

THERMODYNAMIC STUDY OF THE SOLUBILITY OF SODIUM SULFADIAZINE IN SOME ETHANOL + WATER COSOLVENT MIXTURES

ESTUDIO TERMODINÁMICO DE LA SOLUBILIDAD DE LA SULFADIAZINA SÓDICA EN ALGUNAS MEZCLAS COSOLVENTES ETANOL + AGUA

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ABSTRACT

Sodium sulfadiazine (SD-Na) is a drug extensively used for the treatment of certain infections caused by several kinds of microorganisms. Although SD-Na is widely used nowadays in therapeutics, the physicochemical information about their aqueous solutions is not complete at present. In this context, by using the van't Hoff and Gibbs equations the thermodynamic functions Gibbs energy, enthalpy, and entropy of solution for SD-Na in ethanol + water cosolvent mixtures, are evaluated from solubility data determined at temperatures from 278.15 to 308.15 K. The drug solubility is greatest in neat water and lowest in neat ethanol at all the temperatures studied. This behavior shows the negative cosolvent effect for this electrolyte drug in this solvent system. By means of enthalpy-entropy compensation analysis, non-linear $\Delta H_{\text{soln}}^{0\text{-app}}$ vs. $\Delta G_{\text{soln}}^{0\text{-app}}$ plot with positive slope from neat ethanol up to 0.60 in mass fraction of water and negative from this composition to neat water is obtained; accordingly to this result, it follows that the dissolution process of this drug in ethanol-rich is entropy-driven, whereas, in water-rich mixtures the process is enthalpy-driven. Nevertheless, the molecular and ionic events involved in the dissolution of this drug in this cosolvent system are unclear.

Keywords: Sodium sulfadiazine, solubility, cosolvency, ethanol, solution thermodynamics.

RESUMEN

La sulfadiazina sódica (SD-Na) es un fármaco ampliamente utilizado en el tratamiento de ciertas infecciones causadas por diferentes microorganismos. Si bien la Na-SD es ampliamente usada en la terapéutica actual, la información fisicoquímica de sus soluciones acuosas aún no es completa. En este contexto, se estudian las funciones termodinámicas aparentes de solución, energía de Gibbs, entalpía y entropía, a partir de valores de solubilidad de este fármaco en mezclas cosolventes etanol + agua en el intervalo de temperatura desde 278,15 hasta 308,15 K. La solubilidad del fármaco es mayor en agua pura y menor en etanol puro a todas las temperaturas estudiadas. Este resultado demuestra el efecto cosolvente negativo del etanol sobre este fármaco del tipo electrolito. Mediante análisis de compensación entálpica-entrópica se obtiene un gráfico no lineal $\Delta H_{\text{soln}}^{0\text{-app}}$ vs. $\Delta G_{\text{soln}}^{0\text{-app}}$ exhibiendo pendiente positiva desde el etanol puro hasta la mezcla cosolvente de 0,60 en fracción másica de agua y pendiente negativa desde esta mezcla

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hasta el agua pura; de acuerdo a este resultado, se tiene que el proceso de disolución de este fármaco en mezclas ricas en etanol es conducido entrópicamente, mientras que en mezclas ricas en agua el proceso es conducido entálpicamente. Sin embargo, los eventos moleculares e iónicos involucrados en el proceso de disolución de este fármaco en este sistema cosolventes no son claros.

Palabras clave: Sulfadiazina sódica, solubilidad, cosolventencia, etanol, termodinámica de soluciones.

INTRODUCTION

Sodium sulfadiazine (SD-Na, molecular structure is presented in figure 1) is a drug extensively used for the treatment of certain infections caused by several kinds of microorganisms (1). Although SD-Na is widely used nowadays in therapeutics, the physicochemical information about their aqueous solutions is not complete at present, although several physicochemical studies have been done. In this way, the solution thermodynamics in aqueous media for this drug (as dissociate and non-dissociate compound) has been presented in the literature (2, 3). Moreover, the physicochemical aspects of transfer of this drug (as non-dissociate compound) from aqueous media up to octanol and some phospholipidic vesicles have also been reported (4). Ultimately, the apparent molar volumes in water and ethanol have also been studied as a function of drug concentration at 298.15 K (2, 5).

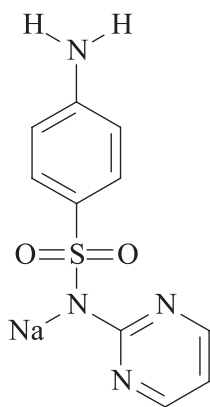


Figure 1. Molecular structure of sodium sulfadiazine.

On the other hand, it is well known that injectable homogeneous liquid formulations supply high doses of drug in small volumes, and thus, the solubility of drugs and other formulation components is very important, because it facilitates the design process of pharmaceutical dosage forms (6).

As has been already described, the solubility behavior of drugs in cosolvent mixtures is very important because cosolvent blends are frequently used

in purification methods, preformulation studies, and pharmaceutical dosage forms design, among other applications (7, 8). For these reasons, it is important to determine systematically the solubility of pharmaceutical compounds. Besides, temperature-solubility dependence allows us to carry out the respective thermodynamic analysis, which, on the other hand, also permits inside the molecular mechanisms, involved toward the solution processes (6).

The main objective of this study was to evaluate the effect of the cosolvent composition on the solubility and solution thermodynamics of SD-Na in ethanol (EtOH) + water cosolvent mixtures based on the van't Hoff method as has been done earlier with the local anesthetic procaine hydrochloride (9).

MATERIALS AND METHODS

Materials

Sodium sulfadiazine (4-Amino-*N*-2-pyrimidinylbenzenesulfonamide sodium salt; CAS: [68-35-9]; purity: 0.9990 in mass fraction) used is in agreement with the quality requirements indicated in the American Pharmacopeia, USP (10); on similar way, absolute ethanol A.R. (Merck) (CAS: 64-17-5; purity: 0.9990 in mass fraction), distilled water (CAS: 7732-18-5; conductivity $< 2 \mu\text{S}\cdot\text{cm}^{-1}$), molecular sieve (Merck, numbers 3 and 4), and Millipore Corp. Swinnex[®]-13 filter units, were also used.

Cosolvent mixtures preparation

All EtOH + water cosolvent mixtures were prepared in quantities of 10.000 g by mass using an Ohaus Pioneer TM PA214 analytical balance with sensitivity ± 0.1 mg, in mass fractions from 0.10 to 0.90 varying by 0.10, to study nine binary mixtures and the two pure solvents.

Solubility determinations

An excess of SD-Na was added to 5 cm³ of each cosolvent mixture, in stoppered dark glass flasks. Solid-liquid mixtures were stirred in a mechanical

shaker (Burrel, Wrist Action Shaker, Model 75) at room temperature at least for four hours. The flasks were kept at each temperature (± 0.05 K) in recirculating thermostatic baths (Neslab RTE 10 Digital One Thermo Electron Company) with sporadic stirring at least for seven days to reach the equilibrium. After this time the supernatant solutions were filtered (at isothermal conditions) to ensure that they were free of particulate matter before sampling. Drug concentrations were determined by measuring absorbance after appropriate dilution with water and interpolation from a previously constructed UV spectrophotometric calibration curve (UV/VIS BioMate 3 Thermo Electron Company spectrophotometer). All the solubility experiments were run at least in triplicate. In order to make the equivalence between molarity and mole fraction concentration scales, the density of the saturated solutions was determined with a digital density meter (DMA 45 Anton Paar) connected to the same recirculating thermostatic baths.

RESULTS AND DISCUSSION

Before to show the solubility results, it is important to consider that this drug like procaine hydrochloride has electrolyte behavior (9), and thus, it dissociates in aqueous solution interacting with the cosolvent mixture by strong ion-dipole interactions, as well as by other weak non covalent interactions; on this way, it also could acts as a Lewis acid ($-\text{NH}_2$ group) or Lewis base ($-\text{NH}_2$ and $-\text{SO}_2-$ groups), in order to establish hydrogen bonds with proton-acceptor or donor functional groups in the solvents ($-\text{OH}$ groups) (11, 12).

Experimental Solubility

Tables 1 and 2 summarize the experimental solubility of SD-Na, expressed in $\text{mol}\cdot\text{dm}^{-3}$ and mole fraction, respectively, at all the temperatures studied. In all cases the percent coefficients of variation were smaller than 1.0 %.

Table 1. Experimental solubility of sodium sulfadiazine in ethanol + water cosolvent mixtures expressed in $\text{mol}\cdot\text{dm}^{-3}$ at several temperatures. ^a

μ_{EtOH}^b	T / K						
	278.15	283.15	288.15	293.15	298.15	303.15	308.15
0.00	1.7227 (0.0020)	1.7751 (0.0011)	1.8267 (0.0015)	1.8754 (0.0005)	1.9207 (0.0012)	1.9731 (0.0007)	2.0257 (0.0025)
0.10	1.3607 (0.0012)	1.4200 (0.0001)	1.4779 (0.0005)	1.5323 (0.0029)	1.5896 (0.0021)	1.643 (0.003)	1.6948 (0.0004)
0.20	1.0113 (0.0003)	1.0702 (0.0002)	1.1328 (0.0006)	1.1897 (0.0019)	1.254 (0.004)	1.3121 (0.0023)	1.372 (0.006)
0.30	0.6951 (0.0005)	0.742 (0.003)	0.7943 (0.0007)	0.8471 (0.0025)	0.894 (0.004)	0.9480 (0.0011)	1.0027 (0.0003)
0.40	0.4736 (0.0012)	0.5103 (0.0008)	0.5486 (0.0011)	0.584 (0.004)	0.6267 (0.0025)	0.6690 (0.0022)	0.7061 (0.0008)
0.50	0.2871 (0.0001)	0.3069 (0.0001)	0.3334 (0.0001)	0.3595 (0.0003)	0.3855 (0.0003)	0.4095 (0.0009)	0.4380 (0.0020)
0.60	0.1627 (0.0009)	0.1759 (0.0005)	0.1891 (0.0003)	0.2016 (0.0001)	0.2173 (0.0001)	0.2324 (0.0004)	0.2473 (0.0011)
0.70	8.625 (0.028) $\times 10^{-2}$	9.252 (0.005) $\times 10^{-2}$	9.878 (0.005) $\times 10^{-2}$	0.1058 (0.0001)	0.1120 (0.0002)	0.1188 (0.0002)	0.1257 (0.0001)
0.80	3.320 (0.017) $\times 10^{-2}$	3.502 (0.007) $\times 10^{-2}$	3.692 (0.012) $\times 10^{-2}$	3.842 (0.005) $\times 10^{-2}$	4.023 (0.004) $\times 10^{-2}$	4.218 (0.018) $\times 10^{-2}$	4.385 (0.016) $\times 10^{-2}$
0.90	9.11 (0.07) $\times 10^{-3}$	9.56 (0.04) $\times 10^{-3}$	9.98 (0.03) $\times 10^{-3}$	1.037 (0.004) $\times 10^{-2}$	1.076 (0.005) $\times 10^{-2}$	1.116 (0.001) $\times 10^{-2}$	1.146 (0.012) $\times 10^{-2}$
1.00	1.309 (0.001) $\times 10^{-3}$	1.352 (0.001) $\times 10^{-3}$	1.396 (0.003) $\times 10^{-3}$	1.439 (0.001) $\times 10^{-3}$	1.482 (0.002) $\times 10^{-3}$	1.522 (0.005) $\times 10^{-3}$	1.811 (0.002) $\times 10^{-3}$

^a Values in parentheses are standard deviations.

^b μ_{EtOH} is the mass fraction of ethanol in the cosolvent mixture free of solute.

Table 2. Experimental solubility of sodium sulfadiazine in ethanol + water cosolvent mixtures expressed in mole fraction at several temperatures. ^a

μ_{EtOH}^b	T / K						
	278.15	283.15	288.15	293.15	298.15	303.15	308.15
0.00	4.082 (0.007) $\times 10^{-2}$	4.255 (0.005) $\times 10^{-2}$	4.429 (0.005) $\times 10^{-2}$	4.604 (0.003) $\times 10^{-2}$	4.779 (0.005) $\times 10^{-2}$	4.966 (0.003) $\times 10^{-2}$	5.150 (0.004) $\times 10^{-2}$
0.10	3.241 (0.002) $\times 10^{-2}$	3.410 (0.001) $\times 10^{-2}$	3.583 (0.001) $\times 10^{-2}$	3.751 (0.011) $\times 10^{-2}$	3.924 (0.007) $\times 10^{-2}$	4.096 (0.013) $\times 10^{-2}$	4.262 (0.001) $\times 10^{-2}$
0.20	2.460 (0.001) $\times 10^{-2}$	2.619 (0.001) $\times 10^{-2}$	2.784 (0.002) $\times 10^{-2}$	2.942 (0.006) $\times 10^{-2}$	3.132 (0.013) $\times 10^{-2}$	3.306 (0.006) $\times 10^{-2}$	3.491 (0.024) $\times 10^{-2}$
0.30	1.747 (0.001) $\times 10^{-2}$	1.877 (0.001) $\times 10^{-2}$	2.006 (0.002) $\times 10^{-2}$	2.145 (0.009) $\times 10^{-2}$	2.275 (0.013) $\times 10^{-2}$	2.427 (0.004) $\times 10^{-2}$	2.580 (0.002) $\times 10^{-2}$
0.40	1.264 (0.003) $\times 10^{-2}$	1.365 (0.003) $\times 10^{-2}$	1.469 (0.003) $\times 10^{-2}$	1.564 (0.012) $\times 10^{-2}$	1.687 (0.007) $\times 10^{-2}$	1.810 (0.008) $\times 10^{-2}$	1.919 (0.003) $\times 10^{-2}$
0.50	8.282 (0.003) $\times 10^{-3}$	8.849 (0.005) $\times 10^{-3}$	9.623 (0.002) $\times 10^{-3}$	1.038 (0.001) $\times 10^{-2}$	1.115 (0.001) $\times 10^{-2}$	1.185 (0.002) $\times 10^{-2}$	1.272 (0.006) $\times 10^{-2}$
0.60	5.17 (0.03) $\times 10^{-3}$	5.605 (0.018) $\times 10^{-3}$	6.040 (0.011) $\times 10^{-3}$	6.455 (0.003) $\times 10^{-3}$	6.975 (0.002) $\times 10^{-3}$	7.483 (0.012) $\times 10^{-3}$	7.98 (0.04) $\times 10^{-3}$
0.70	3.092 (0.010) $\times 10^{-3}$	3.331 (0.002) $\times 10^{-3}$	3.571 (0.003) $\times 10^{-3}$	3.843 (0.003) $\times 10^{-3}$	4.082 (0.005) $\times 10^{-3}$	4.351 (0.007) $\times 10^{-3}$	4.626 (0.002) $\times 10^{-3}$
0.80	1.358 (0.007) $\times 10^{-3}$	1.440 (0.003) $\times 10^{-3}$	1.527 (0.005) $\times 10^{-3}$	1.596 (0.002) $\times 10^{-3}$	1.681 (0.001) $\times 10^{-3}$	1.772 (0.008) $\times 10^{-3}$	1.855 (0.006) $\times 10^{-3}$
0.90	4.35 (0.03) $\times 10^{-4}$	4.591 (0.020) $\times 10^{-4}$	4.826 (0.014) $\times 10^{-4}$	5.044 (0.022) $\times 10^{-4}$	5.263 (0.027) $\times 10^{-4}$	5.495 (0.002) $\times 10^{-4}$	5.68 (0.06) $\times 10^{-4}$
1.00	7.510 (0.008) $\times 10^{-5}$	7.797 (0.007) $\times 10^{-5}$	8.095 (0.001) $\times 10^{-5}$	8.386 (0.003) $\times 10^{-5}$	8.674 (0.011) $\times 10^{-5}$	8.95 (0.03) $\times 10^{-5}$	9.270 (0.009) $\times 10^{-5}$

^a Values in parentheses are standard deviations.

^b μ_{EtOH} is the mass fraction of ethanol in the cosolvent mixture free of solute.

It could be observed that the solubility expressed in both concentration scales was greatest in neat water and lowest in neat EtOH at all temperatures studied. This behavior shows the negative cosolvent effect present for this electrolyte drug in this solvent system, and is in agreement with that expected according to the literature (7, 8), since the SD-Na solubility is greatest in neat water as could be expected because of its large dielectric constant value (78.5 at 298.15 K) (11). Our solubility values in neat water are in good agreement with those reported in the literature at temperatures from (298.15 to 308.15) K (2). Unfortunately, in the literature there are not reported quantitative solubility values for this drug in neat EtOH or EtOH + water mixtures, and therefore, none other direct comparison is possible.

Because SD-Na is an electrolyte drug, it is important to keep in mind that in general terms, it could be stated that a strong electrolyte dissociates according to the expression, $C_{\nu_+} A_{\nu_-} \rightarrow C^{z+} + \nu_- A^{z-}$, where ν_+ is the number of cations (C^{z+}) of valence $z+$ and ν_- is the number of anions (A^{z-}) of valence $z-$. Because is not possible to determine experimentally the activity of ions separately, the concept of mean ionic activity (a_{\pm}^{ν}) is used. Thus,

the thermodynamic activity for an electrolyte can be defined as, $a_2 = a_+^{\nu_+} a_-^{\nu_-} = a_{\pm}^{\nu}$ (13-15).

SD-Na is an electrolyte solute of type one-one, that is, it dissociates in aqueous solutions to generate two species, a monovalent anion and a monovalent cation, respectively. If the inter-ionic interactions are not considered, in a first approach the ν value could be ideally assumed as 2 for this drug, and this value could be used to calculate the apparent thermodynamic functions of solution (3, 9).

Thermodynamic Functions of Solution

According to van't Hoff analysis, the apparent standard enthalpy change of solution ($\Delta H_{\text{soln}}^{0-\text{app}}$) for electrolytes type one-one, such as SD-Na, if the inter-ionic interactions are not considered, is obtained by using the mean harmonic temperature (T_{hm} is 292.8 K in our case) according to equation 1 (9).

$$\left(\frac{\partial \ln x_{\text{SD-Na}}}{\partial (1/T - 1/T_{\text{hm}})} \right)_P = - \frac{\Delta H_{\text{soln}}^{0-\text{app}}}{2 \cdot R} \quad \text{Equation 1.}$$

where, R is the universal gas constant ($8.314 \text{ J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$). As an example, figure 2 shows the modified

van't Hoff plot for SD-Na in mixtures containing 0.20, and 0.30, and 0.40 in mass fraction of EtOH. In all cases studied, linear models with good determination coefficients were obtained.

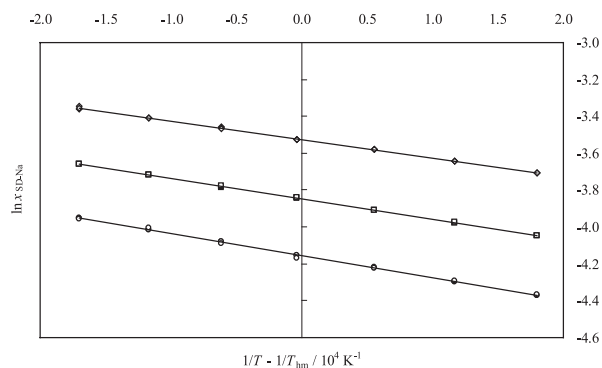


Figure 2. Modified van't Hoff plot for experimental solubility of sodium sulfadiazine in some ethanol + water mixtures expressed in mole fraction. \diamond , 0.20 in mass fraction of ethanol; \square , 0.30 in mass fraction of ethanol; \circ , 0.40 in mass fraction of ethanol. The lines interconnecting points are the respective linear regression models.

The apparent standard Gibbs energy change for the solution process ($\Delta G_{\text{soln}}^{0\text{-app}}$) of electrolytes type one-one, considering the approach proposed

by Krug *et al* (16), is calculated at mean harmonic temperature by means of,

$$\Delta G_{\text{soln}}^{0\text{-app}} = -2 \cdot R \cdot T_{\text{hm}} \cdot \text{intercept} \quad \text{Equation 2.}$$

in which, the intercept used is the one obtained in the analysis by treatment of $\ln x_{\text{Na-SD}}$ as a function of $1/T - 1/T_{\text{hm}}$. Finally, the apparent standard entropic change for solution process ($\Delta S_{\text{soln}}^{0\text{-app}}$) is obtained from the respective $\Delta H_{\text{soln}}^{0\text{-app}}$ and $\Delta G_{\text{soln}}^{0\text{-app}}$ values by using:

$$\Delta S_{\text{soln}}^{0\text{-app}} = \frac{(\Delta H_{\text{soln}}^{0\text{-app}} - \Delta G_{\text{soln}}^{0\text{-app}})}{T_{\text{hm}}} \quad \text{Equation 3.}$$

Table 3 summarizes the apparent standard thermodynamic functions for experimental solution process of SD-Na in all EtOH + water cosolvent mixtures. In order to calculate the thermodynamic quantities for the experimental solution processes some propagation of uncertainties' methods were used (17). It is found that the standard Gibbs energy of solution is positive in all cases as expected because the mole fraction is always lower than the unit and thus, its logarithmic term is negative, and therefore, standard Gibbs energy will be a positive quantity.

Table 3. Apparent thermodynamic functions relative to solution process of sodium sulfadiazine in ethanol + water cosolvent mixtures at 292.8 K.

μ_{EtOH}^a	$\Delta G_{\text{soln}}^{0\text{-app}}/\text{kJ}\cdot\text{mol}^{-1}$	$\Delta H_{\text{soln}}^{0\text{-app}}/\text{kJ}\cdot\text{mol}^{-1}$	$\Delta S_{\text{soln}}^{0\text{-app}}/\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$	$T\Delta S_{\text{soln}}^{0\text{-app}}/\text{kJ}\cdot\text{mol}^{-1}$	ζ_{H}^b	ζ_{TS}^b
0.00	14.996 (0.001)	11.02 (0.02)	-13.59 (0.02)	-3.98 (0.01)	0.735	0.265
0.10	16.004 (0.002)	13.03 (0.03)	-10.15 (0.02)	-2.97 (0.01)	0.814	0.186
0.20	17.168 (0.003)	16.64 (0.05)	-1.80 (0.01)	-0.526 (0.002)	0.969	0.031
0.30	18.733 (0.003)	18.43 (0.05)	-1.041 (0.003)	-0.305 (0.001)	0.984	0.016
0.40	20.234 (0.005)	19.91 (0.08)	-1.105 (0.004)	-0.323 (0.001)	0.984	0.016
0.50	22.278 (0.005)	20.56 (0.07)	-5.87 (0.02)	-1.72 (0.01)	0.923	0.077
0.60	24.548 (0.004)	20.57 (0.06)	-13.60 (0.04)	-3.98 (0.01)	0.838	0.162
0.70	27.122 (0.003)	19.13 (0.04)	-27.30 (0.05)	-7.99 (0.02)	0.705	0.295
0.80	31.358 (0.004)	14.75 (0.06)	-56.73 (0.23)	-16.61 (0.07)	0.470	0.530
0.90	36.992 (0.007)	12.65 (0.10)	-83.1 (0.6)	-24.34 (0.18)	0.342	0.658
1.00	45.714 (0.002)	9.95 (0.02)	-122.1 (0.3)	-35.76 (0.09)	0.218	0.782

^a μ_{EtOH} is the mass fraction of ethanol in the cosolvent mixture free of solute.

^b ζ_{H} and ζ_{TS} are the relative contributions by enthalpy and entropy toward Gibbs energy of solution and these values were calculated by means of equations 4 and 5, respectively.

The apparent enthalpy of solution is positive in all cases, therefore the process is always endothermic. Oppositely, the entropy of solution is also negative indicating nor enthalpy or entropy driving on overall the solution process for all the mixtures and neat solvents. The $\Delta H_{\text{soln}}^{0\text{-app}}$ values increase from neat water up to 0.50 and 0.60 in mass fraction of EtOH and decrease from these EtOH proportions up to neat EtOH. On different way to enthalpy, the negative $\Delta S_{\text{soln}}^{0\text{-app}}$ values increase from neat water to the mixture of 0.30 in mass fraction of EtOH and diminish beyond this composition up to neat EtOH. The apparent enthalpic and entropic values obtained for dissolution process of SD-Na in neat water are in excellent agreement with respect to those reported in the literature ($11.0 \pm 0.6 \text{ kJ}\cdot\text{mol}^{-1}$ and $-13.5 \pm 0.7 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$, respectively) (2), although the temperature intervals studied and the analytical techniques used were so different in both investigations.

With the aim to compare the relative contributions by enthalpy (ζ_H) and by entropy (ζ_{TS}) toward the solution process, equations 4 and 5 were employed, respectively (18).

$$\zeta_H = \frac{|\Delta H_{\text{soln}}^0|}{|\Delta H_{\text{soln}}^0| + |T\Delta S_{\text{soln}}^0|} \quad \text{Equation 4.}$$

$$\zeta_{TS} = \frac{|T\Delta S_{\text{soln}}^0|}{|\Delta H_{\text{soln}}^0| + |T\Delta S_{\text{soln}}^0|} \quad \text{Equation 5.}$$

From Table 3 it follows that the main contributor to standard Gibbs energy of solution process of SD-Na is the enthalpy for neat water and mixtures from 0.10 to 0.70 in mass fraction of EtOH, whereas it is the entropy for the other systems. In the first case,

the ζ_H values are greater than 0.70, indicating the relevance of the energetic factor on the dissolution processes of this drug in water-rich mixtures, while in the mixture of 0.90 in mass fraction of EtOH and in neat EtOH, where the ζ_S values are greater than 0.65 the organizational factor predominates. On the other hand, in the mixture of 0.80 in mass fraction of EtOH both terms are similar.

Thermodynamic Functions of Transfer

In order to verify the effect of cosolvent composition on the thermodynamic function driving the solution process, table 4 summarizes the thermodynamic functions of transfer of SD-Na from the less polar solvents to the more polar ones. These new functions were calculated as the differences between the thermodynamic quantities of solution in the more polar mixtures and the less polar mixtures.

If the addition of water to neat EtOH is considered (being the cosolvent mixture more polar as the water proportion increases), as has been done earlier (9), it happens the following, from pure EtOH to 0.40 in mass fraction of water ($\Delta G_{A \rightarrow B}^{0\text{-app}} < 0$, $\Delta H_{A \rightarrow B}^{0\text{-app}} > 0$, and $\Delta S_{A \rightarrow B}^{0\text{-app}} > 0$) the solubility process is driven by the entropy; whereas, from this composition up to 0.70 in mass fraction of water ($\Delta G_{A \rightarrow B}^{0\text{-app}} < 0$, $\Delta H_{A \rightarrow B}^{0\text{-app}} < 0$, and $\Delta S_{A \rightarrow B}^{0\text{-app}} > 0$) the dissolution process is enthalpy and entropy driven. Ultimately, from 0.70 in mass fraction of water up to neat water ($\Delta G_{A \rightarrow B}^{0\text{-app}} < 0$, $\Delta H_{A \rightarrow B}^{0\text{-app}} < 0$, and $\Delta S_{A \rightarrow B}^{0\text{-app}} < 0$), the solution process is enthalpy driven. These statements are based upon the fact that negative values of Gibbs energy imply spontaneous transfer of the drug, and on the other hand, it is well known that negative values of enthalpy and/or positive values of entropy are favorable for the drug transfer processes (19). Nevertheless, the molecular or ionic events involved on the solution and/or transfer processes are unclear.

Table 4. Apparent thermodynamic functions of transfer of sodium sulfadiazine from less polar solvents to more polar solvents in ethanol + water cosolvent mixtures at 292.8 K.

μ_{Water}^a		$\Delta G_{A \rightarrow B}^{0\text{-app}} / \text{kJ}\cdot\text{mol}^{-1}$	$\Delta H_{A \rightarrow B}^{0\text{-app}} / \text{kJ}\cdot\text{mol}^{-1}$	$\Delta S_{A \rightarrow B}^{0\text{-app}} / \text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$	$T\Delta S_{A \rightarrow B}^{0\text{-app}} / \text{kJ}\cdot\text{mol}^{-1}$
A	B				
0.00	0.40	-21.166 (0.004)	10.61 (0.07)	108.5 (0.3)	31.78 (0.09)
0.40	0.70	-5.816 (0.005)	-2.14 (0.08)	12.56 (0.04)	3.68 (0.01)
0.70	1.00	-3.737 (0.003)	-7.41 (0.05)	-12.55 (0.02)	-3.67 (0.01)

^a μ_{Water} is the mass fraction of water in the cosolvent mixture free of solute; A and B are the less polar and more polar media, respectively.

Enthalpy-Entropy Compensation of Solution

According to the literature, the making of weighted graphs of $\Delta H_{\text{soln}}^{0\text{-app}}$ as a function of $\Delta G_{\text{soln}}^{0\text{-app}}$ at mean harmonic temperature allows us to observe similar mechanisms for the solution process according to the tendencies obtained (19, 20).

In this context, figure 3 shows fully that SD-Na in the EtOH + water cosolvent system present non-linear $\Delta H_{\text{soln}}^{0\text{-app}}$ vs. $\Delta G_{\text{soln}}^{0\text{-app}}$ compensation with positive slope if an interval from pure EtOH up to 0.60 in mass fraction of EtOH is considered, whereas from this EtOH proportion to neat water a negative slope is obtained. Accordingly to this graph it follows that the driving function for drug solubility is the entropy in the former case, while in the second case, the driving function is mainly the enthalpy. It is important to note that the thermodynamic functions of transfer discussed previously bring more information than figure 3 because in the interval from 0.30 and 0.60 in mass fraction of EtOH both entropy and enthalpy driven was found. Nevertheless, the molecular and ionic events involved in the dissolution of this drug in this cosolvent system are unclear as was already said.

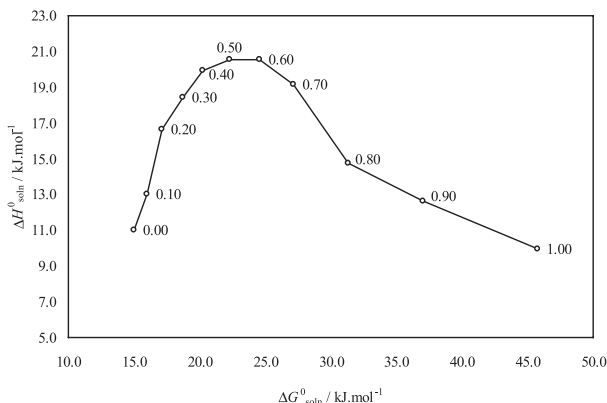


Figure 3. ΔH_{soln}^0 vs. ΔG_{soln}^0 enthalpy-entropy compensation plot for solubility of sodium sulfadiazine in ethanol + water cosolvent mixtures at 292.8 K. The slopes of the lines interconnecting composition points (mass fractions of ethanol) define the thermodynamic functions driving the SD-Na transfer processes.

CONCLUSIONS

From all topics discussed previously it can be concluded that the solution process of SD-Na in EtOH + water mixtures is variable depending on the cosolvent composition. Non linear enthalpy-

entropy compensation was found for this drug in this cosolvent system. In this context, entropy driving was found for the solution processes in compositions from pure EtOH to the mixture having 0.40 in mass fraction of water; whereas, for cosolvent mixtures from this water proportion to the mixture of 0.70 in mass fraction of water, entropy and enthalpy driving was found; moreover, beyond this water proportion up to neat water enthalpy driving is found. Ultimately, it can be said that the data presented in this report expand the physicochemical information about electrolyte drugs in aqueous solutions.

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