Solubility of Dioxopromethazine Hydrochloride in Different Solvents

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The solubilities of dioxopromethazine hydrochloride (DPZ) in water, acetic acid, ethanol, methanol, *N,N*-dimethylformamide, *N*-methyl ketopyrrolidide, and acetone between (278 and 328) K were measured using a laser monitoring observation technique. Results of these measurements were correlated with a semiempirical equation. For seven solvents studied, the data are well fitted with a semiempirical equation.

Introduction

Dioxopromethazine hydrochloride (CAS Registry No. 13754-56-8) is a white or almost white crystalline powder and a phenothiazine antihistamine drug in therapy. It is widely used as antitussives, sedatives, and local anesthetic in clinic.[1]

To determine the proper solvent and design an optimized crystallization process, it is necessary to know its solubility in different solvents. In this paper, the solubilities of dioxopromethazine hydrochloride (DPZ) in water, acetic acid, ethanol, methanol, *N,N*-dimethylformamide (DMF), *N*-methyl ketopyrrolidide (NMP), and acetone between (278 and 328) K were measured using a laser monitoring observation technique at atmospheric pressure. The method employed in this work was classed as a synthetic method, which was much faster and more reliable than the analytical method.[2]

Experimental Section

Materials. DPZ used during the solubility measurements had a mass purity of 0.994 and was purchased from Jilin Liaoyuan Dikang Pharmaceutical Group Co., Ltd. Its mass fraction purity was determined by HPLC. Other reagents are analytical research grade reagents from Shanghai Chemical Reagent Co. Distilled, deionized water of HPLC grade was used.

Apparatus and Procedure. The solubility of DPZ was measured using an apparatus similar to that described in the literature[3,4] and described briefly here. A 200 mL jacketed vessel was used to determine the solubility. The temperature in the vessel was maintained at the desired value by continuous forced water circulation from a thermostat (temperature uncertainty of ± 0.05 K). A mercury-in-glass thermometer (uncertainty of ± 0.05 K) was used for the measurement of the temperature in the vessel. The dissolution of the solute was examined by the laser beam penetrating the vessel. To prevent the evaporation of the solvent, a condenser vessel was introduced. The masses of the samples and solvents were determined using an analytical balance (sartorius CP124S, Germany) with an uncertainty of ± 0.1 mg.

Predetermined excess amounts of solvent and dioxopromethazine hydrochloride of known mass were placed in the inner chamber of the vessel. The contents of the vessel were stirred continuously at the required temperature. In the early stages of the experiment, the laser beam was decreased by the undissolved particles of DPZ in the solution. As the particles of the solute dissolved, the intensity of the laser beam increased gradually. When the solute dissolved completely, the solution was clear, and the laser intensity reached maximum. Then, additional solute of known mass (about (1 to 3) mg, which was determined by a preliminary experiment) was introduced into the vessel. This procedure was repeated until the penetrated laser intensity could not return a maximum or, in other words, the last addition no longer dissolved completely in the solvent. The interval of addition depended on the speed of dissolving at that temperature, and it should last more than 30 min. The total amount of the solute consumed was recorded. The same solubility experiment was conducted three times, and each time had good agreement. The mean values were used to calculate the mole fraction solubility x_1 based on

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \tag{1}$$

where m_1 and m_2 represent the mass of the solute and solvent, respectively, and M_1 and M_2 are the molecular weight of the solute and solvent, respectively. The estimated uncertainty of the solubility values based on error analysis and repeated observations was within 1.0 %.

Results and Discussion

The solubility data of DPZ in water, ethanol, methanol, acetone, *N*-methyl ketopyrrolidide, *N,N*-dimethylformamide, and acetic acid between (278 and 328) K are presented in Table 1. The temperature dependence of DPZ solubility in pure solvents is described by the modified Apelblat equation, which is a semiempirical equation.[5–7]

$$\ln x_1 = A + \frac{B}{T/\mathrm{K}} + C \ln(T/\mathrm{K}) \tag{2}$$

where x_1 is the mole fraction solubility of DPZ; T is the absolute temperature; and A, B, and C are the dimensionless parameters. The calculated solubility values of DPZ are also

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Table 1. Mole Fraction Solubility (x_1) of DPZ in Selected Solvents with the Temperature Range from (278 to 338) K

T/K	$10^3 x_1^{exptl}$	$10^3 x_1^{calcd}$	T/K	$10^3 x_1^{exptl}$	$10^3 x_1^{calcd}$
		DMF			
278.20	3.806	3.855	303.19	5.537	5.567
283.20	4.184	4.124	308.23	6.014	6.044
288.27	4.480	4.431	313.17	6.580	6.564
293.18	4.744	4.764	318.23	7.163	7.157
298.17	5.139	5.142	323.18	7.827	7.804
		Acetone			
278.20	0.1029	0.1034	303.17	0.2163	0.2193
283.16	0.1236	0.1250	308.21	0.2366	0.2413
288.16	0.1502	0.1482	313.20	0.2585	0.2612
293.17	0.1770	0.1721	318.18	0.2783	0.2784
298.18	0.1991	0.1961	323.17	0.2984	0.2928
		NMP			
278.16	6.413	6.448	308.17	9.755	9.716
283.20	6.924	6.905	313.21	10.41	10.41
288.24	7.468	7.395	318.23	11.11	11.16
293.16	7.905	7.909	323.27	11.92	11.95
298.17	8.426	8.471			
		Water			
278.28	1.364	1.374	303.18	3.790	3.824
283.27	1.627	1.639	308.16	4.842	4.872
288.27	2.001	1.987	313.22	6.248	6.297
293.24	2.459	2.441			
298.18	3.025	3.033			
		Ethanol			
278.16	0.2686	0.2688	303.22	0.4999	0.4936
283.21	0.2961	0.2941	308.18	0.5887	0.5809
288.22	0.3225	0.3272	313.17	0.6860	0.6924
293.18	0.3650	0.3694	318.2	0.8286	0.8360
298.21	0.4190	0.4242			
		Acetic Acid			
293.16	2.080	2.105	318.22	6.886	6.803
298.18	2.769	2.719	328.23	10.02	10.18
303.18	3.475	3.469	333.19	12.28	12.29
308.20	4.334	4.386	338.20	14.86	14.75
313.17	5.479	5.478			
		Methanol			
278.17	0.7593	0.7722	303.19	1.852	1.904
283.22	0.9251	0.9206	308.21	2.250	2.300
288.19	1.122	1.098	313.21	2.840	2.783
293.26	1.366	1.319	318.18	3.397	3.369
298.17	1.558	1.580			

Table 2. Parameters of Equation 2 for DPZ in Different Solvents

solvent	A	B	C	10^5rmsd
water	−462.67	16922	70.225	2.07
ethanol	−444.86	17275	66.546	0.55
methanol	−203.66	5984.0	31.090	3.97
DMF	−123.41	4082.0	18.332	3.56
NMP	−57.983	1332.5	8.5549	4.61
acetic acid	67.898	−7053.8	−8.8017	8.19
acetone	331.18	−16953	−49.645	0.60

given in Table 1. The values of parameters A, B, and C and the square deviations (rmsd) are listed in Table 2. The rmsd is defined as

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

where N is the number of experimental points; $x_{1,j}^{\mathrm{calcd}}$ represents the solubility calculated from eq 2; and $x_{1,j}$ represents the experimental solubility values.

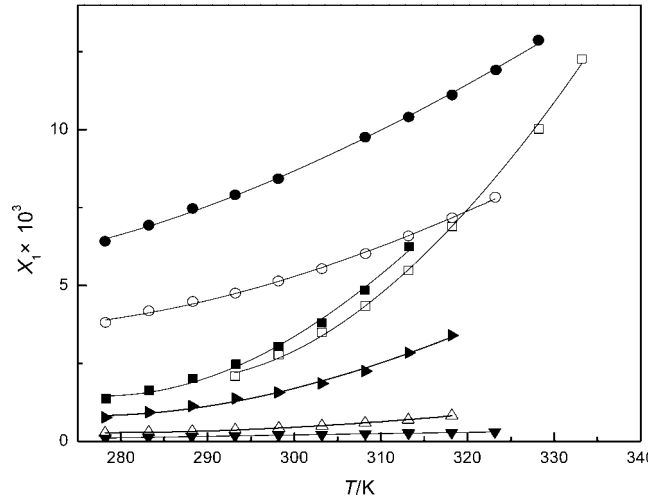

Figure 1. Mole fraction solubility of DPZ x_1 in different solvents: ●, NMP; ○, DMF; ■, water; □, acetic acid; solid triangle pointing right, methanol; Δ, ethanol; ▼, acetone.

From the data listed in Table 1 and Table 2, we can draw the following conclusions: (i) The solubility of DPZ increases with temperature in the seven solvents (see Figure 1). The solubility of DPZ is the lowest in acetone and the largest in NMP. (ii) The experimental solubility and correlation equation in this work can be used as essential data and models in the purification process of DPZ. The solubility calculated by eq 2 shows good agreement with experimental values.

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