

Solubility of Phenothiazine in Water, Ethanol, and Propylene Glycol at (298.2 to 338.2) K and Their Binary and Ternary Mixtures at 298.2 K

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ABSTRACT: The solubilities of phenothiazine in water, ethanol, and propylene glycol were measured at (298.2 to 338.2) K. Also, the solubility of phenothiazine in binary mixtures of ethanol + water, propylene glycol + water, and ethanol + propylene glycol, and the ternary mixture of ethanol + propylene glycol + water was investigated. The van't Hoff equation was used to correlate the solubility of phenothiazine in monosolvents at different temperatures. The solubility values of phenothiazine in binary and ternary mixtures of solvents were calculated using the Jouyban–Acree model (Jouyban, A.; Acree, W. E., Jr. *J. Chem. Eng. Data* **2009**, *54*, 1168–1170). The mean deviation was used as an error criterion. The overall mean deviation of correlated solubility data in monosolvents at different temperatures and in mixed solvents at 298.2 K were 2.8 % and 14.2 %, respectively.

INTRODUCTION

Solubility is an important physicochemical property which plays basic role in most pharmaceutical and industrial processes. To investigate this property different tools have been used such as experimental techniques, mathematical calculations, and simulation. Usually the low solubility of pharmaceutical compounds causes them to fail during the drug development process. Different factors influence the solubility in a medium, some of which include cosolvents, temperature, pH of the solution, and presence of surfactants.

Phenothiazine, a triheterocyclic compound (see Figure 1 for its structure), is a veterinary antihelmintic drug, and its derivatives are widely used in pharmacotherapy. Phenothiazine is one of the oldest lead compounds in medicinal chemistry, synthesized in 1883, and clinical applications of the generated drugs from this lead compound were reported in 1891 as antimalaria drug, in 1930s as antifungal, in 1940s as antihelminthic, in 1947 as antihistaminic, in 1951 as antipsychotic, in 1990 as antioxidant, and in 2009 as a promising drug in Alzheimer disease.¹ Solubility data of phenothiazine could be valuable in pharmaceutical applications as many phenothiazine derivatives are of the main and important pharmaceutical compounds. Hoover et al.² previously presented mathematical correlation of phenothiazine solubilities in organic solvents with the Abraham solvation parameter model following experimental determination of this solute in monosolvents at 298.2 K.² To the best of our knowledge, these are the only reported solubility data for phenothiazine in the literature. Thermodynamic parameters, solubilities, and interactions with micelles of a number of phenothiazine derivative drugs were investigated by Mandal et al.^{3–5}

The aims of this study are to determine the solubility of phenothiazine in water, ethanol, and propylene glycol at (298.2 to 338.2) K and in ethanol + water, propylene glycol + water, ethanol + propylene glycol, and ethanol + propylene glycol + water mixtures at 298.2 K. In addition, the solubility correlations

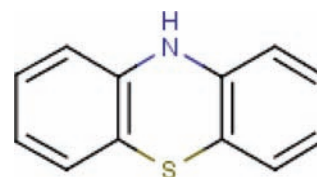


Figure 1. Chemical structure of phenothiazine.

of phenothiazine in the monosolvents at different temperatures and their mixtures are investigated.

EXPERIMENTAL METHOD

Materials. Phenothiazine with the Chemical Abstracts Service (CAS) number of 92-84-2 and International Union of Pure and Applied Chemistry (IUPAC) name of 10H-phenothiazine (purity >0.98 in mass fraction) was purchased from Merck (Germany) and recrystallized from acetone to obtain a purified sample with melting point of 456 K. The measured solubilities at 298.2 K in a number of monosolvents were also compared with available experimentally measured data from the literature (see Results and Discussion section).² Ethanol (0.999 in mass fraction) and propylene glycol (0.995 in mass fraction) were purchased from Scharlau Chemie (Spain). Double-distilled water with a conductance of <1.5 microsiemens was used.

Apparatus and Procedures. The solubility of phenothiazine in ethanol, propylene glycol, and water was measured at (298.2, 308.2, 318.2, 328.2, and 338.2) K. An excess amount of the solid was poured into monosolvents and incubated in ovens

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at (298.2 ± 0.2, 308.2 ± 0.2, 318.2 ± 0.4, 328.2 ± 0.4, and 338.2 ± 0.6) K (Behdad, Tehran, Iran), for three days. The samples were shook manually three times a day to ensure the equilibration. The results of a previous paper revealed that one day (often longer) is enough to reach equilibration condition using periodic agitation.² To prepare the binary and ternary solvent mixtures, appropriate volumes of the solvents were mixed together. The solvents' mole fractions were computed using the densities of the pure solvents. The solvent composition could be calculated to 0.001 mole fraction. The solubility of phenothiazine was determined by equilibrating an excess amount of the solid with the binary and ternary solvent mixtures using a shaker (Behdad, Tehran, Iran) which are incubated in a temperature-controlling system at 298.2 ± 0.2 K (Nabziran, Tabriz, Iran). All recrystallization and incubation processes were done under light proofed conditions. The solutions were filtered using hydrophilic Durapore filters (0.45 μm, Millipore, Ireland). All of the solutions except water were diluted by ethanol; however, water solution samples were diluted by water. For aqueous solutions at (298.2 and 308.2) K, because of very low solubility, no dilution was required, and aqueous solutions at other temperatures were diluted with water. As phenothiazine is dissolved in water significantly less than in ethanol, we have used two calibration curves for water and ethanol diluted samples. Spectrophotometric analysis was performed at 317 nm for all of the samples except of the water samples, which were assayed at 250 nm with a UV–vis spectrophotometer (Beckman DU-650, Fullerton, USA). Concentrations of the diluted solutions were computed using two UV absorbance calibration graphs with the molar absorptivities of phenothiazine ranging from $\epsilon = 3321.167$ (L·mol⁻¹·cm⁻¹) to $\epsilon = 9963.5$ (L·mol⁻¹·cm⁻¹) and concentrations ranging from (1.004·10⁻⁴ to 3.011·10⁻⁴) mol·L⁻¹ for the phenothiazine solutions diluted with ethanol and from $\epsilon = 39854$ (L·mol⁻¹·cm⁻¹) to $\epsilon = 199270$ (L·mol⁻¹·cm⁻¹) with the concentrations ranging from (5.018·10⁻⁶ to 2.509·10⁻⁵) mol·L⁻¹ for aqueous samples. Each experimental data point is the mean of at least three independent measurements with the measured mol·L⁻¹ solubilities reproducible to within the mean relative standard deviations (RSDs) of 2.3 % and 2.7 % in monosolvents at different temperatures and mixed solvents at 298.2 K, respectively. Calculated standard deviations ranged from $\sigma_{n-1} = 1.6 \cdot 10^{-7}$ to $\sigma_{n-1} = 1.1 \cdot 10^{-2}$ mol·L⁻¹ and $\sigma_{n-1} = 3.4 \cdot 10^{-8}$ to $\sigma_{n-1} = 7.5 \cdot 10^{-3}$ mol·L⁻¹ at different temperatures and mixtures of solvents, respectively. Densities of the saturated solutions were obtained using a 5 mL pycnometer with the method uncertainty of 0.001 g·cm⁻³ as a single determination.

Computational Methods. Solubility models such as modified separation of cohesive energy density (MOSCED), universal functional activity coefficient (UNIFAC), nonrandom two-liquid segment activity coefficient (NRTL-SAC), and the Jouyban–Acree models have been previously used for solubility correlation or prediction. Among these models, the Jouyban–Acree model which was exploited in this manuscript is able to correlate solubility with acceptable error. The basic Jouyban–Acree model is⁶

$$\log C_{m,T}^{\text{Sat}} = x_1 \log C_{1,T}^{\text{Sat}} + x_2 \log C_{2,T}^{\text{Sat}} + \frac{x_1 x_2}{T} \sum_{i=0}^2 J_i (x_1 - x_2)^2 \quad (1)$$

where $C_{m,T}^{\text{Sat}}$, $C_{1,T}^{\text{Sat}}$, and $C_{2,T}^{\text{Sat}}$ are the solubility (mol·L⁻¹) of the solute in a mixture of solvents, solvent 1, and solvent 2, respectively; x_1 and x_2 are the mole fractions of solvents 1 and 2 in the

absence of the solute (if $\log C_{1,T}^{\text{Sat}} > \log C_{2,T}^{\text{Sat}}$), and J_i coefficients are the solvent–solvent and solute–solvent interaction terms. These constant terms can be obtained by no-intercept least-squares regression of ($\log C_{m,T}^{\text{Sat}} - x_1 \log C_{1,T}^{\text{Sat}} - x_2 \log C_{2,T}^{\text{Sat}}$) against $(x_1 x_2)/T$, $(x_1 x_2 \cdot (x_1 - x_2))/T$, and $(x_1 x_2 \cdot (x_1 - x_2)^2)/T$ using experimentally measured solubility data in the binary solvent mixture. For calculating solubility in ternary solvent mixture, eq 1 could be extended as⁷

$$\begin{aligned} \log C_{m,T}^{\text{Sat}} = & x_1 \log C_{1,T}^{\text{Sat}} + x_2 \log C_{2,T}^{\text{Sat}} + x_3 \log C_{3,T}^{\text{Sat}} \\ & + \frac{x_1 x_2}{T} \sum_{i=0}^2 J_i (x_1 - x_2)^2 + \frac{x_1 x_3}{T} \sum_{i=0}^2 J'_i (x_1 - x_3)^2 \\ & + \frac{x_2 x_3}{T} \sum_{i=0}^2 J''_i (x_2 - x_3)^2 + \frac{x_1 x_2 x_3}{T} \sum_{i=0}^2 J'''_i (x_1 - x_2 - x_3)^2 \end{aligned} \quad (2)$$

where $C_{3,T}^{\text{Sat}}$ shows the molar solubility of the solute in pure solvent 3. The constant terms of this equation can be obtained by no-intercept least-squares regression of $\log C_{m,T}^{\text{Sat}} - (x_1 \log C_{1,T}^{\text{Sat}} + x_2 \log C_{2,T}^{\text{Sat}} + x_3 \log C_{3,T}^{\text{Sat}} + (x_1 x_2/T) \sum_{i=0}^2 J_i (x_1 - x_2)^2 + (x_1 x_3/T) \sum_{i=0}^2 J'_i (x_1 - x_3)^2 + (x_2 x_3/T) \sum_{i=0}^2 J''_i (x_2 - x_3)^2)$ against $(x_1 x_2 x_3/T)$, $(x_1 x_2 x_3 (x_1 - x_2 - x_3))/T$, and $(x_1 x_2 x_3 (x_1 - x_2 - x_3)^2)/T$ using the experimentally measured solubility data for ternary solvent mixtures and calculated J_i terms for the binary solvent mixtures.

For the solubility correlation of a solute in a solvent at different temperatures, the van't Hoff equation is used⁸

$$\log C_T^{\text{Sat}} = \frac{a}{T} + b \quad (3)$$

where C_T^{Sat} is the saturated molar solubility at different temperatures and a and b are the model constants calculated using a least-squares method.

Comparing correlated solubilities with the corresponding experimental values, the following equation was used to calculate the mean deviation (MD)

$$\text{MD} = \frac{1}{N} \sum \frac{|C_{\text{cor}} - C_{\text{expt}}|}{C_{\text{expt}}} \quad (4)$$

RESULTS AND DISCUSSION

Table 1 lists the density of the saturated solutions, experimental and correlated molar solubilities of phenothiazine along with mole fraction solubilities, and the statistical coefficients of eq 3 for water, ethanol, and propylene glycol solutions at different temperatures. Densities of the solutions gradually decrease with increased temperature which could be explained by volume expansion at higher temperatures. As expected the solubility of phenothiazine increases with increasing temperature for the three monosolvents investigated in this work. There is good agreement between the reported solubilities of phenothiazine at 298.2 K in water (7.94·10⁻⁶ mol·L⁻¹)¹ and ethanol (0.149 mol·L⁻¹ and 0.00890 mole fraction)² with the results of this work (8.63·10⁻⁶ mol·L⁻¹ in water; and 0.146 mol·L⁻¹ and 0.00868 mole fraction in ethanol). The measured data extend the available solubility databases^{9,10} of drug/drug-like molecules in monosolvent systems and could be used to develop more accurate models to predict the solubility of drug candidates, which is in demand in the pharmaceutical industry.

Table 1. Saturated Solution Densities, Experimental and Correlated Molar Solubilities, and Experimental Mole Fraction Solubility of Phenothiazine in Ethanol, Propylene Glycol, and Water at (298.2 to 338.2) K and Their a and b Constants of eq 3, Coefficient of Determination, and Mean Deviation Values

T	$\rho/\text{g}\cdot\text{cm}^{-3}$	$C_{m,T}^{\text{Sat}}/\text{mol}\cdot\text{L}^{-1}$		mole fraction solubility
		expt.	cor.	
Ethanol ($a = -661.816, b = 1.377, R^2 = 0.992, \text{MD} = 1.2\%$)				
298.2	0.797	$1.46\cdot 10^{-1}$	$1.44\cdot 10^{-1}$	$8.76\cdot 10^{-3}$
308.2	0.791	$1.65\cdot 10^{-1}$	$1.70\cdot 10^{-1}$	$1.00\cdot 10^{-2}$
318.2	0.787	$1.98\cdot 10^{-1}$	$1.98\cdot 10^{-1}$	$1.22\cdot 10^{-2}$
328.2	0.780	$2.31\cdot 10^{-1}$	$2.29\cdot 10^{-1}$	$1.45\cdot 10^{-2}$
Propylene Glycol ($a = -751.620, b = 1.285, R^2 = 0.984, \text{MD} = 3.0\%$)				
298.2	1.034	$5.59\cdot 10^{-2}$	$5.81\cdot 10^{-2}$	$4.16\cdot 10^{-3}$
308.2	1.030	$7.21\cdot 10^{-2}$	$7.02\cdot 10^{-2}$	$5.40\cdot 10^{-3}$
318.2	1.022	$8.66\cdot 10^{-2}$	$8.37\cdot 10^{-2}$	$6.56\cdot 10^{-3}$
328.2	1.017	$1.00\cdot 10^{-1}$	$9.88\cdot 10^{-2}$	$7.63\cdot 10^{-3}$
338.2	1.013	$1.11\cdot 10^{-1}$	$1.16\cdot 10^{-1}$	$8.52\cdot 10^{-3}$
Water ($a = -1254.254, b = -0.882, R^2 = 0.985, \text{MD} = 4.3\%$)				
298.2	0.996	$0.86\cdot 10^{-5}$	$0.82\cdot 10^{-5}$	$1.56\cdot 10^{-7}$
308.2	0.994	$1.09\cdot 10^{-5}$	$1.12\cdot 10^{-5}$	$1.98\cdot 10^{-7}$
318.2	0.993	$1.39\cdot 10^{-5}$	$1.50\cdot 10^{-5}$	$2.52\cdot 10^{-7}$
328.2	0.992	$1.97\cdot 10^{-5}$	$1.98\cdot 10^{-5}$	$3.58\cdot 10^{-7}$
338.2	0.991	$2.70\cdot 10^{-5}$	$2.57\cdot 10^{-5}$	$4.91\cdot 10^{-7}$

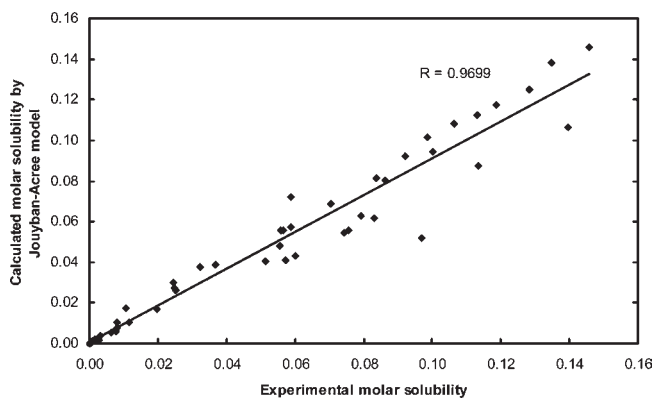


Figure 2. Calculated molar solubility of phenothiazine versus experimental values.

Table 2 gives the densities of the saturated solutions and the experimental molar and mole fraction solubilities of phenothiazine (see Figure 2) in binary and ternary solvent mixtures using the Jouyban–Acree model according to eqs 1 and 2, respectively. The generated solubility of phenothiazine in binary and ternary solvent mixtures extends the available solubility database.⁹ The correlated solubilities were compared with the corresponding experimental data and the computed MD values along with the model constants are listed in Table 3. The overall MD value is relatively high when compared with the overall MD (i.e., 5.9 %) for the correlated solubility data using the same number of model constants.¹¹ However, the MD could be considered as an acceptable error where the error of <30 % is the acceptable margin in the pharmaceutical

Table 2. Experimental Molar and Mole Fraction Solubilities of Phenothiazine in Binary and Ternary Mixture of Ethanol (1) + Propylene Glycol (2) + Water (3) and Their Densities at 298.2 K

x_1	x_2	x_3	expt. (molar)	expt. (mole fraction)	$\rho/\text{g}\cdot\text{cm}^{-3}$
1.000	-	-	0.145901	$8.753\cdot 10^{-3}$	0.797
0.816	0.184	-	0.134649	$8.759\cdot 10^{-3}$	0.820
0.663	0.337	-	0.128240	$8.880\cdot 10^{-3}$	0.837
0.535	0.465	-	0.118503	$8.526\cdot 10^{-3}$	0.858
0.425	0.575	-	0.113011	$8.376\cdot 10^{-3}$	0.877
0.330	0.670	-	0.106290	$7.941\cdot 10^{-3}$	0.907
0.247	0.753	-	0.098461	$7.468\cdot 10^{-3}$	0.925
0.174	0.826	-	0.092203	$7.044\cdot 10^{-3}$	0.946
0.110	0.890	-	0.083850	$6.416\cdot 10^{-3}$	0.968
0.052	0.948	-	0.070415	$5.274\cdot 10^{-3}$	1.009
-	1.000	-	0.055924	$4.226\cdot 10^{-3}$	1.018
0.948	-	0.052	0.100319	$5.559\cdot 10^{-3}$	0.825
0.889	-	0.111	0.083157	$4.307\cdot 10^{-3}$	0.846
0.824	-	0.176	0.057088	$2.738\cdot 10^{-3}$	0.869
0.751	-	0.249	0.024856	$1.098\cdot 10^{-3}$	0.890
0.668	-	0.333	0.010659	$4.322\cdot 10^{-4}$	0.909
0.572	-	0.428	0.008166	$2.999\cdot 10^{-4}$	0.929
0.463	-	0.538	0.006371	$2.088\cdot 10^{-4}$	0.948
0.334	-	0.666	0.003020	$8.594\cdot 10^{-5}$	0.963
0.182	-	0.818	0.000175	$4.129\cdot 10^{-6}$	0.980
-	-	1.000	0.000009	$1.628\cdot 10^{-7}$	0.996
-	0.974	0.027	0.036979	$2.743\cdot 10^{-3}$	1.013
-	0.942	0.058	0.025361	$1.833\cdot 10^{-3}$	1.011
-	0.905	0.095	0.019768	$1.389\cdot 10^{-3}$	1.008
-	0.859	0.141	0.011580	$7.826\cdot 10^{-4}$	1.007
-	0.803	0.197	0.007907	$5.094\cdot 10^{-4}$	1.005
-	0.731	0.269	0.003285	$1.982\cdot 10^{-4}$	1.003
-	0.636	0.364	0.001735	$9.518\cdot 10^{-5}$	1.002
-	0.505	0.495	0.000638	$3.018\cdot 10^{-5}$	1.001
-	0.312	0.688	0.000389	$1.407\cdot 10^{-5}$	0.999
0.186	0.768	0.046	0.075689	$6.055\cdot 10^{-3}$	0.863
0.103	0.846	0.051	0.060069	$4.623\cdot 10^{-3}$	0.922
0.302	0.623	0.075	0.096862	$6.680\cdot 10^{-3}$	0.928
0.044	0.912	0.044	0.032218	$2.710\cdot 10^{-3}$	0.865
0.494	0.408	0.098	0.074487	$4.863\cdot 10^{-3}$	0.866
0.191	0.786	0.024	0.058986	$4.728\cdot 10^{-3}$	0.873
0.161	0.829	0.010	0.086227	$7.171\cdot 10^{-3}$	0.867
0.427	0.440	0.133	0.051492	$3.335\cdot 10^{-3}$	0.868
0.053	0.880	0.066	0.024630	$1.971\cdot 10^{-3}$	0.887
0.230	0.759	0.011	0.113575	$8.793\cdot 10^{-3}$	0.908
0.183	0.756	0.061	0.055583	$4.785\cdot 10^{-3}$	0.790
0.234	0.723	0.044	0.079084	$5.779\cdot 10^{-3}$	0.927
0.186	0.768	0.046	0.056494	$4.180\cdot 10^{-3}$	0.928
0.141	0.580	0.279	0.008187	$4.487\cdot 10^{-4}$	1.017
0.647	0.333	0.020	0.139559	$9.047\cdot 10^{-3}$	0.884
0.029	0.964	0.007	0.058752	$5.086\cdot 10^{-3}$	0.876

area.^{12,13} It should be added that a number of data points produced relatively high deviations, including the solvent compositions of ($x_1 = 0.302, x_2 = 0.623, x_3 = 0.075$), ($x_1 = 0.334, x_2 = 0.000, x_3 = 0.666$), ($x_1 = 0.000, x_2 = 0.505, x_3 = 0.495$), ($x_1 = 0.182, x_2 = 0.000,$

Table 3. Numerical Values of the Jouyban–Acree Model Constants (J Terms) Computed Using Molar Solubilities, Number of Data Points in Each Set (N), the Mean Deviation (MD) for the Correlated Solubilities of Phenothiazine in Binary and Ternary Mixture of Ethanol + Propylene Glycol + Water Using Jouyban–Acree Model, and Their Overall MD Value

solvent 1	solvent 2	solvent 3	J terms	N	100 · MD	
ethanol	propylene glycol		128.142	11	1.6	
			–149.777			
			179.885			
propylene glycol	water		132.636	11	13.2	
			–847.486			
			NS ^a			
ethanol	water		927.150	11	25.1	
			–821.184			
			NS ^a			
ethanol	propylene glycol	water	1902.292	16	16.7	
						NS ^a
						NS ^a
				overall	14.2	

^a NS: not significant.

$x_3 = 0.818$), and ($x_1 = 0.667, x_2 = 0.000, x_3 = 0.333$) which produced the percent deviations of (34.1, 41.9, 44.4, 54.3, and 64.4) %, respectively. By excluding these five data points the overall MD reduces to 10.6 %; however, to avoid any bias, these data points have not been excluded from the calculations. The Jouyban–Acree model could be trained at one temperature (usually 298.2 K) and then used to predict the solubility of phenothiazine in the mixed solvents at other temperatures of interest employing the experimental data in monosolvents at these temperatures as shown in previous works.^{6,14} The generated data in monosolvents at various temperatures of Table 1 and the model constants of Table 3 could be combined to provide a predictive computational method for the solubility of phenothiazine in the ethanol + propylene glycol + water mixtures for the solubilization/desolubilization of the solute using solvent composition and/or temperature changes. This prediction method facilitates the process design and speed up the formulation and/or crystallization investigations in the pharmaceutical industry.

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