Solubilities of Nizatidine in Water, Methanol, Ethanol, Acetone, and Ethyl Acetate from (273.15 to 343.15) K

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The solubilities of nizatidine in water, methanol, ethanol, acetone, and ethyl acetate were determined in the temperature range from (273.15 to 343.15) K by a static analytical method. The concentrations of nizatidine in saturated solution were analyzed by reverse-phase high-performance liquid chromatography. An empirical equation was proposed to correlate the experimental data, which fit the data very well.

Introduction

Nizatidine (*N*-[2-[[[2-[(dimethylamino)methyl]-4-thiazolyl-]methyl]thio]ethyl]-*N*′-methyl-2-nitro-1,1-ethenediamine, Figure 1) is a specific H_2-receptor antagonist and is used to treat gastroesophogeal reflux disease by preventing the release of acid and pepsin into the stomach.[1]

Usually, crystallization in organic solvents such as ethanol and acetone is employed in the final step of nizatidine preparation.[2,3] In our laboratory, an environmentally friendly process of crystallization of nizatidine in water has been under development. Unfortunately, no experimental solubility data of nizatidine in different solvents are currently available in the literature. In this study, the solubilities of nizatidine in water, methanol, ethanol, acetone, and ethyl acetate were determined in the temperature range from (273.15 to 343.15) K so as to provide essential data for the development of crystallization processes.

Experimental Section

Chemicals. Nizatidine (> 99.5 % purity) was obtained from Hengdian Group Jiayuan Chemistry Industry Co., Ltd., China. Analytical reagent (AR) grade methanol, ethanol, and ethyl acetate were from Sinopharm Chemical Reagent Co., Ltd., and AR grade acetone was from Hangzhou Chemical Reagent Co., Ltd., China. High-performance liquid chromagraphy (HPLC) grade methanol and acetonitrile were from Merck. All chemicals were used as received.

Apparatus and Procedure. The solubility determination in this study was carried out by a static analytical method similar to that described in our previous works.[4,5] The uncertainty of temperature was ± 0.05 K. Three hours of stirring and 9 h of settling were employed to ensure reaching equilibrium with the data reproducibility within 0.5 %. Samples were taken with a Pasteur pipet and analyzed by HPLC.

Analysis. About 0.5 g of saturated solution was quickly taken out, put into the bottom of a volumetric flask with stopper, weighed, and diluted with solvent to a certain volume. Then the composition of the pretreated samples was directly determined by reverse-phase HPLC (Agilent 1100 series). An external standard method was employed for quantitative analysis. The HPLC column was an Extend-C18 (Agilent Technologies, 250 × 4.6 mm, 5 μm). A portion of 0.02 mol·L^{-1} disodium hydrogen phosphate aqueous solution, acetonitrile, methanol, and triethylamine in a volume ratio of 77.95:10:10:0.05 was used as the mobile phase at a flow rate of 0.8 mL·min^{-1}.[6] The column temperature was 303.15 K, and the UV wavelength was set at 254 nm. The linear range was (0.02 to 0.65) mg·mL^{-1} with the correlation coefficient close to 1 and relative standard deviation (RSD, $n = 6$) at 0.0008.

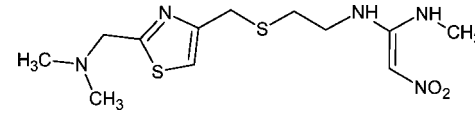

Figure 1. Chemical structure of nizatidine.

Results and Discussion

At each temperature, six samples were analyzed. The average experimental data for the mass fraction solubilities of nizatidine in water, methanol, ethanol, acetone, and ethyl acetate are listed in Table 1, together with error limits using the 95 % confidence level. The solubility data are also depicted as a function of temperature in Figure 2. The dielectric constants of water, methanol, ethanol, acetone, and ethyl acetate are 79.7, 32.6, 22.4, 20.6, and 6.02 at 293.15 K, respectively.[7] From the results, we can see that the solubilities of nizatidine increased with increasing polarity of the solvents except for water, which may indicate that the polarity of nizatidine is close to methanol.

An empirical equation is proposed to correlate the solubility of nizatidine.

$$w = (a + bT)^{-1/c} \tag{1}$$

where w is the mass fraction solubility, T is the absolute temperature, and a, b, and c are parameters.

The values of a, b, and c in eq 1 for water, methanol, ethanol, acetone, and ethyl acetate are presented in Table 2, together with the root-mean-square deviation defined by

$$\sigma = [\sum_{i=1}^{n} (S_{ci} - S_i)^2/n]^{1/2} \tag{2}$$

where S_i is experimental solubility, S_{ci} is the calculated solubility, and n is the number of experimental points.

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Table 1. Mass Fraction Solubilities of Nizatidine in Water, Methanol, Ethanol, Acetone, and Ethyl Acetate, Together with Error Limits Using the 95 % Confidence Level

T/K	water	methanol	ethanol	acetone	ethyl acetate
273.15	0.02245 ± 0.00012	0.01665 ± 0.00021	0.00287 ± 0.00006	0.00283 ± 0.00004	0.00029 ± 0.00001
278.15	0.02319 ± 0.00015	0.02112 ± 0.00017	0.00381 ± 0.00002	0.00340 ± 0.00006	0.00033 ± 0.00001
283.15	0.02377 ± 0.00016	0.02704 ± 0.00017	0.00487 ± 0.00007	0.00432 ± 0.00011	0.00043 ± 0.00001
288.15	0.02470 ± 0.00023	0.03469 ± 0.00022	0.00653 ± 0.00002	0.00552 ± 0.00009	0.00058 ± 0.00001
293.15	0.02573 ± 0.00013	0.04465 ± 0.00037	0.00867 ± 0.00001	0.00701 ± 0.00012	0.00063 ± 0.00001
298.15	0.02973 ± 0.00019	0.05886 ± 0.00092	0.01330 ± 0.00006	0.00806 ± 0.00003	0.00082 ± 0.00001
303.15	0.03253 ± 0.00022	0.07653 ± 0.00108	0.01666 ± 0.00015	0.01025 ± 0.00009	0.00093 ± 0.00003
308.15	0.03596 ± 0.00020	0.10318 ± 0.00135	0.02117 ± 0.00023	0.01283 ± 0.00027	0.00148 ± 0.00006
313.15	0.04016 ± 0.00039	0.14694 ± 0.00107	0.03013 ± 0.00046	0.01644 ± 0.00009	0.00187 ± 0.00002
318.15	0.04630 ± 0.00020	0.20253 ± 0.00304	0.03757 ± 0.00025	0.02350 ± 0.00064	0.00219 ± 0.00002
323.15	0.05352 ± 0.00023		0.06204 ± 0.00086	0.03848 ± 0.00107	0.00269 ± 0.00003
328.15	0.06530 ± 0.00069		0.09548 ± 0.00128		0.00343 ± 0.00006
333.15	0.08095 ± 0.00031		0.17930 ± 0.00067		0.00420 ± 0.00007
338.15	0.10875 ± 0.00030				0.00550 ± 0.00011
343.15	0.16353 ± 0.00064				

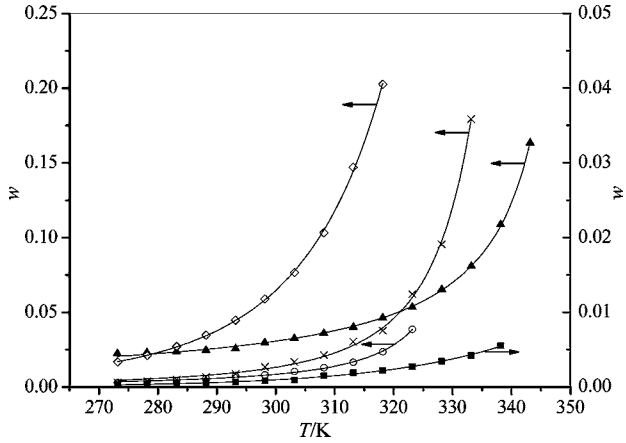

Figure 2. Solubilities of nizatidine in water, methanol, ethanol, acetone, and ethyl acetate: ▲, water; ◇, methanol; ×, ethanol; ○, acetone; ■, ethyl acetate. Solid line, calculated from eq 1.

Table 2. Parameters in Equation 1 for Water, Methanol, Ethanol, Acetone, and Ethyl Acetate, Together with σ

solvent	*a*	*b*/K^{-1}	*c*	σ
water	241.88475	−0.68611	1.02977	0.00078
methanol	6.9262	−0.01754	0.18569	0.00117
ethanol	36.52507	−0.10377	0.38897	0.00159
acetone	164.84344	−0.4873	0.61233	0.00046
ethyl acetate	0.92794	0.00016	−0.00353	0.00021

The calculated curves from eq 1 are shown in Figure 2, too, suggesting that the equation fits the data very well.

Conclusion

The solubilities of nizatidine in water, methanol, ethanol, acetone, and ethyl acetate were determined in the temperature range from (273.15 to 343.15) K by a static analytical method and are essential for the industrial development of the purification process of nizatidine. In addition, an empirical equation was proposed, which fit the data very well.

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