001 g. The Petri dish with clear solution was quickly weighed (m_1) to determine the mass of the sample ($m_1 - m_0$) and placed in the vacuum drying oven (type DFZ-6020, Shanghai Yiheng Technical Co., Ltd., China) at 323.15 K for 12 h. After the solvent in the Petri dish completely evaporated, the Petri dish was reweighed (m_2) for several times until the weight of Petri dish was kept constant to determine the mass of the residue solid ($m_2 - m_0$). Samples were analyzed by HPLC to make sure that there was no thermal decomposition effect of Minoxidil during the experiments. Each measurement was repeated three times, and an arithmetic average value was used for the calculation of the solubility.

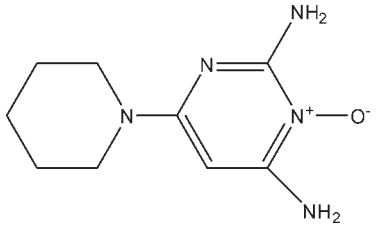

Figure 1. Chemical structure of minoxidil.

The mole fraction solubility of the Minoxidil (x_i) in solvents was calculated as follows

$$x_i = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2} \quad (1)$$

where M_1 (M_1 = 209.25) is the molar mass of minoxidil and M_2 is the molar mass of the solvent. The uncertainty of experimental values is estimated to be less than 0.62 %.

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Table 1. Mole Fraction Solubility x_i of Minoxidil in Different Solvents at Temperatures Ranging from (278.15 to 333.15) K

T/K	$10^3\ x_i$	$10^3\ x_{ci}$	10^2 RD
		Methanol	
278.15	7.42	7.40	0.22
283.15	8.01	8.00	0.11
288.15	8.70	8.69	0.20
293.15	9.44	9.46	−0.22
298.15	10.3	10.3	−0.14
303.15	11.3	11.3	−0.31
308.15	12.4	12.4	−0.42
313.15	13.8	13.7	0.55
318.15	15.0	15.1	−0.54
323.15	16.8	16.7	0.57
328.15	18.6	18.5	0.29
333.15	20.5	20.6	−0.34
		Ethanol	
278.15	3.91	3.90	0.30
283.15	4.35	4.35	0.07
288.15	4.87	4.86	0.17
293.15	5.44	5.43	0.10
298.15	6.03	6.07	−0.65
303.15	6.78	6.78	−0.10
308.15	7.58	7.58	−0.07
313.15	8.51	8.48	0.40
318.15	9.40	9.48	−0.80
323.15	10.6	10.6	0.49
328.15	11.9	11.8	0.51
333.15	13.2	13.2	−0.39
		1-Propanol	
278.15	4.31	4.25	1.39
283.15	4.82	4.81	0.22
288.15	5.37	5.43	−1.17
293.15	6.00	6.12	−1.97
298.15	6.96	6.89	1.01
303.15	7.86	7.74	1.47
308.15	8.58	8.68	−1.19
313.15	9.70	9.72	−0.16
318.15	10.9	10.9	0.38
323.15	12.2	12.1	0.39
328.15	13.5	13.5	−0.39
333.15	15.0	15.0	0.04
		2-Propanol	
278.15	2.21	2.20	0.34
283.15	2.58	2.57	0.45
288.15	2.96	2.98	−0.68
293.15	3.43	3.43	−0.21
298.15	3.92	3.93	−0.46
303.15	4.45	4.49	−0.90
308.15	5.19	5.09	1.83
313.15	5.80	5.75	0.94
318.15	6.36	6.46	−1.68
323.15	7.26	7.23	0.37
328.15	8.05	8.07	−0.23
333.15	8.98	8.96	0.18
		1-Butanol	
278.15	3.91	3.83	2.08
283.15	4.40	4.39	0.09
288.15	4.93	5.02	−1.65
293.15	5.62	5.70	−1.43
298.15	6.49	6.46	0.40
303.15	7.36	7.29	0.82
308.15	8.14	8.21	−0.75
313.15	9.22	9.20	0.24
318.15	10.4	10.3	0.68
323.15	11.5	11.5	0.27
328.15	12.6	12.7	−0.82
333.15	14.1	14.1	0.23
		Water	
278.15	0.153	0.155	−1.15
283.15	0.168	0.169	−0.65
288.15	0.188	0.186	0.91
293.15	0.205	0.206	−0.85
298.15	0.235	0.230	2.14
303.15	0.258	0.257	0.30
308.15	0.287	0.288	−0.51
313.15	0.325	0.325	0.14
318.15	0.368	0.367	0.05
323.15	0.416	0.417	−0.18
328.15	0.470	0.475	−1.07
333.15	0.546	0.542	0.71

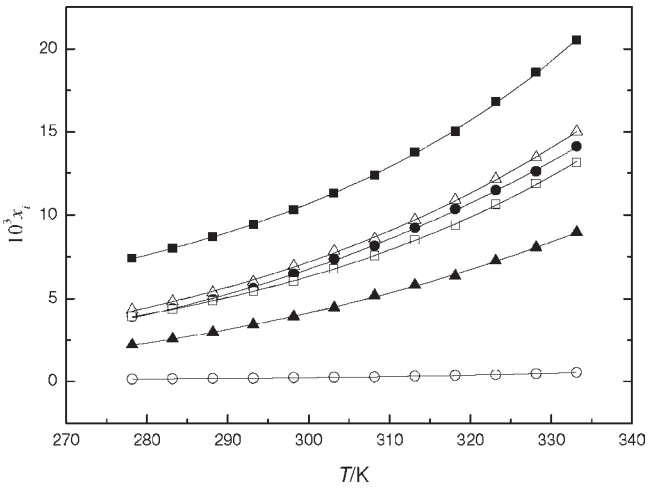

Figure 2. Mole fraction solubility of minoxidil in different solvents at temperatures ranging from (278.15 to 333.15) K: ■, methanol; △, 1-propanol; ●, 1-butanol; □, ethanol; ▲, 2-propanol; ○, water. The corresponding lines were the calculated values based on eq 1.

RESULTS AND DISCUSSION

The mole fraction solubility of minoxidil in methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, and water at temperatures ranging from (278.15 to 333.15) K was listed in Table 1 and shown in Figure 2.

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Table 2. Parameters of the Apelblat Equation for Minoxidil in Different Solvents

solvent	A	B	C	10^5 rmsd	10^2 AAD
methanol	−139.46	4642.89	20.94	5.36	0.33
ethanol	−91.26	2151.75	13.86	3.85	0.34
1-propanol	−49.01	186.69	7.62	6.91	0.82
2-propanol	19.82	−3152.54	−2.60	4.76	0.69
1-butanol	−9.01	−1682.83	1.69	6.19	0.79
water	−199.26	6848.24	29.47	0.26	0.72

The experimental data can be well-correlated as a function of temperature using the Apelblat equation[8]

$$\ln x_i = A + \frac{B}{(T/\mathrm{K})} + C \ln(T/\mathrm{K}) \quad (2)$$

in which x_i is the mole fraction of minoxidil and T is the absolute temperature. The parameters A, B, and C were obtained by fitting the experimental solubility data and are summarized in Table 2 together with the root-mean-square deviations (rmsd's) and the average absolute deviation (AAD).

The rmsd is defined as the following

$$\mathrm{rmsd} = \left[\sum_{i=1}^{N} \frac{(x_i - x_{ci})^2}{N}\right]^{1/2} \quad (3)$$

where x_{ci} is the calculated value by the Apelblat equation; N is the number of experiment points. AAD is defined as follows

$$\mathrm{AAD} = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{x_i - x_{ci}}{x_i}\right| \quad (4)$$

The relative deviations (RDs) between the experimental and the calculated values of the solubility are given in Table 1.

$$\mathrm{RD} = \frac{x_i - x_{ci}}{x_i} \quad (5)$$

From Table 1 and Figure 2, it can be seen that the solubility of minoxidil in all the solvents increases with increasing temperature. The solubility of minoxidil in alcohols is much higher than that in water, which may result from the hydrophobic groups in the minoxidil framework and formation of hydrogen bonds between minoxidil and alcohols. The minoxidil framework is comprised of an N-oxide moiety, giving rise to the only hydrogen bond acceptor site for alcohols to bind.[6] Out of the alcohols, the solubility of minoxidil in methanol is highest, while the solubility of minoxidil in 2-propanol is lowest due to the steric congestion around the respected moieties.

CONCLUSIONS

The solubility of minoxidil in methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, and water was investigated in the temperature range from (278.15 to 333.15) K by a gravimetrical method. The mole fraction solubility is a function of temperature and increases with an increase of temperature. At the same temperature, the mole fraction solubility decreases in the order: methanol > 1-propanol > 1-butanol > ethanol > 2-propanol > water. The Apelblat equation was employed in correlating the experimental data with good agreement.

AUTHOR INFORMATION

Corresponding Author

*Fax: +86-22-27374971. E-mail: junbo_gong@tju.edu.cn.

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