Solubility of Sulpiride in Pure Organic Solvents between (278 and 333) K

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The solubility of sulpiride in organic solvents of acetone, *N*-methylpyrrolidone (NMP), ethanol, tetrahydropyran (THF), *N*,*N*-dimethylformamide (DMF), and methanol between (278 and 328) K was measured using a laser monitoring observation technique. Results of these measurements were correlated with a semiempirical equation. For the seven solvents studied, the data are fitted well with a semiempirical equation.

Introduction

Sulpiride has the IUPAC name of (*R*,*S*)-5-(aminosulfonyl)-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-2-methoxybenzamide (CAS Registry No. 15676-16-1, formula: $C_{15}H_{23}N_3O_4S$), and its molecular structure[1] is shown in Figure 1.

Sulpiride has been reported to be an effective antipsychotic agent and displays marked pharmacological differences from those of the "classical" neuroleptic drugs, for example, haloperidol and chloroprornazine.[2] Sulpiride has a relatively low neuroleptic potency in both animals[2,3] and humans,[4] which could be due to a low degree of biological availability including low penetration into the brain.[5] Thus, it should be of interest to synthesize and evaluate other types of neuroleptic benzamides[3,6] modified from sulpiride. Before modification, we need high-purity sulpiride, and crystallization is an effective production method. Hence it is necessary to know its solubility to design the crystallization process of sulpiride.

In the present paper, by considering the practical crystallization process, ethanol, acetone, *N*,*N*-dimethylformamide (DMF), tetrahydropyran (THF), *N*-methylpyrrolidone (NMP), and methanol were selected as solvents, and solubilities of sulpiride in these solvents were measured using a laser monitoring observation technique at atmospheric pressure.

Experimental Section

Materials. Sulpiride used during the solubility measurements had a mass purity of 0.997 and was purchased from Ningbo JieRun Imp & Exp Co., Ltd. Its mass fraction purity was determined by high-performance liquid chromatography (HPLC). Other reagents are analytical research grade reagents from Beijing Chemical Reagent Co.

Apparatus and Procedure. The solubility of sulpiride was measured using an apparatus similar to that described in the literature[7,8] and described briefly here. A 200 mL jacked vessel was used to determine the solubility. A mercury-in-glass thermometer (uncertainty of ± 0.05 K) was used for the measurement of the temperature in the vessel. The masses of the samples and solvents were determined using an accurate electronic analytical balance (Sartorius CP124S, Germany) with an uncertainty of ± 0.1 mg.

During experiments, the fluid in the glass vessel was monitored by a laser beam. Predetermined excess amounts of solvent and sulpiride of known mass were placed in the inner chamber of the vessel. The contents of the vessel were stirred continuously at certain temperatures. In the early stage of the experiment, the laser beam was decreased by the undissolved particles of sulpiride 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 a maximum. Then additional solute of known mass of about (1 to 3) mg, which was determined by preliminary experiments, was introduced into the vessel. This procedure was repeated until the penetrated laser intensity could not return a maximum. The interval of addition depended on the speed of dissolving at that temperature; usually, it will last more than 30 min. The total amount of the solute consumed was recorded. The same solubility experiment was conducted three or four times, and each time has a 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 uncertainty of the mole fractions in the solubility values is established to be ± 3.0 %.

Results and Discussion

The solubility data of sulpiride in ethanol, acetone, DMF, THF, and methanol between (278.15 and 333.15) K are presented in Table 1. The temperature dependence of sulpiride solubility in pure solvents is described by the modified Apelblat equation, which is a semiempirical equation.[9,10]

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

where x_1 is the mole fraction solubility of sulpiride; T is the absolute temperature; and A, B, and C are the dimensionless parameters and were obtained using a nonlinear regression. The calculated solubility values of sulpiride are also given in Table 1. The values

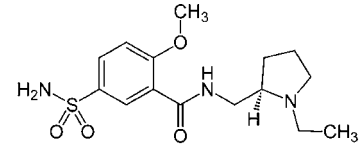

Figure 1. Structure of sulpiride.

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Table 1. Mole Fraction Solubility (x_1) of Sulpiride in Selected Solvents with the Temperature Range from (278.15 to 333.15) K

T/K	$10^2\ x_1^{exp}$	$10^2\ (x_1 - x_1^{calc})/x_1$	T/K	$10^2\ x_1^{exp}$	$10^2\ (x_1 - x_1^{calc})/x_1$
		Ethanol			
288.76	0.045	0.21	313.40	0.1561	2.36
294.01	0.0576	2.46	318.20	0.2019	1.25
298.74	0.07638	−1.50	324.00	0.2687	2.37
303.65	0.09904	−2.25	328.10	0.3429	−1.04
308.00	0.123	−1.54	332.70	0.4334	−0.96
		Acetone			
278.25	0.09696	−1.79	303.05	0.2499	0.00
283.30	0.1229	2.51	308.00	0.3003	0.48
287.85	0.142	−0.22	313.50	0.3565	−2.04
293.50	0.1757	−0.06	318.55	0.4346	−0.03
298.25	0.2097	0.01	323.45	0.5213	1.05
		DMF			
277.95	3.884	−0.24	308.03	7.165	−0.29
283.15	4.366	0.09	313.13	7.874	−0.28
288.30	4.878	0.27	318.28	8.643	−0.23
293.05	5.376	0.20	323.05	9.444	0.26
297.95	5.931	0.21	327.85	10.35	1.18
303.00	6.504	−0.42	333.25	11.10	−0.80
		THF			
282.95	0.1088	0.32	313.05	0.3972	−1.50
288.30	0.1373	−2.37	318.25	0.4825	−1.56
293.25	0.1775	0.49	323.20	0.5827	−0.49
298.15	0.2244	2.16	328.25	0.6941	−0.46
303.05	0.2744	1.47	333.05	0.8305	1.51
308.05	0.3326	0.32			
		Methanol			
278.18	0.08554	−1.05	308.21	0.3496	−1.77
283.27	0.1115	0.94	313.19	0.4574	2.36
288.20	0.1417	1.35	318.26	0.5678	1.05
293.45	0.1831	2.12	323.17	0.7039	0.54
298.55	0.2209	−3.00	328.28	0.8932	1.65
303.20	0.2764	−2.19	333.37	1.076	−2.11
		NMP			
283.68	8.099	0.40	303.20	11.87	1.76
288.50	8.742	−2.36	308.50	12.35	−1.75
293.85	9.881	0.33	313.50	13.34	−0.85
298.75	11.06	2.72	318.50	14.04	−1.94

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

solvent	A	B	C	10^4 rmsd
ethanol	−201.97	4786.4	31.363	0.36
acetone	−90.785	984.69	14.271	0.33
DMF	−10.961	−1131.9	2.0946	4.9
THF	53.183	−5922.6	−6.9223	0.56
methanol	−128.61	1922.1	20.370	0.14
NMP	317.97	−15783	−46.916	12

of parameters A, B, and C and the root-mean-square deviations (rmsd) are listed in Table 2. The rmsd is defined as[11]

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

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

In Figure 2 the solubility is plotted versus temperature, and the figure shows that the solubility of sulpiride is the lowest in ethanol and the largest in NMP and increases with temperature in selected solvents. We can see from Figure 1 that there is a ring structure, which has a carbonyl in the sulpiride molecule, and DMF and NMP each have a carbonyl, so the hydrogen bond will be formed between these solvents and sulpiride, consequently resulting in a relative high solubility value when compared with the other four solvents. Even though THF has a similar ring structure with sulpiride, the solubilities of sulpiride in NMP and DMF are both larger than in THF. However, a similar ring structure is still beneficial to the solve the process of sulpiride in solvents such as in NMP.

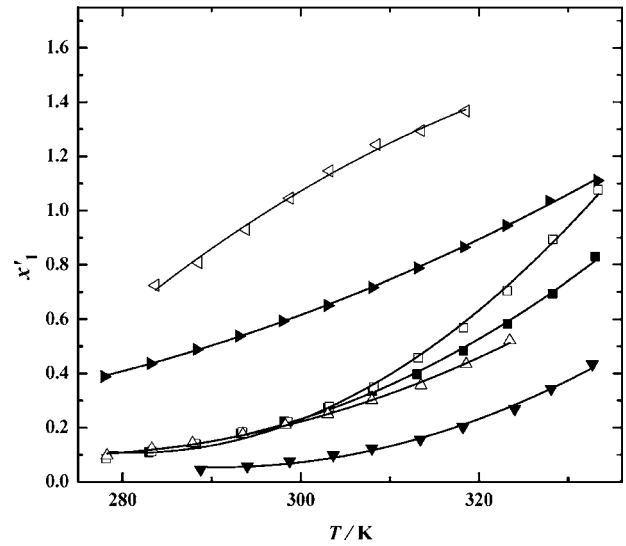

Figure 2. Mole fraction solubility of sulpiride (x_1) in different solvents between (278 and 333) K: open right-pointing triangle, NMP ($x_1 = x'_1/10$); ■, THF ($x_1 = x'_1/10^2$); □, methanol ($x_1 = x'_1/10^2$); ▼, ethanol ($x_1 = x'_1/10^2$); solid left-pointing triangle, DMF ($x_1 = x'_1/10$); △, acetone ($x_1 = x'_1/10^2$).

On the contrary, the same effect between solvents and sulpiride cannot be found, and the solubilities of sulpiride in these four solvents change with temperature evidently (as shown in Figure 2). All discussions show that hydrogen bonds make more of a contribution than a similar structure of sulpiride in all of solvents used in this article.

From the data listed in Tables 1 and 2, we can draw the following conclusions: The solubility calculated by eq 2 shows good agreement with experimental values. The experimental solubility and correlation equation in this work can be used as essential data and models in the purification process of sulpiride.

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