

Thermodynamic Properties of Sulfasalazine in Binary Aqueous Mixtures of Polyethylene Glycol 600 and 1,2-Propanediol: Computational Modeling and Solubilization

S. Hamzehlou^{a,b}, E. Rahimpour^{c,d}, A. Fathi Azarbayjani^{b,e,*} and A. Jouyban^{c,f}

^a Student Research Committee, Urmia University of Medical Sciences, Urmia, Iran

^b Department of Pharmaceutics, School of Pharmacy, Urmia University of Medical Sciences, Urmia, Iran

^c Pharmaceutical Analysis Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

^d Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

^e Experimental and Applied Pharmaceutical Research Center, Urmia University of Medical Sciences, Urmia, Iran

^f Pharmaceutical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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The aim of this work is to investigate the temperature dependant solubility of sulfasalazine (Sulf) in binary solutions of polyethylene glycol (PEG) 600 and 1,2-propanediol. Solubility studies were carried out using the saturation shake-flask method between 298.15 K and 313.15 K. Generally, Sulf solubility increase was directly proportional to temperature and mass fraction of the co-solvent. The highest drug solubility was observed in pure PEG-600 (56.67×10^{-3} M) while the lowest drug solubility was observed in pure water (0.14×10^{-3} M). Drug solubility in pure 1,2-propanediol was 3.56×10^{-3} M. The same results were observed at each temperature. Apparent thermodynamic parameters including Gibbs free energy, enthalpy, and entropy, were calculated. Analysis indicates endothermic solubilization in aqueous mixtures in each of the investigated binary solvent mixtures. Overall, the findings of this work suggest that the various co-solvents could be used to solubilize poorly water-soluble drugs such as Sulf. The experimental solubility data of Sulf were regressed using the van't Hoff, the mixture response surface, the Jouyban-Acree, the Jouyban-Acree-van't Hoff, and the modified Wilson models.

Keywords: Sulfasalazine, Solubility, PEG-600, 1,2-Propanediol, Apparent thermodynamic parameters

INTRODUCTION

Sulfasalazine (Sulf) is a class IV biopharmaceutical classification system sulfonamide with very low aqueous solubility and permeability (Fig. 1). About 30% of Sulf is adsorbed in the upper gastrointestinal tract and the rest is adsorbed in the colon following bacterial metabolism. This drug is used for the treatment of various disorders including rheumatoid arthritis and Crohn's disease [1,2].

Solubility enhancement studies on this drug are scarce. Sulf suspensions have been developed for improved drug dissolution [1].

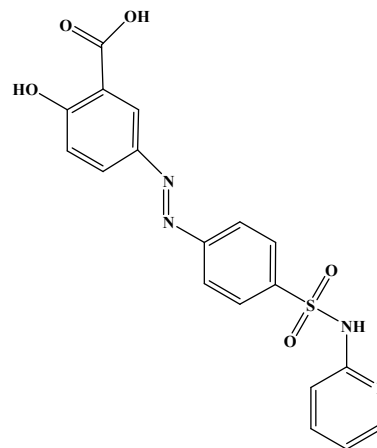


Fig. 1. Chemical structure of Sulf.

*Corresponding author. E-mail: fathi-a@umsu.ac.ir

Recrystallization of Sulf has been investigated as a method to enhance its saturated solubility [2]. Sulf solubility in some mono-solvents including water, methanol, ethanol, 1-propanol, acetone, and chloroform was determined from 15 to 45 °C [3]. In another study, its solubility was investigated in some binary aqueous mixtures including ethanol, 1,2-propanediol, glycerol, methanol, acetone, and polyethylene glycol (PEG) 400 as co-solvents at 298.15 K [4]. Specifically, there is a lack of temperature-dependent data on Sulf solubility in cosolvent systems. The aim of this work is to evaluate the effect of temperature on the solubility of Sulf in PEG-600 + water and 1,2-propanediol + water between 298.15 K and 313.15 K. The apparent thermodynamic properties of Sulf were investigated based on van't Hoff and Gibbs method. In addition, experimental solubility data were correlated with some mathematical models.

MATERIALS AND METHODS

Materials

Sulf was purchased from Zahravi Pharmaceutical, Tabriz, Iran. PEG-600 and 1,2-propanediol with mass fraction purity of 99.5% were obtained from Merck (Darmstadt, Germany). Deionized water was collected from Mili-Q unit (Direct Q, Millipore, France).

Sulf Solubility in Binary Aqueous Mixtures of PEG-600 and 1,2-Propanediol

The solubility of Sulf in different temperatures was measured using Higuchi and Connors saturation shake-flask method [5]. Solubility was measured at various temperatures from 298.15 to 313.15 K under atmospheric pressure. Experiments were prepared in triplicate. Briefly, an excess amount of the drug was dispersed in various mass ratios of binary solvent mixture ($w_1 = 0.1-0.9$) and allowed to equilibrate for 24 h on a shaker (Behdad, Tehran, Iran). An electronic balance with a standard uncertainty of 0.0001 g was used to weigh the mass fraction of the solvent mixture (Sartorius Scientific Instrument; model: BSA224S. All samples were centrifuged at 10000 rpm for about 20 minutes, the supernatant was collected and diluted and concentration was quantified spectrophotometrically at 365 nm using a double beam spectrophotometer (Cecil CE 7200, 7000 series, U.K.). Standard solutions (0.01-0.05 M) were prepared in methanol: water with a ratio of 1:1 [6].

Apparent Thermodynamic Parameters

Apparent thermodynamic parameters including standard

apparent enthalpy (ΔH_{sol}^o), standard apparent Gibbs free energy (ΔG_{sol}^o), and standard apparent entropy (ΔS_{sol}^o) were determined.

Thermodynamic changes of the solution are obtained by means of the harmonic temperature, T_{hm} , defined as [7]:

$$T_{hm} = n / \sum_{i=1}^n (1/T) \quad (1)$$

n denotes the number of temperatures analyzed. ΔH_{sol}^o was calculated from the slope of $\ln C$ as a function of $\frac{1}{T} - \frac{1}{T_{hm}}$ by

applying van't Hoff expression:

$$\frac{\partial \ln C}{\partial \left(\frac{1}{T} - \frac{1}{T_{hm}} \right)_p} = -\frac{\Delta H_{sol}^o}{R} \quad (2)$$

where C is the molar solubility in the co-solvent system, T denotes the absolute temperature (K), and R represents the gas constant.

The apparent standard Gibbs energies, ΔG_{sol}^o , for the dissolution process were calculated at T_{hm} by [7]:

$$\Delta G_{sol}^o = -RT_{hm} \times \text{intercept} \quad (4)$$

Where the intercept is obtained by regressing $\ln C$ as a function of $\frac{1}{T} - \frac{1}{T_{hm}}$. The apparent dissolution entropy, ΔS_{sol}^o , is obtained as

$$\Delta S_{sol}^o = -\Delta H_{sol}^o - T_{hm} \Delta G_{sol}^o \quad (5)$$

$$\Delta S_{sol}^o = \frac{(\Delta H_{sol}^o - \Delta G_{sol}^o)}{T_{hm}} \quad (6)$$

Lastly, the relative contributions of enthalpy (ζ_H) and entropy (ζ_{TS}) to the Gibbs free energy were determined by applying the following equations [7]:

$$\zeta_H = \frac{|\Delta H_{sol}^o|}{(|\Delta H_{sol}^o| + |T\Delta S_{sol}^o|)} \quad (7)$$

$$\zeta_{TS} = \frac{|T\Delta S_{sol}^o|}{(|\Delta H_{sol}^o| + |T\Delta S_{sol}^o|)} \quad (8)$$

Computational Models

The experimentally obtained data was fitted to some co-solvency models reported for binary systems as described below [8-11]. The van't Hoff equation:

$$\ln C = A + \frac{B}{T} \quad (9)$$

The mixture response surface (MRS):

$$\ln C_m = \beta_1 w'_1 + \beta_2 w'_2 + \beta_3 \left(\frac{1}{w'_1} \right) + \beta_4 \left(\frac{1}{w'_2} \right) + \beta_5 w'_1 w'_2 \quad (10)$$

The Jouyban-Acree model,

$$\ln C_{m,T} = w_1 \ln C_{1,T} + w_2 \ln C_{2,T} + \frac{w_1 w_2}{T} \sum_{i=0}^2 J_i (w_1 - w_2)^i \quad (11)$$

The Jouyban-Acree-van't Hoff equation:

$$\ln C_{m,T} = w_1 \left(A_1 + \frac{B_1}{T} \right) + w_2 \left(A_2 + \frac{B_2}{T} \right) + \frac{w_1 w_2}{T} \sum_{i=0}^2 J_i (w_1 - w_2)^i \quad (12)$$

and the modified Wilson:

$$-\ln C_m = 1 - \frac{w_1 [1 + \ln(C_1)]}{w_1 + w_2 \lambda_{12}} - \frac{w_2 [1 + \ln(C_2)]}{w_1 \lambda_{21} + w_2} \quad (13)$$

Where x_m , x_1 and x_2 represent the solubility data obtained for the mixture, solvent 1 and solvent 2 respectively. W_1 and W_2 denote the mass fractions of mono-solvents 1 and 2 respectively. T is the temperature in Kelvin unit. A , B , A_1 , B_1 , A_2 , B_2 , λ_{12} , λ_{21} and J_i are the model's constants obtained by simple regression.

The trained equations with experimental solubility data was used to back-calculate the Sulf solubility data. The mean relative deviation (MRD%) of the predicted solubility data is calculated using Eq. (14) and the model accuracy is reported.

$$MRD\% = \frac{100}{N} \sum \left(\frac{|Calculated\ Value - Observed\ Value|}{Observed\ Value} \right) \quad (14)$$

N is the number of data points.

RESULTS AND DISCUSSIONS

Experimental Solubility of Sulf and Data Modeling

The measured solubility data in different binary solvent mixtures at respective temperatures are given in Table 1.

Table 1. Experimental Solubility of Sulf in a) 1,2-Propanediol (w_1) + Water and b) PEG-600 (w_1) + Water Cosolvent Mixtures Expressed as Molar Solubility at Different Temperatures

1,2-Propanediol (w_1)	$c_m 10^{-3}$ M			
	298.15 K	303.15 K	308.15 K	313.15 K
0.000	0.144	0.165	0.187	0.203
0.100	0.175	0.202	0.230	0.253
0.200	0.218	0.241	0.279	0.319
0.300	0.312	0.337	0.425	0.457
0.400	0.447	0.502	0.584	0.655
0.500	0.586	0.675	0.777	0.879
0.600	0.879	1.012	1.156	1.337
0.700	1.266	1.477	1.690	1.936
0.800	1.759	2.074	2.392	2.716
0.90	2.257	2.698	3.179	3.518
1.000	3.567	4.174	4.921	5.632

PEG 600 (w_1)	$c_m 10^{-3}$ M			
	298.15 K	303.15 K	308.15 K	313.15 K
0.000	0.145	0.165	0.187	0.203
0.100	0.118	0.218	0.231	0.258
0.200	0.264	0.292	0.346	0.384
0.300	0.530	0.616	0.691	0.783
0.400	1.440	1.656	1.891	2.166
0.500	3.171	3.719	4.265	4.855
0.600	6.975	8.254	9.525	10.819
0.700	13.246	15.768	18.083	20.986
0.800	27.819	33.375	39.463	43.865
0.900	50.079	58.053	68.339	79.7070
1.000	57.671	67.246	80.649	94.293

*The relative standard uncertainty of the mass fraction of co-solvent in the binary solvent mixture is $u(w) = 0.0001$.

In general, a linear increase is seen in both cosolvent systems and drug solubility increases with the addition of the cosolvent and elevation of temperature. The maximum solubility of sulfasalazine was obtained in neat PEG-600 and 1,2-propanediol. Results of the experimental solubility indicate the highest drug solubility value in pure PEG-600 (56.67×10^{-3} M) and 1,2-propanediol (3.56×10^{-3} M) at each temperature studied.

The dielectric constant value of the PEG-600 (10.71) and 1,2-propanediol (32.00) at 25 °C are lower with respect to neat water (78.36) [12,13]. The lowest solubility data was observed in pure

Table 2. Model parameters and the corresponding *MRD%* for back-calculate Sulf solubility data using the van't Hoff Model

1,2 - Propanediol (w_1) + water			
w_1	A	B	MRD%
0.00	-1.664	-2138.039	1.1
0.10	-0.943	-2295.383	1.0
0.20	-0.451	-2383.103	1.1
0.30	-0.187	-2460.996	1.7
0.40	0.409	-2423.373	0.7
0.50	1.064	-2535.779	0.2
0.60	1.669	-2596.773	0.3
0.70	2.156	-2631.590	0.3
0.80	2.724	2701.623	0.7
0.90	3.300	-2796.823	1.7
1.00	3.980	-2867.150	0.4
Overall			0.8
PEG-600 (w_1) + water			
w_1	A	B	MRD%
0.00	-1.664	-2138.039	1.1
0.10	-1.391	-2149.129	2.5
0.20	-0.161	-2411.403	1.3
0.30	0.518	-2401.667	0.6
0.40	1.960	-2535.902	0.1
0.50	3.125	-2645.894	0.5
0.60	4.297	-2729.692	0.8
0.70	5.192	-2835.187	0.6
0.80	6.053	-286.166	1.6
0.90	6.753	-2908.220	0.4
1.00	7.516	-3093.873	0.6
Overall			0.9

water (0.14×10^{-3} M) at 298.15 K mainly due to the high polarity. The solubility enhancement in pure PEG-600 was 404-folds higher relative to its solubility in neat water. A similar trend is reported in previous literature where PEG 400 and 1,2-propanediol caused a linear increase in Sulf solubility [3].

Model parameters were used to back-calculate the solubility data employing some mathematical models including the van't Hoff equation, MRS, the Jouyban-Acree and the Jouyban-Acree-van't Hoff, and the modified Wilson models. Tables 2 to 5 present the model's parameters *MRD%* of back-calculated solubility data.

The overall *MRD%* values for back-calculated Sulf solubility data in the mixtures of 1,2-propanediol + water were 0.8% for the van't Hoff equation, 3.4% for the MRS model, 2.6% for Jouyban-Acree model, 2.6 for the Modified Wilson model, and 2.7% for Jouyban-Acree-van't Hoff model.

Also, overall *MRD%* values Sulf solubility data in PEG-600 + water was 0.9% for the van't Hoff equation, 8.9% for the MRS model, 5.4% for Jouyban-Acree model, 18.2 for the Modified Wilson model, and 5.5% for Jouyban-Acree-van't Hoff model. Low *MRD%* values for the studied models demonstrate the reliability of the investigated models to predict solubility data for pharmaceutical industries.

Table 3. The MRS Model Parameters at Relative Temperatures and the *MRD%* Back-calculate Sulf Solubility Data

1,2 - Propanediol (w_1) + water						
T (K)	β_1	β_2	β_3	β_4	β_5	MRD%
298.2	-5.618	-9.170	0.005	0 ^a	0 ^a	3.3
303.2	-5.447	-9.066	0.006	0 ^a	0 ^a	3.5
308.2	-5.293	-8.923	0.005	0 ^a	0 ^a	3.4
313.2	-5.161	-8.818	0.005	0 ^a	0 ^a	3.6
Overall MRD%						3.4
PEG-600 (w_1) + water						
T (K)	β_1	β_2	β_3	β_4	β_5	MRD%
298.2	-1.830	-9.851	0.018	-0.018	0 ^a	8.3
303.2	1.658	-9.704	0.017	-0.018	0 ^a	9.7
308.2	-1.481	-9.613	0.018	-0.018	0 ^a	8.8
313.2	-1.339	-9.499	0.017	-0.018	0 ^a	8.7
Overall MRD%						8.9

^aNot statistically significant (p -value >0.05).

Table 4. Parameters of the Jouyban-Acree and Jouyban-Acree-van't Hoff Models for Back-calculate Sulf Solubility Data

1,2-Propanediol (w ₁) + water			
Jouyban-Acree		Jouyban-Acree-van't Hoff	
J ₀	-184.913	A ₁	3.980
J ₁	179.346	B ₁	-2867.150
J ₂	-277.933	A ₂	-1.664
		B ₂	-2138.039
		J ₀	184.598
		J ₁	178.972
		J ₂	-277.145
MRD%	2.6		2.7
PEG-600 (w ₁) + water			
Jouyban-Acree		Jouyban-Acree-van't Hoff	
J ₀	70.114	A ₁	7.516
J ₁	1619.576	B ₁	-3093.873
J ₂	-324.499	A ₂	-1.664
		B ₂	-2138.039
		J ₀	70.461
		J ₁	1619.262
		J ₂	-323.630
MRD%	5.4		5.5

Table 5. The Modified Wilson Model Parameters at the Investigated Temperatures and the MRD% for Back-calculate Sulf Solubility Data

1,2-Propanediol (w ₁) + water			
T (K)	λ ₁₂	λ ₂₁	MRD%
298.2	0.517	1.337	2.6
303.2	0.475	1.384	2.8
308.2	0.521	1.304	2.6
313.2	0.525	1.296	2.6
Overall			2.6
PEG-600 (w ₁) + water			
T (K)	λ ₁₂	λ ₂₁	MRD%
298.2	15.047	0.631	17.5
303.2	17.349	0.651	18.0
308.2	21.351	0.664	18.8
313.2	25.329	0.689	18.4
Overall			18.2

Apparent Thermodynamic Parameters

The apparent thermodynamic parameters for the drug dissolution process in PEG-600 + water and 1,2-propanediol + water along with R² values are summarized in Table 6. ΔH_{sol}^o value for the dissolution of Sulf in neat water, neat PEG-600, neat 1,2-propanediol as well as in the different mass ratios of the aqueous binary mixtures were observed to be positive in the range of 18.45-25.71 kJ mol⁻¹. In both solvent systems, ΔH_{sol}^o increased with the mass fraction of the cosolvent in the aqueous system and the maximum ΔH_{sol}^o value was observed in neat PEG-600 and 1,2-propanediol at 25.71 and 23.92 kJ mol⁻¹. ΔS_{sol}^o values follow a similar trend as the enthalpy of the solution and increase from pure water to pure PEG-600 or 1,2-propanediol. The maximum ΔG_{sol}^o is found in neat water at 22.07 kJ mol⁻¹. The lowest ΔG_{sol}^o value was obtained in pure PEG-600 and 1,2-propanediol, indicating that minimum energy is used for Sulf solubilization in these neat solvents.

The standard Gibbs free energy was positive and decreased from neat water to neat cosolvent. This indicates that as the concentration of the co-solvent increases, less energy is needed to generate the cavity to accommodate the drug molecule. The positive ΔH_{sol}^o and ΔG_{sol}^o values indicate that the process is always endothermic in both solvent mixtures. Positive ΔG_{sol}^o value represents non-spontaneous dissolution process. Calculations were based on experimental solubility data obtained at temperatures 298.15-313.15 and local atmospheric pressure. This is supported by the relative contribution of the enthalpy toward the solution processes. The entropy of mixing was negative from w₁ = 0 to w₁ = 0.2 of each of the co-solvents PEG 600 and 1,2-propanediol mixture. This may indicate that the solution process is disfavoured by the mixing enthalpy in this region. In water-rich region, the enthalpy decreases due to solvent-solvent bond breakage. However, for the rest of the solvent mixture, the dissolution process is endothermic and enthalpy-driven. In both solvent mixtures, the main contributor to standard Gibbs energy of the solution process is the enthalpy where the (ζH) is greater than 60% which highlights the impact of energy on the dissolution of Sulf in the studied solvent systems.

Table 6. Apparent Thermodynamic Function of Sulf in a) 1,2-Propanediol (w_1) + Water and b) PEG-600 (w_1) + Water

w_1	ΔG°	ΔH°	ΔS°	$T\Delta S^\circ$	$\% \zeta_H$	$\% \zeta_{TS}$
1,2- Propanediol	kJ mol ⁻¹	kJ mol ⁻¹	J K ⁻¹ mol ⁻¹	kJ mol ⁻¹		
0.00	22.07	18.45	-11.84	-3.61	83.63	16.36
0.10	21.53	19.45	-6.81	-2.08	90.33	9.66
0.20	21.02	19.96	-3.46	-1.05	95.00	4.99
0.30	20.01	20.21	0.63	0.19	99.06	0.93
0.40	19.13	20.48	4.42	1.35	93.81	6.18
0.50	18.40	21.05	8.67	2.64	88.85	11.14
0.60	17.36	21.78	14.47	4.42	83.12	16.87
0.70	16.40	22.03	18.41	5.62	79.67	20.32
0.80	15.54	22.61	23.15	7.07	76.17	23.82
0.90	14.87	23.29	27.56	8.42	73.44	26.55
1.00	13.72	23.92	33.37	10.19	70.12	29.87

w_1	ΔG°	ΔH°	ΔS°	$T\Delta S^\circ$	$\% \zeta_H$	$\% \zeta_{TS}$
PEG-600	kJ mol ⁻¹	kJ mol ⁻¹	J K ⁻¹ mol ⁻¹	kJ mol ⁻¹		
0.00	22.07	18.45	-11.84	-3.61	83.63	16.36
0.10	21.47	19.43	-6.68	-2.04	90.49	9.50
0.20	20.49	20.14	-1.14	-0.34	98.33	1.66
0.30	18.67	20.81	7.01	2.14	90.67	9.32
0.40	16.11	21.32	17.05	5.20	80.39	19.60
0.50	14.06	21.96	25.86	7.90	73.54	26.45
0.60	12.03	22.68	34.85	10.64	68.06	31.93
0.70	10.38	23.58	43.19	13.19	64.12	35.87
0.80	8.47	23.85	50.35	15.38	60.79	39.20
0.90	7.02	24.17	56.14	17.15	58.49	41.50
1.00	6.62	25.71	62.47	19.08	57.40	42.59

CONCLUSION

This work was carried out to investigate, the solubility and apparent thermodynamic properties of sulfasalazine in aqueous binary solvent mixtures of PEG-600 and 1,2-propanediol from 298.15 K and 313.15 K. Mass fraction solubilities were determined using Higuchi shake-flask method. Generally, Sulf solubility increased with the elevation of temperature and increase in the mass fraction of the co-solvent. Maximum drug solubility was recorded in neat PEG-600 and minimum drug solubility was observed in neat water. The apparent thermodynamic analysis suggests an endothermic-driven dissolution in each of the investigated binary

solvent mixtures. Over all the findings of this work suggest that the various co-solvents could be used for the solubilization of poorly water-soluble drugs such as Sulf. Furthermore, the generated data were correlated with various cosolvency models. Low deviation rate was obtained for back-calculated data with the experimental values. This confirms the applicability of such models for solubility prediction.

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