Solubility of Chlorpheniramine Maleate in Ethanol, 1-Propanol, 1-Butanol, Benzene, Ethyl Acetate, Ethyl Formate, and Butyl Acetate between 283 K and 333 K

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The solubility of chlorpheniramine maleate in ethanol, 1-propanol, 1-butanol, benzene, ethyl acetate, ethyl formate, and butyl acetate was measured using a laser technique with the temperature range from 283 K to 333 K and at atmospheric pressure. The solubility of chlorpheniramine maleate in pure solvents increases with temperature and in the following order: alcohol solvents > ester solvents > benzene. The experimental solubility data were correlated with a semiempirical equation.

Introduction

Solubility is an important physicochemical property and is particularly useful in a wide variety of phenomena relevant to the chemical and pharmaceutical industries, such as solvent selection for a reaction and for separation processes. A variety of pure solvents and solvent mixtures (e.g., binary, ternary mixtures) have usually been employed in a particular crystallization process during manufacturing of pharmaceuticals.[1] Chlorpheniramine maleate (CAS Registry No. 113-92-8), $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$, is a salt of organic acid and has a strong polarity. Its structural formula is given in Figure 1. In the pharmaceutical industry, it acts as an antihistamine and is usually used in the treatment of respiratory infections and allergic conditions. To select the proper solvent and design an optimized separation process, studies of phase equilibrium behavior, especially solubility data, are essential.[2] However, a survey of the literature indicates that studies on chlorpheniramine maleate have been focused on preparations or clinical treatments, whereas little work has been carried out on the solubility data. In this paper, the solubility of chlorpheniramine maleate in ethanol, 1-propanol, 1-butanol, benzene, ethyl acetate, ethyl formate, and butyl acetate between 283 K and 333 K was experimentally determined using a laser monitoring observation technique at atmospheric pressure. The method employed in this work was classified as a synthetic method, which was much faster and more readily usable than the analytical method.[3] In this work we report extensive experimental data and correlate the values with a semiempirical equation.

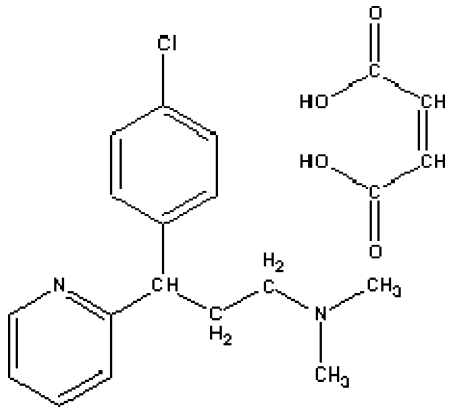

Figure 1. Molecular structure of chlorpheniramine maleate (CAS Registry No. 113-92-8).

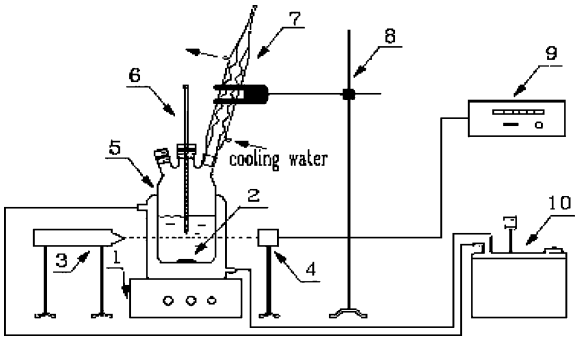

Figure 2. Schematic setup for the solubility measure: 1, magnetic stirrer; 2, stir bar; 3, laser generator; 4, photoelectric converter; 5, dissolution vessel; 6, thermometer; 7, condenser; 8, ring stand and clamp; 9, digital display; 10, thermostat.

Experimental Section

Materials. Chlorpheniramine maleate used during the solubility measurement had a purity of 0.995 (mass fraction), purchased from Shijiazhuang Pharmaceutical Group Co., Ltd. (CSPC). Ethanol, 1-propanol, 1-butanol, benzene, ethyl acetate, ethyl formate, and butyl acetate were analytical research grade regents from Beijing Chemical Reagent Co.

Apparatus and Procedures. The solubility of chlorpheniramine maleate was determined by a laser technique.[4−7] The apparatus (Figure 2) was similar to that described in the literature[8] and is described briefly here. Jacketed vessels of 100 mL and 350 mL were used to determined the solubility; the temperature was controlled to be constant (fluctuates by 0.05 K) through a thermostated water bath. During experiments the fluid in the glass vessel was monitored by a laser beam. Predetermined amounts of solvent that had been weighed and chlorpheniramine maleate of known mass were placed in the inner chamber of the vessel. The contents of the vessel were

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Table 1. Mole Fraction Solubility of Chlorpheniramine Maleate x_1 in Different Solvents between 283 K and 333 K

T/K	$10^3 x_1$	$10^3(x_1 - x_1^{calcd})$	T/K	$10^3 x_1$	$10^3(x_1 - x_1^{calcd})$
		Ethanol			
282.65	2.6158 ± 0.0145	0.002	312.93	17.794 ± 0.015	0.075
289.15	3.7752 ± 0.0146	0.000	318.33	26.190 ± 0.015	0.089
294.05	5.0769 ± 0.0145	0.009	323.20	37.668 ± 0.015	0.302
298.15	6.5584 ± 0.0149	0.007	327.85	53.180 ± 0.015	0.136
303.45	9.1899 ± 0.0147	−0.060	331.07	67.313 ± 0.014	−0.577
308.44	12.868 ± 0.015	−0.091			
		1-Propanol			
283.00	1.6064 ± 0.0077	−0.027	313.04	12.528 ± 0.008	−0.145
288.27	2.2839 ± 0.0079	0.021	317.97	18.473 ± 0.008	0.060
293.00	3.1438 ± 0.0082	0.070	323.15	27.613 ± 0.007	0.106
298.15	4.3572 ± 0.0082	0.010	328.53	42.244 ± 0.007	0.135
303.15	6.1200 ± 0.0077	−0.041	332.96	60.167 ± 0.007	0.001
308.06	8.6870 ± 0.0079	−0.084			
		1−Butanol			
282.73	1.0586 ± 0.0075	−0.070	313.27	9.1583 ± 0.0076	−0.087
288.22	1.7418 ± 0.0077	0.125	318.15	13.226 ± 0.008	0.036
293.45	2.3672 ± 0.0076	0.070	323.27	19.205 ± 0.008	−0.025
297.73	3.1028 ± 0.0077	0.024	328.15	27.980 ± 0.008	0.334
303.38	4.4798 ± 0.0078	−0.084	333.40	41.183 ± 0.007	0.183
308.65	6.3824 ± 0.0077	−0.249			
		Ethyl Formate			
282.90	1.0428 ± 0.0086	0.003	308.10	5.3387 ± 0.0092	−0.04
288.65	1.5435 ± 0.0085	−0.033	313.15	7.0663 ± 0.0087	−0.039
293.65	2.2614 ± 0.0087	0.045	318.15	9.1291 ± 0.0089	−0.094
298.65	3.0746 ± 0.0089	0.014	323.10	11.798 ± 0.0092	0.019
303.15	4.0683 ± 0.0089	0.036	328.10	14.987 ± 0.0092	0.102
		Ethyl Acetate			
282.86	0.5947 ± 0.0077	−0.008	313.15	2.1522 ± 0.0084	−0.021
289.45	0.8069 ± 0.0075	0.021	318.15	2.7072 ± 0.0080	−0.012
293.65	0.9306 ± 0.0078	−0.005	323.15	3.4322 ± 0.0078	0.022
298.60	1.1364 ± 0.0079	−0.016	328.10	4.2694 ± 0.0078	−0.009
302.25	1.3634 ± 0.0081	0.016	333.15	5.4172 ± 0.0082	0.014
308.15	1.7435 ± 0.0083	0.002			
		Butyl Acetate			
283.15	0.1650 ± 0.0030	0.001	308.10	0.6440 ± 0.0027	−0.047
288.15	0.2149 ± 0.0027	−0.014	313.15	0.8805 ± 0.0025	0.012
294.95	0.3681 ± 0.0029	0.022	318.15	1.0234 ± 0.0030	−0.047
298.71	0.4513 ± 0.0027	0.023	323.05	1.3170 ± 0.0028	0.024
303.31	0.5493 ± 0.0031	0.003	327.65	1.5496 ± 0.0026	0.028
		Benzene			
283.05	0.0767 ± 0.0035	−0.011	312.95	0.3661 ± 0.0041	−0.016
288.05	0.1228 ± 0.0044	0.011	318.27	0.4557 ± 0.0038	−0.040
293.75	0.1651 ± 0.0041	0.017	323.15	0.6189 ± 0.0037	−0.011
298.78	0.2011 ± 0.0038	0.011	327.53	0.7808 ± 0.0035	0.000
303.04	0.2363 ± 0.0037	0.002	333.45	1.1196 ± 0.0022	0.077
308.25	0.2882 ± 0.0035	−0.015			

stirred continuously at a required temperature. In the early stage of the experiment, the laser beam was blocked by the undissolved particles of chlorpheniramine maleate in the solution, so the intensity of the laser beam penetrating the vessel was lower. Along with the dissolution of the particles of the solute, the intensity of the laser beam increased gradually. When the solute dissolved completely, the solution was clear and transparent, and the laser intensity reached a maximum. Then additional solute of known mass [about (1 to 5) mg] was introduced into the vessel at intervals. This procedure was repeated until the penetrated laser intensity did not return to a maximum, or, in other words, the last addition of solute could not dissolve completely. The interval of addition was 30 min. To prevent the evaporation of the solvent, a condenser vessel was introduced. The total amount of the solute consumed was recorded. We used an analytical balance (Sartorius CP124S, Goettingen, Germany) with an uncertainty of ± 0.0001 g to weigh the masses of the samples and solvents. The same solubility experiment was conducted three times, and the mean values were used to calculate the mole fraction solubility x_1 based on eq 1

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

where m_1 and m_2 represent the mass of the solute and solvent and M_1 and M_2 are the molecular weights of the solute and solvent, respectively. The uncertainty in the solubility values is estimated to be about 2 %.

Results and Discussion

The solubility values of chlorpheniramine maleate in different solvents are listed in Table 1 and visually shown in Figure 3.

The temperature dependence of chlorpheniramine maleate solubility in solvents is correlated with the semiempirical equation[9]

$$\ln x_1 = a + \frac{b}{(T/\mathrm{K})} + c \ln(T/\mathrm{K}) \tag{2}$$

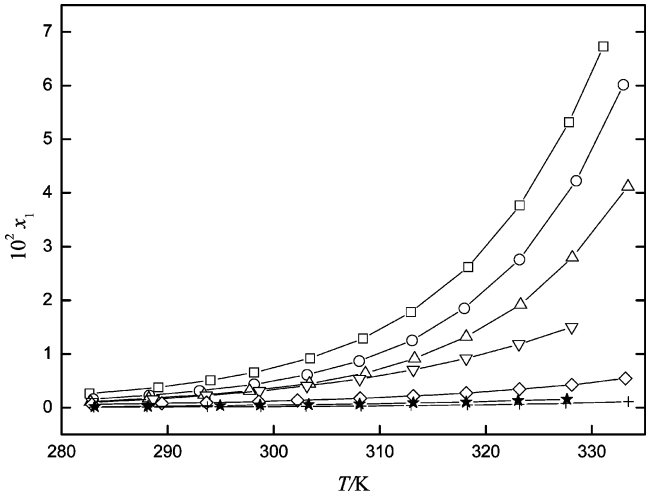

Figure 3. Mole fraction solubility of chlorpheniramine maleate x_1 in different solvents: □, ethanol; ○, 1-propanol; △, 1-butanol; ▽, ethyl formate; ◇, ethyl acetate; ★, butyl acetate; +, benzene.

Table 2. Parameters of Equation 5 for Chlorpheniramine Maleate in Different Solvents

solvent	*a*	*b*	*c*	10^4 RMSD
ethanol	−553.54	19598.59	84.73	2.16
1-propanol	−543.20	18752.99	83.34	0.83
1-butanol	−410.45	12790.39	63.50	1.58
ethyl formate	171.81	−12681.94	−23.71	0.55
ethyl acetate	−257.39	7942.45	39.31	0.15
butyl acetate	292.28	−17531.98	−42.35	0.28
benzene	−195.07	4582.84	30.03	0.29

where *T* is the absolute temperature, and *a*, *b*, and *c* are the dimensionless parameters. The calculated solubility values of chlorpheniramine maleate are also given in Table 1. The values of the three parameters *a*, *b*, and *c* together with the root-mean-square deviations (RMSD) are listed in Table 2. The RMSD is defined as

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

where *N* is the number of experimental points, $x_{1,j}^{\mathrm{calcd}}$ is the solubility calculated from eq 2, and $x_{1,j}$ is the experimental value of solubility. From Figure 3 we can see the solubility increases with temperature and changes with different solvents.

Relative permittivity is commonly regarded as a measure of molecular polarity, whereas dipole moment is a degree of polarization.[10] Relative permittivities and dipole moments of the solvents studied are listed in Table 3. The polarity of the solvents is in the order benzene < butyl acetate < ethyl acetate < ethyl formate < 1-butanol < 1-propanol < ethanol (Table 3), as are the solubilities determined by experiments (see Table 1). Polar molecules dissolve easily in polar solvent, which is the so-called empirical rule that "like dissolves like". The molecular structure of the title compound (see Figure 1) shows that chlorpheniramine maleate has a strong polarity; hence, the more polar the solvent is, the higher the solubility is. The process of dissolution is comparatively complex and mainly influenced by the characteristics of the solute and solvent as well as temperature.[2]

Table 3. Physicochemical Properties of the Solvents Studied[a,10]

solvent	*M* / g·mol^{-1}	ϵ	*D* / 10^{-30} C·m
ethanol	46.07	25.7	5.60
1-propanol	60.10	22.2	5.53
1-butanol	74.12	17.10	5.60
ethyl formate	74.08	7.16	6.47
ethyl acetate	88.11	6.02 (293.15 K)	6.27
butyl acetate	116.16	5.01 (292.15 K)	6.14
benzene	78.11	2.283 (293.15 K)	0.00

[a] *M* = molecular mass, *R* = relative permittivity at 298.15 K, *D* = dipole moment at 293.15 K and 298.15 K.

Conclusions

From Table 1 and Figure 3, the following conclusions can be drawn: (1) For these seven pure solvent systems, the solubility of chlorpheniramine maleate is a function of temperature, and solubility increases with temperature. (2) The solubility of chlorpheniramine maleate in seven solvents decreases in the order ethanol > 1-propanol > 1-butanol > ethyl formate > ethyl acetate > butyl acetate > benzene. (3) These experimental data can be regressed by eq 2 for each solvent.

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