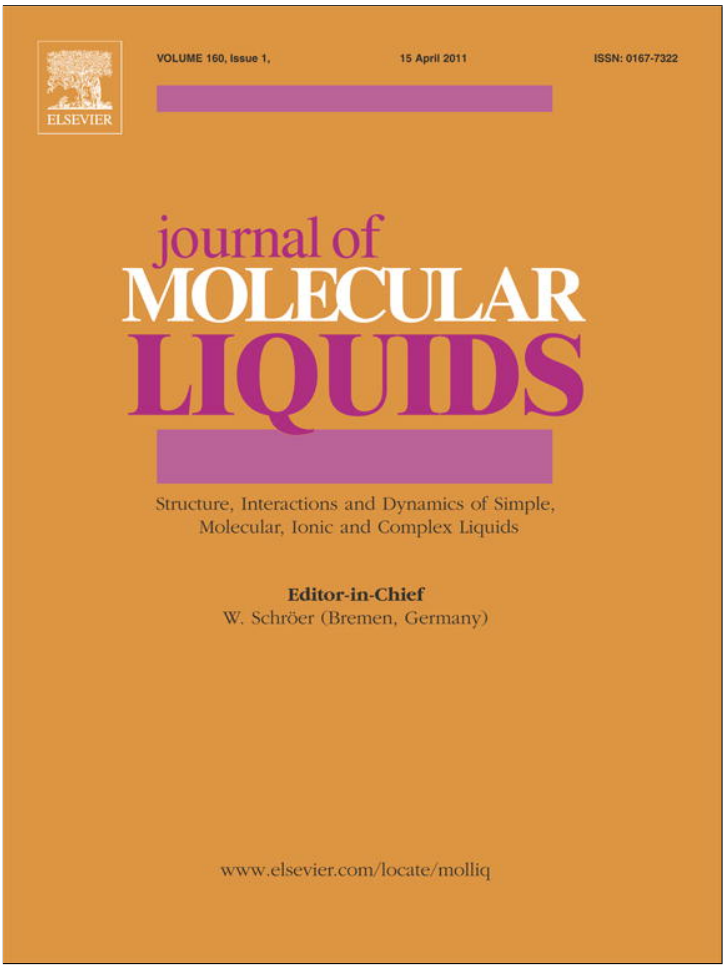

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Solubility of salicylic acid in ethanol, propylene glycol, and *N*-methyl-2-pyrrolidone at various temperatures and their binary mixtures at 298.2 K

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ABSTRACT

Solubility of salicylic acid in ethanol (EtOH), propylene glycol (PG), and *N*-methyl-2-pyrrolidone (NMP) at temperatures of 298.2, 308.2, 318.2, and 328.2 K and in the binary mixtures of EtOH + PG, NMP + EtOH, and NMP + PG were reported at 298.2 K. The generated data in mono-solvents at different temperatures were fitted to van't Hoff plot, the data in solvent mixtures were fitted to the Jouyban–Acree model, and the overall mean deviations were 3.5 and 0.8%, respectively.

1. Introduction

Salicylic acid or 2-hydroxybenzoic acid with the CAS number of 69-72-7 is an inhibitor of cyclo-oxygenases 1 and 2, and it is able to reduce the formation of prostaglandins and thromboxanes from arachidonic acid. This alteration in the production of prostaglandins and thromboxanes is employed in the therapeutics to manage majority of disorders that originated from inflammations. Salicylic acid is a precursor of a well-known drug, aspirin, and also it is an active metabolite produced in the biological fluids. Salicylic acid is one of the active components of cosmetic products. In addition to its applications in the biomedical sciences, it has an important position in plant sciences in which it has been used as a plant growth regulator. Various methods were employed to maximize plant growth and productivity under environmental stress conditions such as salt stress. One of the simple methods is to induce salt tolerance through exogenous plant growth regulating compounds. Among these compounds, salicylic acid is the most extensively studied compound [1]. Hayat et al. [2] reviewed the effects of salicylic acid on the plant against different biotic and abiotic stresses.

Salicylic acid is a compound slightly soluble in water according to the United States Pharmacopeia [3], and its solubilities in various mono-solvents and mixed solvents were investigated. The solubility of salicylic acid in a variety of solvent mixtures (e.g., binary and ternary mixtures) is very important because these mixtures are frequently used in purification processes and also in the preparation of liquid pharmaceutical formulations. There is a significant lack of solubility data for most of pharmaceutical compounds and efforts are devoted to obtain a number of mathematical models for solubility prediction of pharmaceutical compounds in the mixture of solvent. A summary of the models is found in the literature [4].

For correlation of experimental solubility data in mono-solvents at different temperatures, the van't Hoff equation is used [5]

$$\ln C_T^{\mathrm{Sat}} = A + \frac{B}{T} \tag{1}$$

where C_T^{Sat} is the saturated molar solubility at temperature T, A and B are the model constants calculated using a least square method.

For solubility correlation/prediction in the solvent mixtures, one of the most accurate studied models is the Jouyban–Acree model. The model is shown as [4]

$$\ln C_{m,T}^{\mathrm{Sat}} = \varphi_1 \ln C_{1,T}^{\mathrm{Sat}} + \varphi_2 \ln C_{2,T}^{\mathrm{Sat}} + \frac{\varphi_1 \varphi_2}{T} \sum_{i=0}^{2} J_i (\varphi_1 - \varphi_2)^i \tag{2}$$

where $C_{m,T}^{\mathrm{Sat}}$ is the solute solubility (mol L^{-1}) in the binary solvent mixtures; ϕ_1 and ϕ_2 are the volume fractions of solvents 1 and 2 in the absence of the solute; $C_{1,T}^{\mathrm{Sat}}$ and $C_{2,T}^{\mathrm{Sat}}$ denote mol L^{-1} solubility of the solute in mono-solvents 1 and 2 at temperature T (K); and J_i coefficients are the solvent–solvent and solute–solvent interaction

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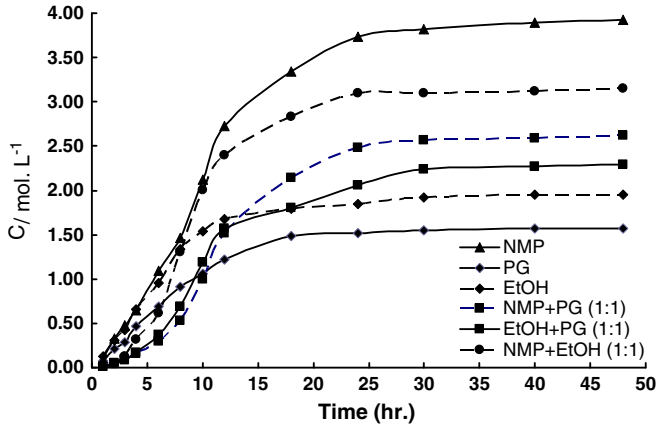

Fig. 1. Dissolution rate profile of salicylic acid in different solvent systems.

terms. These constant terms could be calculated using a no intercept least square regression of

$$\left(\ln C_{m,T}^{Sat} - \phi_1 \ln C_{1,T}^{Sat} - \phi_2 \ln C_{2,T}^{Sat}\right)$$

against

$$\frac{\varphi_1\varphi_2}{T}, \frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)}{T}, and \frac{\varphi_1\varphi_2(\varphi_1-\varphi_2)^2}{T}$$

using experimental solubility data in the binary solvent mixture [6]. Eq. (2) could be written in its simpler version:

$$\ln C_m^{Sat} = \varphi_1 \ln C_1^{Sat} + \varphi_2 \ln C_2^{Sat} + \varphi_1\varphi_2 \sum_{i=0}^{2} B_i(\varphi_1-\varphi_2)^i \quad (3)$$

which is used in many previous works by our group and several other authors. However, we recommend to use Eq. (2), since it could be trained at one temperature (usually 298.2 K) and then used to predict the solubility of the solute in the mixed solvents at other temperatures of interest employing the experimental data in mono-solvents at these temperatures [7,8].

The aims of this work are (1) to report the experimental solubility of salicylic acid in ethanol (EtOH), propylene glycol (PG), and *N*-methyl-2-pyrrolidone (NMP) at 298.2, 308.2, 318.2, and 328.2 K; (2) to report the experimental solubility of salicylic acid in EtOH + PG, NMP + EtOH, and NMP + PG at 298.2 K; and (3) to provide the Jouyban–Acree model constants for representing the solubility of salicylic acid in the investigated solvent mixtures.

2. Experimental

2.1. Materials

Salicylic acid (>0.980 in mass fraction) was purchased from Merck (Germany) and was used as received from the company. The measured solubilities in a number of mono-solvents were compared with corresponding data from the literature. EtOH (mass fraction purity of 0.995), NMP (0.995 in mass fraction), and PG (0.995 in mass fraction) were purchased from Merck (Germany).

2.2. Apparatus and procedures

The solvent mixtures were prepared by mixing the appropriate volumes of the solvents with the uncertainty of 0.1 mL. The solubility of salicylic acid was determined by equilibrating an excess amount of the solid with the binary solvent mixtures at 298.2 K using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature-controlling system with the uncertainty of 0.2 K (Nabziran, Tabriz, Iran). The saturated solubility equilibrium was got in a number of solvent systems, and it was verified by solubility measurements at different time intervals and was reached after 2 days (Fig. 1). The solutions were filtered using Durapore filters (0.45 μm, Millipore, Ireland), and then diluted with EtOH + water mixture (96:4 v/v) and absorbance of these solutions was recorded at 236 nm using a UV–Vis spectrophotometer (Beckman DU-650, Fullerton, CA, USA). Concentrations of the dilute solutions were determined from a UV absorbance calibration graph with the molar absorptivities of salicylic acid ranging from $\varepsilon = 6353.5$ to $6952.0\ L \cdot mol^{-1} \cdot cm^{-1}$ for concentrations ranging from 7.24×10^{-5} to $2.17 \times 10^{-4}\ mol \cdot L^{-1}$. Each experimental data point is an average of at least three experimental measurements with the measured mol·per liter solubilities being reproducible to within the mean relative standard deviations (RSDs) of 1.5% (the RSDs vary between 0.6 and 3.5%). Calculated standard deviations ranged from $\sigma_{n-1} = 0.0037$ to $0.026\ mol \cdot L^{-1}$. Densities of the saturated solutions of salicylic acid in mono-solvents at different temperatures were measured using a 5-mL pycnometer with the uncertainty of $0.001\ g \cdot cm^{-3}$.

2.3. Computational methods

The solubility of salicylic acid in mono-solvents was fitted to Eq. (1) to get *A* and *B* values using them to compute the solubilities and the mean percentage deviations (MPD). The B_i terms of the Jouyban–Acree model for solubility of salicylic acid in binary solvents were computed using a no intercept least square analysis. The model constants of Eq. (3) along with the experimental solubility of salicylic acid in mono-solvents were employed to calculate the solubilities. All calculated C_m^{Sat} values were compared with the corresponding

Table 1
Experimental and calculated molar solubilities of salicylic acid in mono-solvents at different temperatures along with the back-calculated data, *A* and *B* values, mean percentage deviations (MPD), and the density (mL^{-1}) of the saturated solutions.

Solvent	Solubility										
	298.2		308.2		318.2		328.2		*A*	*B*	MPD
	Experimental	Calculated	Experimental	Calculated	Experimental	Calculated	Experimental	Calculated			
EtOH	1.9749	1.9663	2.5003	2.5874	3.5422	3.3465	4.1478	4.2609	9.135	−2522.063	3.0
NMP	3.9340	4.0255	5.74865	5.6905	8.29550	7.8710	10.2581	10.6739	12.059	−3180.274	3.1
PG	1.5919	1.6302	2.14416	2.1566	3.06131	2.8031	3.3819	3.5857	9.111	−2570.680	4.4
										Overall	3.5
					Density						
EtOH	0.9080		0.9220		0.9540		0.9640				
NMP	1.1160		1.1240		1.1360		1.1540				
PG	1.0620		1.0700		1.0880		1.0960				

Table 2
Experimental solubility of salicylic acid data taken from the literature and the corresponding generated data in parentheses.

Solvent	Solubility	Solubility unit	Temperature	Reference
EtOH	2.1109 (1.9749)	mol·L^{-1}	298.2 K	[9]
PG	1.8017 (1.5919)	mol·L^{-1}	298.2 K	[9]
EtOH	0.1450 (0.1251)	Mole fraction	298.15 K	[10]
EtOH	0.1397 (0.1251)	Mole fraction	298.15 K	[11]
EtOH	0.1386 (0.1251)	Mole fraction	298 K	[12]
EtOH	0.3851 (0.1663)	Mole fraction	308 K	[12]
EtOH	0.4274 (0.2596)	Mole fraction	318 K	[12]
EtOH	0.4779 (0.3279)	Mole fraction	328 K	[12]

experimental solubilities and MPD was calculated as an accuracy criterion by

$$\mathrm{MPD} = \frac{100}{N}\sum \frac{\left|\left(C_{m,T}^{\mathrm{Sat}}\right)_{\mathrm{Predicted}} - \left(C_{m,T}^{\mathrm{Sat}}\right)_{\mathrm{Experimental}}\right|}{\left(C_{m,T}^{\mathrm{Sat}}\right)_{\mathrm{Experimental}}} \quad (4)$$

in which N is the number of data points in each set.

3. Results and discussion

Table 1 lists the experimental solubility of salicylic acid in four investigated mono-solvents at different temperatures, along with the back-calculated solubilities using Eq. (1), A and B values, and the densities of the respective saturated solutions. The solubility data obtained agree with the published solubility data of the solute at 298.2 K in EtOH and PG as shown in Table 2 and slightly different data obtained at higher temperatures [9–12]. The data were fitted to Eq. (1), and the A and B terms were computed. Using these terms, it is possible to predict the solubility of salicylic acid at different temperatures using interpolation technique. The back-calculated data using trained versions of Eq. (1) showed good agreement with the experimental data and the overall MPD was 3.5%.

Table 3
Experimental and calculated molar solubilities of salicylic acid in binary solvent mixtures at 298.2 K.

φ_1	Experimental (mol·L^{-1})	Calculated (mol·L^{-1})
EtOH (1) + PG (2)		
0.000	1.5919	1.5919
0.100	1.6410	1.6117
0.200	1.7582	1.7341
0.300	1.8746	1.9107
0.400	2.0383	2.0953
0.500	2.2548	2.2419
0.600	2.4023	2.3142
0.700	2.2883	2.2981
0.800	2.1796	2.2085
0.900	2.0699	2.0836
1.000	1.9749	1.9749
NMP (1) + EtOH (2)		
0.000	1.9749	1.9749
0.100	2.1988	2.2089
0.200	2.4400	2.4414
0.300	2.6560	2.6684
0.400	2.9264	2.8863
0.500	3.0910	3.0924
0.600	3.2786	3.2852
0.700	3.4168	3.4642
0.800	3.6514	3.6303
0.900	3.8165	3.7857
1.000	3.9341	3.9340
NMP (1) + PG (2)		
0.000	1.5919	1.5919
0.100	1.7950	1.8050
0.200	1.9864	1.9935
0.300	2.1654	2.1712
0.400	2.3984	2.3538
0.500	2.5591	2.5556
0.600	2.7463	2.7874
0.700	3.0243	3.0539
0.800	3.3969	3.3501
0.900	3.6635	3.6567
1.000	3.9340	3.9340

Table 4
Numerical values of the model constants, number of data points in each set (N), the mean percentage deviation (MPD) for the calculated solubilities of salicylic acid in NMP, EtOH, and PG mixtures and their overall values.

		B terms[a]	N	MPD
NMP	EtOH	0.180 −0.038 –[b] 0.036	11	0.5
NMP	PG	−0.054 0.141 0.408	11	0.7
EtOH	PG	0.254 −0.388	11	1.3
Overall				0.8

[a] The orders of B terms are B_0, B_1, and B_2.
[b] The constant is not statistically significant.

Table 3 lists the experimental and calculated solubilities of salicylic acid in three non-aqueous binary solvents. The maximum solubility was observed for neat NMP (3.9340 mol·L^{-1}) and the minimum value was observed in neat PG. All investigated binary solvents enhanced the low aqueous solubility of salicylic acid (0.0137 mol·L^{-1}) [9] and could be used in crystallization/solubilization procedures in the pharmaceutical industries. The generated data were fitted to Eq. (3), and the B terms were computed. Using these terms and the experimental solubility at T, it is possible to predict the solubility at temperature T and all binary solvent compositions. The obtained MPD values for $T = 298.2$ K were listed in Table 4, in which the overall MPD was 0.8%.

As a conclusion, the solubility of salicylic acid in three non-aqueous solvents at various temperatures and their binary mixtures at 298.2 K were reported. The data extend the available solubility database of pharmaceuticals [13] and could be used in pharmaceutical industry.

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