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Solubility of naproxen in 2-propanol + water mixtures at various temperatures

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ABSTRACT

The experimental solubility of naproxen in 2-propanol + water mixtures at different temperatures (298.2, 303.2, 308.2 and 313.2 K) was reported. The solubility was correlated and/or predicted using three numerical methods; i.e., the combined van't Hoff equation and Jouyban–Acree model (method I), the extended version of the Jouyban–Acree model with Abraham parameters (method II), and the minimum number of data points (N = 10) were used to train the combined model. The accuracies of the calculated solubilities were evaluated by computing the mean percentage deviation (MPD). The obtained MPDs for investigated numerical analyses varied between 13 and 30%.

1. Introduction

Naproxen or (+)-6-methoxy-α-methyl-2-naphthaleneacetic acid (Fig. 1), a non-steroidal anti-inflammatory drug (NSAID) that is commonly used for the reduction of pain (mild to moderate), is also used for reduction of fever, stiffness and inflammation of osteoarthritis, rheumatoid arthritis, psoriatic arthritis and treatment of dysmenorrhea [1,2]. Its mechanism of action is inhibition of cyclo-oxygenases 1 and 2 which inhibits prostaglandin synthesis.

Naproxen is a BCS (biopharmaceutics classification system) class II drug whose bioavailability is rate-limited by its dissolution. The most challenging problem associated with naproxen formulation development is its limited aqueous solubility. To improve the low bioavailability of poorly soluble drugs several solubilization techniques could be found in the literature including the addition of pharmaceutical cosolvents which is the commonly used technique [3–5]. In order to design the process of pharmaceutical dosage forms for injectable formulation, knowing some physicochemical properties such as solubility and the occupied volumes by the drugs and other components in the solution is needed [6,7]. The solubility behavior of drugs in cosolvent mixtures at different temperatures is used in pre-formulation studies, purification methods and pharmaceutical dosage form design, among other applications [4,8].

The solubility of naproxen was reported in ethyl acetate + ethanol [9], ethanol + propylene glycol [10], propylene glycol + water [11], ethanol + water [12] and polyethylene glycol 200 + water [13] mixtures and in the mono-solvents 1-butanol [14], 1-octanol [15] and 1,4-dioxane [16].

Solubility measurement is a laborious and time consuming procedure and mathematical models could be used as an alternative approach. A number of models have been developed to predict the solubility of drugs in mixed solvent [4,17,18]. The Jouyban–Acree model is one of the well-established models providing the most accurate computations for solubility of solutes with respect to temperature and composition of the solvent mixture and is [19]:

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

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 absence of solute, $C_{1,T}^{sat}$ and $C_{2,T}^{sat}$ are the molar solubility of the solute in the neat solvents 1 and 2, respectively, and J_i denotes the constants of the model which are computed by a regression analysis. Eq. (1) requires experimental values of $C_{1,T}^{sat}$ and $C_{2,T}^{sat}$ 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 could be

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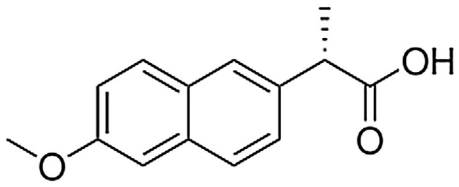

Fig. 1. Chemical structure of naproxen.

combined with the van't Hoff equation [20] by replacing the $C_{1,T}^{sat}$ and $C_{2,T}^{sat}$ values with the corresponding terms from van't Hoff equation. The combined version is [21]:

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

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.

Solubility of drugs is influenced by the interactions in the solutions between solvents and the solute represented by physical and chemical parameters similar to those proposed by Acree and Abraham [22]. The Abraham model includes five parameters for each solute and six solvent coefficients which were previously calculated for a number of solvents [23]. The general Abraham model is:

$$\log\left(\frac{C_S}{C_W}\right) = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + v \cdot V \quad (3)$$

where C_s and C_w are the solubilities of solute (in molarities) in the organic solvent and water, respectively, E is the excess molar refraction, S the is dipolarity/polarizability of solute, A denotes the solute's hydrogen-bond acidity, B indicates the solute's hydrogen-bond basicity and V is the McGowan volume of the solute. The c, e, s, a, b and v are the Abraham solvent coefficients and E, S, A, B and V are the Abraham solute parameters [23].

The Jouyban–Acree model and the Abraham solvation parameters could be combined for providing a globally trained model to predict the solubility of drugs in mixed solvents. The trained model for solubility of drugs in cosolvent + water mixtures at various temperatures [24] is:

$$\begin{aligned}\log C_{m,T}^{sat} = {} & \varphi_1 \log C_{1,T}^{sat} + \varphi_2 \log C_{2,T}^{sat} + \frac{\varphi_1.\varphi_2(\varphi_1-\varphi_2)^i}{T} + \frac{\varphi_1.\varphi_2}{T} \\ & \times \left\{ \begin{matrix} 1639.07 - 561.01\left[(c_1-c_2)^2\right] - 1344.81\left[E(e_1-e_2)^2\right] - 18.22\left[S(s_1-s_2)^2\right] \\ -3.65\left[A(a_1-a_2)^2\right] + 0.86\left[B(b_1-b_2)^2\right] + 4.40\left[V(v_1-v_2)^2\right] \end{matrix} \right\} \\ & + \frac{\varphi_1.\varphi_2(\varphi_1-\varphi_2)}{T} \\ & \times \left\{ \begin{matrix} -1054.03 + 1043.54\left[(c_1-c_2)^2\right] + 359.47\left[E(e_1-e_2)^2\right] \\ -1.20\left[S(s_1-s_2)^2\right] + 30.26\left[A(a_1-a_2)^2\right] - 2.66\left[B(b_1-b_2)^2\right] \\ -0.16\left[V(v_1-v_2)^2\right] \end{matrix} \right\} \\ & + \frac{\varphi_1.\varphi_2(\varphi_1-\varphi_2)^2}{T} \\ & \times \left\{ \begin{matrix} 2895.07 - 1913.07\left[(c_1-c_2)^2\right] - 901.29\left[E(e_1-e_2)^2\right] - 10.87\left[S(s_1-s_2)^2\right] \\ +24.62\left[A(a_1-a_2)^2\right] + 9.79\left[B(b_1-b_2)^2\right] - 24.38\left[V(v_1-v_2)^2\right] \end{matrix} \right\} \end{aligned} \quad (4)$$

in which c_1, e_1, s_1, a_1, b_1 and v_1 terms are the Abraham solvent coefficients of solvent 1 (2-propanol in this work) with the numerical values of 0.063, 0.320, 1.024, 0.445, −3.824 and 4.067, respectively and c_2, e_2, s_2, a_2, b_2 and v_2 are those of solvent 2 (water in this work) with the numerical values of −0.994, 0.577, 2.549, 3.813, 4.841 and −0.869, respectively. The numerical values of Abraham solvent coefficients were computed for a number of solvents and listed in some publications of Abraham et al. [25]. This extended version provided another prediction tool for solubility of drugs in aqueous binary solvent mixtures [24]. The first two terms of Eq. (4) represent the ideal mixing behaviors of the saturated solutions of the analyte in the mono-solvents, and the other model constants and variables present the effects of solvent composition and temperature on non-ideal mixing behavior of the saturated solution and the interactions between solvent 1 and solvent 2 and the solute in the mixed solvent system. These model constants for a single analyte have been explained in more detail in earlier reports [26,27]. Concerning modeling of the solubility of different solutes in cosolvent + water mixtures at various temperatures, we included the Abraham solute parameters and Abraham solvent coefficients for representing the effects of different chemical structures of drugs and physico-chemical properties of binary solvents on the solubilities.

Therefore, the objectives of this work are the following.

1) Reporting the experimental solubility of naproxen in binary mixtures of 2-propanol and water at 298.2, 303.2, 308.2, and 313.2 K.
2) Predicting the solubility of naproxen at different temperatures using a combination of Jouyban–Acree model with van't Hoff equation in 2-propanol + water.
3) Predicting the solubility of naproxen at different temperatures using a globally trained Jouyban–Acree model employing the Abraham solute parameters and Abraham solvent coefficients.

2. Experimental

2.1. Materials

Naproxen (230.29 $g \cdot mol^{-1}$) was purchased from Daana Pharmaceutical Company (Tabriz, Iran) and used without further purification. The claimed value for the purity of the solute in its certificate was 98.5%. 2-Propanol (mass fraction purity of 0.997) was obtained from Merck company (Germany). Ethanol with a purity of 96% v/v (or 0.935 in mass fraction) was supplied by Jahan Teb Alcohol (Arak, Iran) and used for dilution of naproxen solutions prior to spectrophotometric analysis. Distilled water was used throughout this work.

2.2. Solubility determination procedure

Available solubility determination methods were reviewed in a recent work [28]. The solubility of naproxen was determined using the saturation shake-flask method. Briefly, 2-propanol + water binary mixtures were prepared by mixing appropriate volumes of solvents (0.00 to 1.00 in volume fractions) varying by 0.10 intervals. The solvent volumes were measured using a pipette (Silber, Germany) with an uncertainty of 0.06 mL. Excess amount of naproxen 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 298.2 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 with UV/Vis spectrophotometer, aliquots of 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 an 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.

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