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Solubility of naproxen in some aqueous mixtures of *N*-methyl-2-pyrrolidone at various temperatures

Mohammad Barzegar-Jalali [a], Mahdis Mohammadzade [b], Fleming Martinez [c], Abolghasem Jouyban [d,e,*]

[a] Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Grupo de Investigaciones Farmacéutico-Fisicoquímicas, Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia-Sede Bogotá, Cra. 30 No. 45-03, Bogotá, D.C., Colombia
[d] Pharmaceutical Analysis Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran
[e] Kimia Idea Pardaz Azarbayjan (KIPA) Science Based Company, Tabriz University of Medical Sciences, Tabriz 51664, Iran

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ABSTRACT

The experimental solubility of naproxen in some *N*-methyl-2-pyrrolidone + water mixtures at different temperatures (293.2, 298.2, 303.2, 308.2 and 313.2 K) was reported. The solubility was mathematically represented using two numerical methods; i.e., the combined van't Hoff equation and Jouyban–Acree model and its derived version employing all solubility data points (method I) and the minimum number of data points ($N = 10$, method II) were used to train the combined models. The accuracies of the correlated/predicted solubilities were evaluated by computing mean relative percentage deviation (MRPD). The obtained MRPDs for investigated numerical analyses were less than 6 %. A number of thermodynamic parameters were also computed using the generated solubility data to provide more details on the mechanism of dissolution.

1. Introduction

Naproxen (NAP) or (+)-6-methoxy-α-methyl-2-naphthaleneacetic acid (Fig. 1), a non-steroidal anti-inflammatory drug (NSAID) is a pain killer (mild to moderate), a common drug for reduction of fever, stiffness and inflammation of osteoarthritis, rheumatoid arthritis, psoriatic arthritis and treatment of dysmenorrhea [1,2]. NAP is a class II drug of biopharmaceutics classification system whose bioavailability is limited by its dissolution rate. To increase the low bioavailability of poorly soluble drugs, several solubilization techniques are employed including the addition of pharmaceutical cosolvents which is commonly used in the industry [3]. In order to design liquid formulations (either oral or parenteral), knowledge of solubility is required [4].

N-methyl-2-pyrrolidone (NMP) is a strong solubilizing agent [5] and an important solvent in extraction, purification and crystallization of drugs. Its pharmaceutical applications were reviewed in our published work [6]. The solubility data of some drugs in aqueous mixtures of NMP including cefotaxime [7], dioxopromethazine HCl [8], estrone and griseofulvin [9], clonazepam, diazepam, lamotrigine and phenobarbital [10], pioglitazone HCl [11] and amiodarone HCl [12] in NMP + water mixtures have been reported in the literature.

The solubility of NAP was reported in ethyl acetate + ethanol [13], ethanol + propylene glycol [14], and aqueous mixtures of propylene glycol [15], ethanol [16], polyethylene glycol 200 [17], 2-propanol [18] and methanol [19], as well as in a number of the mono-solvents including 1-butanol [20], 1-octanol, isopropyl myristate, chloroform and cyclohexane [21] and 1,4-dioxane [22].

In addition to the experimental solubility measurement method which is a time consuming procedure, a number of cosolvency models were developed to describe the solubility of drugs in mixed solvents [3,23,24]. These models include the linear [25] and non-linear [26] models. Despite of their different appearance of the models, they could be converted as a unified cosolvency model as has been shown in an earlier work [27]. The Jouyban–Acree model provides accurate computations for solute's solubility as a function of temperature and solvent composition of the binary solvent mixture and is [28]:

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

in which $C_{m,T}^{sat}$ is the solute solubility in the solvent mixtures at temperature T, φ_1 and φ_2 are the volume fractions of the solvents 1 and 2 in the

* Corresponding author at: Pharmaceutical Analysis Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran.
E-mail address: ajouyban@hotmail.com (A. Jouyban).

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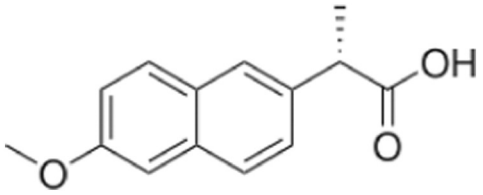

Fig. 1. Chemical structure of naproxen.

absence of solute, $C_{1,T}^{sat}$ and $C_{2,T}^{sat}$ are the molar solubility of the solute in the mono-solvents 1 and 2, respectively, and J_i denotes the constants of the model which computed by a regression analysis. Eq. (1) requires $C_{1,T}^{sat}$ and $C_{2,T}^{sat}$ values at each temperature of interest and could be considered as a limiting factor for its practical applications in the pharmaceutical industry. To cover this limitation, it is combined with the van't Hoff equation by replacing the $\log C_{1,T}^{sat}$ and $\log C_{2,T}^{sat}$ from van't Hoff equation. The combined version is [29]:

$$\log C_{m,T}^{sat} = \varphi_1\left(A_1 + \frac{B_1}{T}\right) + \varphi_2\left(A_2 + \frac{B_2}{T}\right) + \frac{\varphi_1 \cdot \varphi_2}{T}\sum_{i=0}^{2} J_i \cdot (\varphi_1 - \varphi_2)^i. \quad (2)$$

The A_1, B_1, A_2, B_2 and J_i terms are the model constants and could be computed using a no intercept least square analysis. It is possible to derive another equation by replacing φ_2 with $(1-\varphi_1)$ in Eq. (2) and subsequent rearrangements [30,31] as:

$$T \log C_{m,T} = W_0 + W_1\varphi_1 + W_2 T + W_3\varphi_1 T + W_4\varphi_1^2 + W_5\varphi_1^3 + W_6\varphi_1^4 \quad (3)$$

where W terms are the model constants computed using a common least square analysis.

This work aimed to 1) report the experimental solubility of NAP in some binary mixtures of NMP and water at 293.2 to 313.2 K, 2) predict the solubility of NAP at different temperatures using a combination of Jouyban–Acree model with van't Hoff equation in NMP + water, and 3) provide some thermodynamic parameters computed using generated data.

2. Experimental

2.1. Materials

NAP (230.29 $g \cdot mol^{-1}$) was purchased from Daana pharmaceutical company (Tabriz, Iran) and used as received from the company. The claimed value for the purity of the solute in its certificate was 98.5%. NMP (mass fraction purity of 0.995) was obtained from Scharlau Chemie (Spain). Ethanol with purity of 96% v/v (or 0.935 in mass fraction) was supplied by Jahan Teb Alcohol (Arak, Iran) and used for dilution of NAP solutions prior to spectrophotometric analysis. Double distilled water was used to prepare the solutions in this work.

2.2. Solubility determination procedure

Solubility determination methods were been reviewed in a previous work [32]. To measure the solubility of NAP, NMP + water binary mixtures were prepared by mixing appropriate volumes of the solvents (0.00 to 0.60 in volume fractions) varying by 0.10 intervals. The solvent volumes were measured using a pipette (Silber, Germany) with uncertainty of 0.1 mL. Excess amount of NAP was added to each flask and the flasks were placed in an incubator-shaker (Heidolph Unimax 1010, Germany) with a temperature controlling system having an uncertainty of 0.1 K. All the experiments were carried out at temperatures ranging from 293.2 to 313.2 K. The solutions were shaken until the solubility equilibrium was reached and the saturation is verified by the presence of un-dissolved drug. The saturated solutions were filtered using regenerated cellulose membrane filters (0.45 μm, Albet Lab Science, Spain). In order to analyze concentrations of NAP with UV/Vis spectrophotometer, aliquots of the solutions were diluted by distilled water–ethanol (50:50) mixture. Both centrifuging and diluting steps were performed at temperature of interest using an incubator (Kimia Idea Pardaz Azarbayjan (KIPA) Co., Tabriz, Iran) with uncertainty of 0.1 K. The absorbance of the diluted solutions was recorded at 262 nm using a UV–Vis spectrophotometer (Cecil CE 7250, UK) and the molar concentrations were determined using UV absorbance calibration curve. Each experimental data is an average of at least three repeated measurements.

2.3. Computational method

The A, B and J_i constants of Eq. (2) for solubility of NAP in NMP + water mixtures at various temperatures were obtained using a no intercept least square analysis (method I). The computed constants were used to back-calculate the solubility using Eq. (2). The experimental solubility data at the lowest and highest temperatures were fitted to Eq. (2) and the model constants, i.e. A, B and J_i values were calculated. Then the solubility at other temperatures was predicted using an interpolation technique (method II). The similar computations were also carried out employing Eq. (3).

The mean relative percentage deviations (MRPDs) were calculated as an accuracy criterion of the computations using:

$$\mathrm{MRPD} = \frac{100}{N}\sum\left(\frac{\left|C_{m,T}^{Calculated} - C_{m,T}^{Exprimental}\right|}{C_{m,T}^{Exprimental}}\right) \quad (4)$$

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

3. Results and discussion

3.1. Experimental solubility and correlation analysis

Volume fractions of NMP + water binary solvent mixtures and the experimental solubility of NAP at investigated temperatures (293.2, 298.2, 303.2, 308.2 and 313.2 K) are listed in Table 1. NAP solubility at all temperatures is increased at higher temperatures as it is expected for the solubility of solid solutes. The solubility is increased at a given temperature with the addition of NMP. The measured aqueous solubility of NAP in this work is 3.00×10^{-4} $mol \cdot L^{-1}$ at 298.2 K which is in agreement with the published data (2.84×10^{-4} $mol \cdot L^{-1}$ [33] and 3.32×10^{-4} $mol \cdot L^{-1}$ [34]). Figs. 2a and 2b compare the linear and logarithmic molar solubility of NAP in several aqueous cosolvent mixtures at 298.2 K [14,16,18,19]. Eq. (2) was used to fit the experimental data points (numerical method I) and the obtained model for representing the solubility of NAP in NMP + water mixtures at various temperatures

Table 1
Experimental molar solubility of naproxen in NMP (1) + water (2) mixtures at different temperatures.

φ_1	T/K				
	293.2	298.2	303.2	308.2	313.2
0.00	2.70×10^{-4}	3.00×10^{-4}	3.90×10^{-4}	4.70×10^{-4}	5.50×10^{-4}
0.10	8.30×10^{-4}	1.08×10^{-3}	1.22×10^{-3}	1.38×10^{-3}	1.75×10^{-3}
0.20	2.40×10^{-3}	2.98×10^{-3}	3.85×10^{-3}	4.64×10^{-3}	5.63×10^{-3}
0.30	8.10×10^{-3}	1.07×10^{-2}	1.27×10^{-2}	1.69×10^{-2}	2.01×10^{-2}
0.40	2.35×10^{-2}	3.02×10^{-2}	3.71×10^{-2}	5.25×10^{-2}	6.05×10^{-2}
0.50	8.91×10^{-2}	1.04×10^{-1}	1.42×10^{-1}	1.63×10^{-1}	2.09×10^{-1}
0.60	3.50×10^{-1}	4.02×10^{-1}	4.71×10^{-1}	5.26×10^{-1}	6.99×10^{-1}

The relative standard uncertainty for the solubilities is 5.0% or $u_r(x) = 0.05$, the standard uncertainty for temperature is 0.1 K and the measurements were made at atmospheric pressure.