Solubilities of Proxetine Hydrochloride Hemihydrate between 286 K and 363 K

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Using a laser monitoring observation technique, we determined the solubilities of paroxetine hydrochloride hemihydrate in *N*,*N*-dimethylformamide, methyl isobutyl ketone, tetrahydrofuran, ethyl acetate, methanol, ethanol, 1-propanol, 1-butanol, and 2-butanol by the synthetic method from 286 K to 363 K. Results of these measurements were correlated by an empirical equation.

Introduction

Solubility is no doubt one of the most important physicochemical properties and is particularly useful in a wide variety of phenomena relevant to the biological, pharmaceutical, environmental, and petroleum industries. It is also important to know the solubility of the reagents and product in order to design the separation process properly. Paroxetine hydrochloride hemihydrate (Figure 1) is a potent selective reuptake inhibitor (SSRI) with indications for the treatment of a variety of human diseases including depression, obsessive compulsive disorder, and panic disorder.[1−3] The published works relating to paroxetine are mainly concerned with synthesis, clinical study, and solid-state characterization, and solubilities of this drug have not been reported in the literature. In this paper, we have employed a laser monitoring observation technique to study the solubilities of paroxetine hydrochloride hemihydrate in *N*,*N*-dimethylformamide, methyl isobutyl ketone, tetrahydrofuran, ethyl acetate, methanol, ethanol, 1-propanol, 1-butanol, and 2-butanol. The melting point of paroxetine hydrochloride hemihydrate measured with a NETZSCH STA449C differential scaning calorimeter is 399.8 K and compares with the literature value of 401.2 K.[4]

Experimental Section

Pure (99.5% on a dry substance, determined by a Varian 5500 HPLC) paroxetine hydrochloride hemihydrate crystals were obtained from Zhejiang Huahai Pharmaceutical. *N*,*N*-Dimethylformamide, methyl isobutyl ketone, tetrahydrofuran, ethyl acetate, methanol, ethanol, 1-propanol, 1-butanol, and 2-butanol are analytical research grade reagents from Tianjin Chemical Reagent Co.

Solubilities were measured by a synthetic method.[5−7] The apparatus for solubility measurement (Figure 2) is the same as that described in the literature.[8,9] A laser beam was used to determine the solubilities of the solute in different solvents at a known temperature. The laser monitoring system consisted of a laser generator, a photoelectric transformer, and a light intensity display. The solubility apparatus consisted of a jacketed glass vessel maintained at a desired temperature by water circulating from a water bath with a thermoelectric controller (type 501, China). The jacket temperature could be maintained within ±0.02 K of the required temperature. Continuous stirring was achieved with a magnetic stir bar. A condenser was connected to the vessels to prevent the solvents from evaporating. A mercury-in-glass thermometer was inserted into the inner chambers of the vessels for the measurement of the temperature. The thermometer had an uncertainty of ±0.05 K.

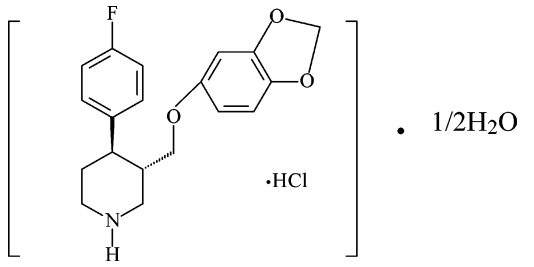

Figure 1. Structure of paroxetine hydrochloride hemihydrate.

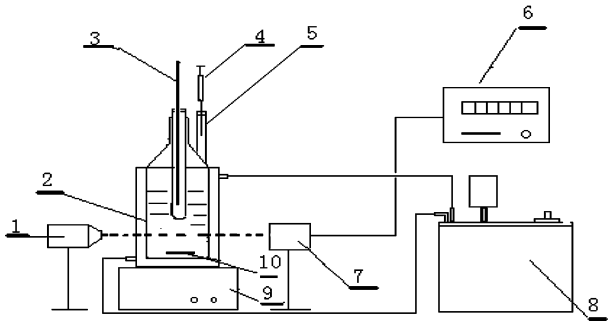

Figure 2. Schematic setup for the solubility determination: (1) laser generator, (2) dissolution kettle, (3) thermometer, (4) injector, (5) inlet for solid (6) digital display, (7) photoelectric switch, (8) superthermostatic bath, (9) magnetic stirrer, and (10) stir bar.

An analytical balance (type TG332A, China) with an uncertainty of ±0.0001 g was used. Predetermined excess amounts of paroxetine hydrochloride hemihydrate and a solvent of known mass were placed in the jacketed vessel. The contents of the vessel were stirred continuously at a required temperature. When the last portion of solute disappeared, the intensity of the laser beam penetrating the vessel reached a maximum, and the solvent mass consumed in the measurement could be recorded. Together

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Table 1. Solubilities of Paroxetine Hydrochloride Hemihydrate in *N*,*N*-Dimethylformamide, Methyl Isobutyl Ketone, Tetrahydrofuran, Ethyl Acetate, Methanol, Ethanol, 1-Propanol, 1-Butanol, and 2-Butanol

T/K	10^5x_1	$10^5x_{1,calcd}$	*T*/K	10^5x_1	$10^5x_{1,calcd}$	T/K	10^5x_1	$10^5x_{1,calcd}$	*T*/K	10^5x_1	$10^5x_{1,calcd}$
					N,*N*-Dimethylformamide						
295.50	123.5391	120.8683	326.15	315.4883	314.5575	310.15	202.3759	202.3107	342.15	441.0725	439.8703
298.55	136.5925	135.8644	330.15	346.8482	345.2287	314.05	233.0703	227.7448	346.20	472.1952	471.8453
302.05	152.4400	154.3731	334.20	377.6325	376.8969	317.85	254.9656	253.8335	350.45	505.0563	504.9410
306.15	169.7362	177.7745	338.35	409.4701	409.7214	322.25	284.7027	285.4573	355.15	537.0729	540.6398
					Methyl Ethyl Ketone						
300.95	0.9060	0.8895	328.90	8.6290	8.9670	312.65	2.3464	2.3098	339.05	21.3143	21.1957
303.35	1.0809	1.0798	331.35	11.1199	11.0280	316.7	3.1412	3.2294	341.7	25.3570	26.6792
306.6	1.4210	1.4120	333.35	13.9348	13.0619	323.75	5.8650	5.8153	343.00	29.3879	29.6825
310.65	1.8800	1.9592	336.6	17.9885	17.2823						
					Tetrahydrofuran						
294.75	0.0088	0.0087				306.7	0.0314	0.0312	326.95	0.1185	0.1201
297.15	0.0116	0.0116	316.15	0.0660	0.0657	310.05	0.0413	0.0417	330.55	0.1384	0.1392
300.00	0.0158	0.0160	319.45	0.0807	0.0811	312.65	0.0529	0.0511	334.15	0.1602	0.1574
303.15	0.0222	0.0223	323.05	0.0977	0.0994						
					Ethyl Acetate						
293.65	0.4407	0.4459				310.85	3.0339	3.1371	335.2	17.6042	17.7673
296.6	0.6632	0.6590	323.15	8.8742	8.60912	314.05	4.1467	4.1971	338.2	20.3900	20.5149
300.05	1.0134	0.9988	326.00	10.7844	10.4483	317.0	5.4427	5.3903	341.15	23.3391	23.3190
303.55	1.5383	1.4892	329.80	12.9277	13.2330	320.2	6.9380	6.9380	344.2	26.4244	26.2678
307.15	2.1140	2.1817	332.1	15.0593	15.1308						
					Ethanol						
300.15	325.9752	340.7132				313.10	431.0254	422.5287	334.30	508.8866	515.8673
303.20	362.0106	361.0196	325.25	477.8698	483.7542	316.15	443.5845	439.6154	337.10	520.8837	523.2157
306.10	391.6185	379.8369	328.00	491.4636	494.8294	319.05	451.1534	454.8550	340.20	535.0948	529.8895
310.00	416.3748	404.1647	331.30	494.0851	506.6171	322.05	464.4011	469.4939	343.20	547.8234	534.8835
					1-Propanol						
299.15	27.0896	28.3559				315.15	39.5699	38.5613	343.15	58.1654	60.0023
303.45	31.2966	30.9363	331.15	50.3052	50.3122	319.15	42.0544	41.3621	347.35	62.9327	63.5472
307.25	33.7187	33.3175	335.15	52.3415	53.4656	323.15	44.2460	44.2565	351.15	66.6931	66.8157
311.25	36.9525	35.9239	339.25	55.8473	56.7788	327.25	46.7401	47.3169	355.10	73.4519	70.2703
					2-Butanol						
286.90	37.7937	36.4693				307.35	50.3587	51.2532	339.45	128.8859	127.3922
291.40	38.5123	38.5321	323.00	76.5173	76.13154	311.30	56.0093	56.0822	343.65	148.0750	147.2932
295.75	40.5425	41.0963	327.20	87.1948	86.06784	315.15	61.2691	61.6330	347.40	166.6737	168.3820
299.15	43.0514	43.5334	331.15	99.5268	97.14465	319.40	69.2674	68.8931	351.30	188.4768	194.2965
303.20	45.5747	46.9937	335.55	114.214	111.8538						
					Methanol						
287.50	69.1270	71.0338	313.25	180.1494	180.1737	300.80	128.066	124.3396	323.25	217.0587	221.2496
290.60	81.1099	82.2887	316.05	189.524	192.3329	303.70	138.3240	137.2444	327.70	235.3588	236.7296
293.60	95.8070	93.9420	318.10	199.1462	200.9616	306.40	147.2623	149.4209	331.20	248.7266	247.2842
296.55	108.678	106.0368	321.00	209.7673	212.6611	310.35	168.6472	167.2592	335.30	263.5253	257.6016
					1-Butanol						
295.25	126.7003	124.5804	331.15	216.0196	210.7149	315.15	167.9472	171.318	351.15	260.3367	259.5226
299.15	134.8743	133.4045	335.25	222.7167	220.8445	319.15	180.9486	181.0952	355.10	266.3191	268.8718
303.40	143.5576	143.2346	339.25	235.7990	230.6890	323.00	190.0663	190.5679	358.90	270.4159	277.7309
307.25	149.9764	152.3068	343.15	244.8081	240.2282	327.20	196.0368	200.9434	363.15	276.1772	287.4620
311.00	157.8048	161.2732	347.40	254.0897	250.5316						

with the mass of solute, the solubility could be obtained. The saturated mole fraction solubility of the solute x_1 can be obtained as follows:

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

in which m_1 and m_2 represent the masses of solute and solvent. M_1 and M_2 are the molecular weights of solute and solvent, respectively. To verify the uncertainty of the measurement, one other experiment was done in which the solubility of benzoic acid in water was determined. The solubilities of benzoic acid in water in the literature[10] and in this work were plotted in Figure 3. Compared with the literature data, the deviation of the solubility was lower than 1%.

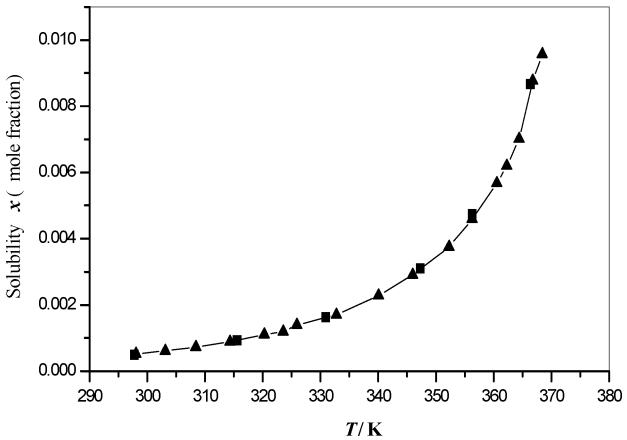

Figure 3. Solubility of benzoic acid in water: ■, solubility values in the literature;[10] ▲, experimental solubility values.

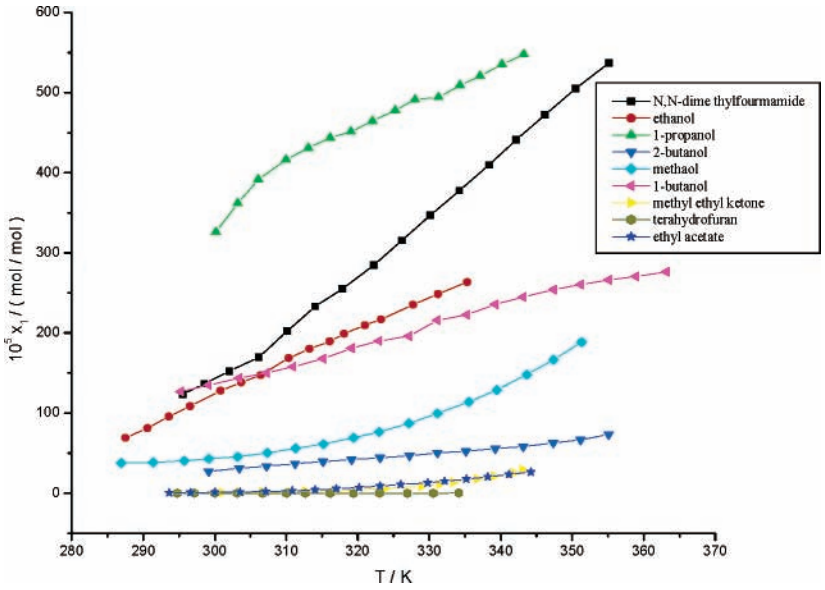

Figure 4. Solubilities of paroxetine hydrochloride hemihydrate in different solvents.

Table 2. Parameters for Correlation Equations of Different Solvents

solvent	*a*	*b*	*c*	$10^5\sigma_x$
N, N-dimethylformamide	−193.64651	−11 765.60914	−28.22256	2.7900
methyl ethyl ketone	−425.62347	12 367.73985	65.34007	0.4820
tetrahydrofuran	1252.39546	−65 024.28672	−184.31460	0.0012
ethyl acetate	976.88128	−53 292.85596	−142.14400	0.1479
methanol	437.43805	−22 646.48341	−64.63576	2.2759
ethanol	228.42553	−11 994.67791	−34.03498	7.3480
1-propanol	29.98493	−3276.23509	−4.77135	0.8775
1-butanol	50.34866	−3848.90703	−7.73592	3.3905
2-butanol	−387.21699	15 582.20853	57.42720	1.2684

Results and Discussion

The solubility of a solid in a liquid may be expressed in a very general manner by eq 2

$$\ln x_1 = -\frac{\Delta H_{f,1}}{RT_{f,1}}\left(\frac{T_{f,1}}{T} - 1\right) - \frac{\Delta C_{p\,f,1}}{R}\left(\frac{T_{f,1}}{T} - 1\right) + \frac{\Delta C_{p\,f,1}}{R}\ln\frac{T_{f,1}}{T} - \ln\gamma_1 \quad (2)$$

where x_1, γ_1, $\Delta H_{f,1}$, $\Delta C_{p\,f,1}$, $T_{f,1}$, R, and T_1 stand for the mole fraction of the solute, activity coefficient, enthalpy of fusion, difference in the solute heat capacity between the solid and liquid at the melting temperature, melting temperature of the solute, gas constant, and equilibrium temperature in the saturated solution, respectively. For regular solutions,[11] the activity coefficient is given by

$$\ln\gamma_1 = A + \frac{B}{T} \quad (3)$$

where A and B stand for empirical constants. Introducing γ_1 from eq 3 into eq 2 and subsequent rearrangements result in eq 4:

$$\ln x_1 = \left[\frac{\Delta H_{f,1}}{RT_{f,1}} + \frac{\Delta C_{p\,f,1}}{R}(1 + \ln T_{f,1}) - A\right] - \left[B + \left(\frac{\Delta H_{f,1}}{RT_{f,1}} + \frac{\Delta C_{p\,f,1}}{R}\right)T_{f,1}\right]\frac{1}{T} - \frac{\Delta C_{p\,f,1}}{R}\ln T \quad (4)$$

Equation 4 can be written as eq 5

$$\ln x_1 = a + \frac{b}{T} + c\ln T \quad (5)$$

where T is the absolute temperature and a, b, and c are empirical constants.

The experimental results of solubilities of paroxetine hydrochloride hemihydrate in *N*,*N*-dimethylformamide, methyl isobutyl ketone, tetrahydrofuran, ethyl acetate, methanol, ethanol, 1-propanol, 1-butanol, and 2-butanol are presented in Table 1, and a plot of the solubility of paroxetine hydrochloride hemihydrate in different solvents at various temperatures is given in Figure 4. For all systems, solubility is a function of temperature, and solubility increases with increasing temperature.

The solubility data were correlated with eq 5, and the calculated solubilities $x_{1,\mathrm{calcd}}$ are listed in Table 1 for comparison with the experimental values. The values of the three parameters a, b, and c together with the root-mean-square deviations are listed in Table 2. The root-mean-square deviations is defined as

$$\sigma_x = \left[\frac{1}{n}\sum_{i=1}^{n}(x_{1,\mathrm{calcd}} - x_{1,i})^2\right]^{1/2} \quad (6)$$

where $x_{1,\mathrm{calcd}}$ stands for the solubility calculated from eq 5 and n is the number of experimental points. For comparison with each other, solubilities of paroxetine hydrochloride hemihydrate in different solvents were plotted in Figure 4.

The ability of a solute to form hydrogen bonds with potential solvents is an important feature of its behavior. Basically, paroxetine hydrochloride hemihydrate can act both as a hydrogen bond acceptor and donor and would be expected to interact with solvents that have both accepting and donating sites with respect to the structure of paroxetine hydrochloride hemihydrate (Figure 1). However,

alcohols (methanol, ethanol, 1-propanol, 1-butanol, and 2-butanol) and *N*,*N*-dimethylformamide are well known to be hydrogen-bonding solvents with both high enthalpies of association and high association constants. Hence, they would be expected to stabilize solutes with hydrogen bond donor sites, and the solubilities of paroxetine hydrochloride hemihydrate in these solvents would be expected to be better than in other organic solvents. This was verified by the experimental solubility data of paroxetine hydrochloride hemihydrate in different solvents, including *N*,*N*-dimethylformamide, methyl isobutyl ketone, tetrahydrofuran, ethyl acetate, methanol, ethanol, 1-propanol, 1-butanol, and 2-butanol in Table 1 and Figure 4.

From Tables 1 and 2 and Figure 4, we can draw the following conclusions: (1) For all systems, solubility is a function of temperature, and solubility increases with increase of temperature. (2) The best solubility of paroxetine hydrochloride hemihydrate was shown in alcohols (methanol, ethanol, 1-propanol, 1-butanol, and 2-butanol), and *N*,*N*-dimethylformamide shows evidence of the strongest solute interaction with these solvents. (3) The calculated solubilities of paroxetine hydrochloride hemihydrate show good agreement with the experimental values, and the experimental solubility and correlation equation in this work can be used as essential data and models in the purification process of paroxetine hydrochloride hemihydrate.

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