

Solubility of phenytoin in aqueous mixtures of ethanol and sodium dodecyl sulfate at 298 K

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SUMMARY

The solubility of phenytoin in binary mixtures of ethanol + water at 298.2 K in the presence of three different concentrations of sodium dodecyl sulfate (SDS) was reported. The Jouyban-Acree model was used for correlating the generated data and the obtained mean relative deviation was 7.3%. When all data points of phenytoin in binary solvents at various SDS concentrations were fitted to the model, the obtained mean relative deviation was 10.1%.

Key words: solubility, phenytoin, ethanol, solvent mixture, sodium dodecyl sulfate, Jouyban-Acree model.

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RESUMEN

Solubilidad de la fenitoína en mezclas acuosas de etanol y dodecil-sulfato sódico a 298 K

Se presenta la solubilidad de la fenitoína a 298,2 K en mezclas binarias de etanol y agua en presencia de tres diferentes concentraciones de dodecil-sulfato sódico (DSS). Se utiliza el modelo de Jouyban-Acree para correlacionar los datos generados obteniendo una desviación media relativa de 7,3%. Al ajustar al modelo todos los datos obtenidos de la fenitoína en los solventes binarios y en las diferentes concentraciones de DSS la desviación media relativa obtenida fue de 10,1%.

Palabras clave: solubilidad, fenitoína, etanol, mezcla solvente, dodecil-sulfato sódico, modelo de Jouyban-Acree.

INTRODUCTION

Poor aqueous solubility of drugs is an obstacle in drug discovery and development investigations. As a general rule, poorly water soluble drugs possess low bioavailability. Unfortunately, nearly 70% of new drug candidates are low water soluble compounds [1]. In addition, low solubility makes a number of problems in preparation of liquid formulations of drugs and also their bioavailability. Various techniques have been used to solve this problem including salt formation, prodrugs, preparation of cocrystals, etc. [2-5]. Solubilization techniques including cosolvency [6] and addition of surfactants [7] are also used to solubilize poorly soluble drugs. In addition to the individual application of cosolvents [8-11] and surfactants [12, 13], their combined forms are also employed in the pharmaceutical investigations [14, 15] for solubilization of drugs.

Phenytoin (see Figure 1 for chemical structure) is an anti-epileptic drug, which is used in the therapeutics. It is an acidic drug with the pKa of 8.33 and the aqueous solubility of 7.53×10^{-5} M [16]. Its salt formations with piperazine, piperidine, ethylenediamine, ethanolamine and sodium were increased the solubility by factors of 59, 418, 468, 507 and 3617 [17]. The solubility of phenytoin was investigated in aqueous solutions of cyclodextrins [18], aqueous mixtures of 1,3-butanediol, ethanol, glycerine, methanol, polyethylene glycol (PEG) 200, PEG 400, propylene glycol and sorbitol at 298 K [19].

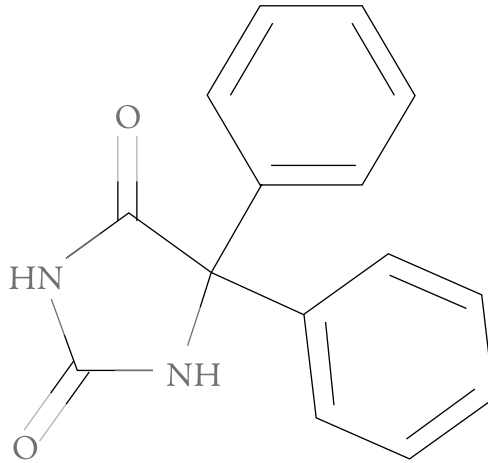


Figure 1. Chemical structure of phenytoin.

To extend our systematic investigations on the solubility of drugs in mixed solvents, the solubility of phenytoin in binary mixtures of ethanol + water at 298.2 K in the absence of sodium dodecyl sulfate (SDS) and in the presence of three different concentrations of SDS was reported and the produced data was mathematically represented by the Jouyban-Acree model. SDS at concentrations above its critical micelle concentrations could form micelles and increase the solubility of hydrophobic drugs by partitioning process. We used lower concentrations of SDS in this work, and no micelles will be formed in the investigated aqueous and also mixed solvent or non-aqueous solutions.

COMPUTATIONAL METHOD

Among several mathematical models for calculating the solubility of drugs in mixed solvents [20], the log-linear model of Yalkowsky [21] is the simplest model and the Jouyban-Acree model is the most accurate model [20, 22]. The Jouyban-Acree model was proposed for representing solvent composition and temperature effects on the solubility of drugs in mixed solvents with the general form of [23]:

$$\log_{10} C_{m,T}^{sat} = \varphi_1 \cdot \log_{10} C_{1,T}^{sat} + \varphi_2 \cdot \log_{10} C_{2,T}^{sat} + \frac{\varphi_1 \cdot \varphi_2}{T} \cdot \sum_{i=0}^2 J_i \cdot (\varphi_1 - \varphi_2)^i \quad (1)$$

in which $C_{m,T}^{sat}$ is the solute solubility in the solvent mixtures at temperature T (Kelvin), φ_1 and φ_2 are the volume fractions of the solvents 1 and 2, respectively, $C_{1,T}^{sat}$ and $C_{2,T}^{sat}$ are the solubility of the solute in the mono-solvents 1 and 2, respectively, and J_i are the constants of the model computed by regression analysis [24]. In this work, one

could consider ethanol + SDS (in various concentrations) as solvent 1 and water + SDS as solvent 2.

To evaluate the accuracy of the computations, the mean relative deviation (MRD) between the calculated and observed solubilities was computed using:

$$MRD = \frac{100}{N} \sum \left(\frac{|C_{m,T}^{Calculated} - C_{m,T}^{Observed}|}{C_{m,T}^{Observed}} \right) \quad (2)$$

where N was the number of data points in each set.

MATERIALS AND METHODS

Materials

Phenytoin was purchased from Alhavi Pharmaceutical company (Tehran, Iran). Ethanol (99.8%) and SDS (purity of 99.0%) were purchased from Merck (Germany), and double distilled water was used for preparation of the solutions. Ethanol with purity of 96% v/v (or 93.5% m/m) was used for dilution of saturated solutions prior to spectrophotometric analyses of the samples.

Preparation of the solvent mixtures

Various concentrations of SDS, i.e. 1.6×10^{-3} , 3.2×10^{-3} and 6.4×10^{-3} mol·L⁻¹, were prepared in water and/or ethanol, then all binary solvent mixtures were made by mixing appropriate volume fractions of the solvents (with or without SDS) by uncertainty of 0.1 mL with the total volume of 30 mL.

Solubility determination

Various solubility determination methods were used in the literature which was reviewed in a recent work [25] and the saturation shake-flask method of Higuchi and Connors [26] was used in this work. The solubility was determined by equilibrating excess amounts of drugs in the prepared solvent systems using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature-controlling system at different temperatures with the uncertainty of 0.2 K (Kimia Idea Pardaz Azarbayjan —KIPA—, Tabriz, Iran) for 3 days to reach the equilibrium at 298.2 K. The saturated solutions were centrifuged at 13,000 rpm for 15 minutes (MSE Micro Center MSB010. CX2.5, Sanyo, Japan) and after diluting with ethanol (96% v/v), the absorbance of

these solutions were recorded at 220 nm using a UV-vis spectrophotometer (Biotech-Ultraspac 2000, England). Concentrations of the diluted solutions were determined by measuring the UV absorbance. Each experimental data is an average of at least three experimental measurements, and the mean relative standard deviation (RSD) of three repetitive experiments is 2.3%.

RESULTS AND DISCUSSIONS

Table 1 lists the volume fractions of ethanol + water, concentrations of SDS and the experimental molar solubilities of phenytoin. There are good agreements between measured aqueous solubilities of phenytoin and the reported values in the literature [16, 19]. In addition to aqueous solubility data, the solubility profile of phenytoin in ethanol + water mixtures at 298 K is in agreement with that reported by Rubino and his coworkers [19] as graphically represented in Figure 2. The minimum solubility is observed in aqueous solution ($8.00 \times 10^{-5} \text{ mol}\cdot\text{L}^{-1}$) and the maximum solubility is observed in ethanol ($\varphi_1 = 0.90$) and SDS of $6.4 \times 10^{-3} \text{ mol}\cdot\text{L}^{-1}$ ($5.72 \times 10^{-5} \text{ mol}\cdot\text{L}^{-1}$), revealing that addition of ethanol and SDS to the aqueous solutions make the solubility enhancement by a factor of 7149. The enhancement factor of SDS ($6.4 \times 10^{-3} \text{ mol}\cdot\text{L}^{-1}$) for aqueous solution in the absence of ethanol is 47 and that of ethanol ($\varphi_1 = 0.90$) in the absence of SDS is 768. These observations reveal that there is a synergistic effect on the solubility of phenytoin when ethanol and SDS are added simultaneously to the aqueous solutions. It should be added that the monomeric SDS molecules act as a secondary cosolvent and no micelles are formed in the investigated concentrations of SDS.

Solubility data of each concentration of SDS was fitted to Eq. (1) and the model constants were computed using least square analysis. Then the solubilities were back-calculated and the MRD values were computed using Eq. (2). These values are listed in Table 2.

When all solubility data of phenytoin in different concentration of SDS was fitted to Eq. (1), the obtained model was:

$$\log_{10} C_{m,T}^{sat} = \varphi_1 \cdot \log_{10} C_{1,T}^{sat} + \varphi_2 \cdot \log_{10} C_{2,T}^{sat} + \frac{\varphi_1 \cdot \varphi_2}{T} \left[\frac{636.00 + 701.02(\varphi_1 - \varphi_2) -}{480.10(\varphi_1 - \varphi_2)^2} \right] \quad (3)$$

Equation (3) back-calculated the solubility of phenytoin with the MRD values of 10.1% ($N = 44$). When the model was trained using a minimum number of experimental solubility data at the highest and lowest SDS concentrations and ethanol fractions of

Table 1. Experimental molar solubility ($C_{m,T}^{Sat}$) of phenytoin in various volume fractions (φ_1) of ethanol (1) + water (2) mixtures and different concentrations of sds at 298.2 K.

φ_1	Without sds	sds 1.6×10^{-3} $\text{mol}\cdot\text{L}^{-1}$	sds 3.2×10^{-3} $\text{mol}\cdot\text{L}^{-1}$	sds 6.4×10^{-3} $\text{mol}\cdot\text{L}^{-1}$
0.00	8.00×10^{-5}	2.50×10^{-3}	2.87×10^{-3}	3.76×10^{-3}
0.10	1.50×10^{-4}	2.53×10^{-3}	3.63×10^{-3}	4.22×10^{-3}
0.20	3.30×10^{-4}	8.96×10^{-3}	1.12×10^{-2}	1.19×10^{-2}
0.30	9.90×10^{-4}	1.85×10^{-2}	2.15×10^{-2}	2.26×10^{-2}
0.40	3.48×10^{-3}	3.69×10^{-2}	4.60×10^{-2}	4.95×10^{-2}
0.50	9.63×10^{-3}	9.85×10^{-2}	1.15×10^{-1}	1.41×10^{-1}
0.60	2.05×10^{-2}	2.05×10^{-1}	2.38×10^{-1}	3.62×10^{-1}
0.70	3.48×10^{-2}	3.30×10^{-1}	3.83×10^{-1}	4.21×10^{-1}
0.80	4.96×10^{-2}	3.94×10^{-1}	4.59×10^{-1}	5.35×10^{-1}
0.90	6.14×10^{-2}	4.74×10^{-1}	5.51×10^{-1}	5.72×10^{-1}
1.00	5.87×10^{-2}	4.12×10^{-1}	4.79×10^{-1}	4.91×10^{-1}

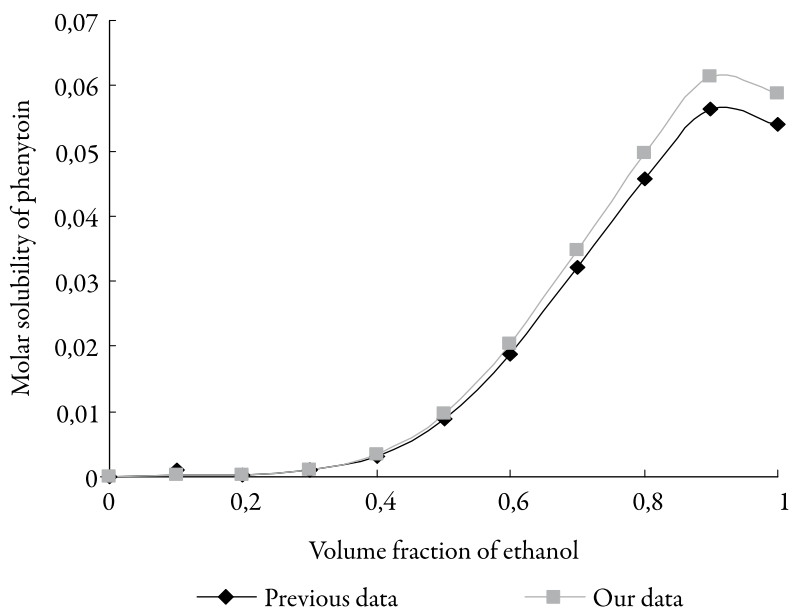


Figure 2. Molar solubilities of phenytoin (our data and reported data in an earlier work [19]).

Table 2. MRDs and overall MRD of the calculated solubilities of phenytoin in aqueous mixtures of ethanol at 298 K and various concentrations of SDS.

SDS	J_0	J_1	J_2	MRD
$0.0 \times 10^{-3} \text{ mol}\cdot\text{L}^{-1}$	743.40	690.08	-568.32	4.2
$1.6 \times 10^{-3} \text{ mol}\cdot\text{L}^{-1}$	587.36	704.65	-490.88	9.5
$3.2 \times 10^{-3} \text{ mol}\cdot\text{L}^{-1}$	589.71	623.35	-322.12	6.7
$6.4 \times 10^{-3} \text{ mol}\cdot\text{L}^{-1}$	623.35	786.00	-539.07	8.7
			Overall MRD	7.3

0.00, 0.30, 0.50, 0.70 and 1.00 and the rest of data points were predicted, the obtained MRD is 13.9% ($N = 34$) which is an acceptable error range considering the similar predictions in the pharmaceutical area. This equation could represent the non-ideal mixing of aqueous and ethanolic solutions of phenytoin in the absence and presence of SDS. The effects of various concentrations of SDS in ethanol + water mixtures could be partially represented in the numerical values of $C_{1,T}^{sat}$ and $C_{2,T}^{sat}$ values.

CONCLUSION

Experimental solubility of phenytoin is reported in aqueous binary mixtures of ethanol and three different concentrations of SDS, which extended the available solubility database of pharmaceuticals in mixed solvents [27]. The Jouyban-Acree model fits well to the experimental solubility data of phenytoin at all composition ranges of solvent mixtures. These findings are supported by acceptable MRD values of the calculated and experimental solubility data.

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