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Solubility of acetaminophen and ibuprofen in polyethylene glycol 600, propylene glycol and water mixtures at 25 °C

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ABSTRACT

The solubilities of acetaminophen and ibuprofen in the mixtures of propylene glycol–water, of polyethylene glycol 600–propylene glycol, and of polyethylene glycol 600–propylene glycol–water at 25 °C are determined and mathematically represented by the Jouyban–Acree model. The solubilities are measured using the shake flask method and the model is used to fit the solubility data of each drug in the solvent mixtures. The density of the solute-free solvent mixtures is measured and employed to train the Jouyban–Acree model and then the density of the saturated solutions is predicted. The obtained overall mean relative deviations (OMRDs) for fitting the solubility data of acetaminophen and ibuprofen in binary mixtures are 1.4% and 11.2%, respectively. The OMRDs for fitting the solubilities in ternary solvent mixtures for acetaminophen and ibuprofen are 16.5% and 37.5%, respectively, and the OMRD values for predicting all solubilities of acetaminophen and ibuprofen by these trained versions of the Jouyban–Acree model were 5.2% and 17.8%, respectively. The prediction of OMRD for the density of saturated solutions was 2.2%.

1. Introduction

A large number of drugs which are used in clinical practice are poorly soluble in water. During drug development, many insoluble pharmaceutical candidates which have a high biological activity are identified. However, because of the low bioavailability, these candidates are never used clinically. Therefore, it is necessary to establish a technique for solubilizing them and controlling their bio-distributions in order to expand the utility of such compounds for various applications. Several carriers such as liposomes, polymeric micelles, solid nanoparticles, lipid emulsions, and synthetic polymers [1] have been used to solubilize poorly water-soluble drugs. In oral and injectable dosage forms, the excipients which are used include pH modifiers, water-soluble organic solvents, surfactants, water-insoluble organic solvents, medium-chain triglycerides, long-chain triglycerides, cyclodextrins and phospholipids [2]. The majority of available oral formulations are solid dosage forms such as tablets and capsules, but there are many solubilized oral formulations such as elixirs, syrups, oral solutions or solutions filled into soft or hard gelatin capsules. Some poorly water-soluble candidates are solubilized in solutions which are made of an aqueous/organic cosolvent; some other poorly water-soluble candidates are solubilized only in solutions that are completely organic and are composed of one solvent or a mixture of solvents/surfactants. The water-soluble organic solvents in available solubilized oral formulations are polyethylene glycols (PEGs), ethanol, propylene glycol (PG) and glycerol with many water-soluble non-ionic surfactants.

Recently, aqueous polymer solutions, especially PEG–water mixtures, have found widespread applications, such as in two-phase aqueous mixtures for separation of biomolecular compounds [3–6]. PEG or polyethylene oxide under the trade name of Carbowax® is the most important type of polyethers. They are neutral polymers, linear or branched, available in a variety of molecular weights. They are soluble in water and in most of the organic solvents. These are widely used in the pharmaceutical industry because of their low toxicity and high water solubility [5,7,8].

PG (1,2-propandiol) is used in oral, intravenous and topical pharmaceutical formulations as a solvent [9]. It is considered as a safe cosolvent. But in high doses, especially if given in a short period of time, it can be toxic. Hyperosmolality, increased anion gap metabolic acidosis, acute kidney injury and sepsis-like syndrome are some of the toxic effects of it. Hemodialysis is the treatment for toxicity, which removes PG effectively; however, prevention is the best treatment which is achieved by limiting the infused dose of PG [9]. The terminal half-life of PG, in adults with normal liver and kidney functions, varies from 1.4 to 3.3 h. Lactate, acetate and pyruvate are formed by metabolizing PG by liver, and the non-metabolized cosolvent in glucoronide conjugate form is excreted in urine. The acceptable level of PG has not been defined and the clinical implication of a PG level is unclear [9,10]. The World Health Organization (WHO) reports a maximum amount of 25 mg/kg/day of PG when used as a food additive, but this report does not limit its use as a drug cosolvent. In most of pharmaceutical formulations, the exact amount of PG present

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is not reported, but in a few formulations, the maximum amount of PG is reported to be up to 55% in oral solutions and elixirs (for children older than 4 years) [2].

To achieve an optimized solvent mixture for dissolving a certain amount of a drug in a given volume of the solvent, the trial-and-error approach is employed in practice, which is time-consuming and expensive. Therefore, using cosolvency models could be an appropriate solution. Among the developed cosolvency models, the Jouyban–Acree model is one of the most versatile models. It provides the accurate mathematical descriptions and shows how the solute solubility varies with both temperature and solvent composition. The model for representing the solubility of a solute in a binary solvent mixture at various temperatures is

$$\log C_{m,T}^{\mathrm{Sat}} = w_1 \log C_{1,T}^{\mathrm{Sat}} + w_2 \log C_{2,T}^{\mathrm{Sat}} + \left[\frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i\right] \quad (1)$$

where $C_{m,T}^{\mathrm{Sat}}$ is the solute molar solubility in the binary solvent mixtures at temperature T (expressed as K); w_1, and w_2 are the mass fractions of solvents 1 and 2 in the absence of the solute; $C_{1,T}^{\mathrm{Sat}}$ and $C_{2,T}^{\mathrm{Sat}}$ denote the molar solubility of the solute in neat solvents 1 and 2, respectively. The J_i terms are the constants of the model and are computed by regressing $(\log C_{m,T}^{\mathrm{Sat}} - w_1 \log C_{1,T}^{\mathrm{Sat}} - w_2 \log C_{2,T}^{\mathrm{Sat}})$ against $\frac{w_1 w_2}{T}$, $\frac{w_1 w_2 (w_1 - w_2)}{T}$, and $\frac{w_1 w_2 (w_1 - w_2)^2}{T}$. The Jouyban–Acree model was used to calculate multiple solubility maxima [11] and also to correlate other physicochemical properties in solvent mixtures [12–16] and the model promises accurate mathematical representations. Eq. (1) was used at a fixed temperature in which the $\frac{1}{T}$ term could be incorporated in J_i terms in some applications [11,17]. However, we prefer to use Eq. (1), since it could be used to predict the solubility at other temperatures of interest by employing the solubility data in mono-solvents at T [18,19].

The Jouyban–Acree model has theoretical justifications [20], among other cosolvency models it shows the most accurate correlations [17], and by employing the solubility data in mono-solvents, it is capable of predicting the solubility data in solvent mixtures at various temperatures [21–26]. In addition to binary solvent mixtures, the extended models for predicting the solubility data of drugs in ternary solvent mixtures are

$$\log C_{m,T}^{\mathrm{Sat}} = w_1 \log C_{1,T}^{\mathrm{Sat}} + w_2 \log C_{2,T}^{\mathrm{Sat}} + w_3 \log C_{3,T}^{\mathrm{Sat}} + \left[\frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i\right] + \left[\frac{w_1 w_3}{T}\sum_{i=0}^{2} J_i' (w_1 - w_3)^i\right] + \left[\frac{w_2 w_3}{T}\sum_{i=0}^{2} J_i'' (w_2 - w_3)^i\right] \quad (2)$$

$$\log C_{m,T}^{\mathrm{Sat}} = w_1 \log C_{1,T}^{\mathrm{Sat}} + w_2 \log C_{2,T}^{\mathrm{Sat}} + w_3 \log C_{3,T}^{\mathrm{Sat}} + \left[\frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i\right] + \left[\frac{w_1 w_3}{T}\sum_{i=0}^{2} J_i' (w_1 - w_3)^i\right] + \left[\frac{w_2 w_3}{T}\sum_{i=0}^{2} J_i'' (w_2 - w_3)^i\right] + \left[\frac{w_1 w_2 w_3}{T}\sum_{i=0}^{2} J_i''' (w_1 - w_2 - w_3)^i\right] \quad (3)$$

where $C_{3,T}^{\mathrm{Sat}}$ is the solute molar solubility in solvent 3 at temperature T, and w_3 is the mass fraction of solvent 3 in the absence of the solute. The J_i' and J_i'' terms are computed using the same procedure of J_i terms. The J_i''' terms are the ternary solvent interaction terms and computed by regressing

$$\left\{\log C_{m,T}^{\mathrm{Sat}} - w_1 \log C_{1,T}^{\mathrm{Sat}} - w_2 \log C_{2,T}^{\mathrm{Sat}} - w_3 \log C_{3,T}^{\mathrm{Sat}} - \left[\frac{w_1 w_2}{T}\sum_{i=0}^{2} J_i (w_1 - w_2)^i\right] - \left[\frac{w_1 w_3}{T}\sum_{i=0}^{2} J_i' (w_1 - w_3)^i\right] - \left[\frac{w_2 w_3}{T}\sum_{i=0}^{2} J_i'' (w_2 - w_3)^i\right]\right\}$$

against $\frac{w_1 w_2 w_3}{T}$, $\frac{w_1 w_2 w_3 (w_1 - w_2 - w_3)}{T}$, and $\frac{w_1 w_2 w_3 (w_1 - w_2 - w_3)^2}{T}$.

The existence of these model constants that require a number of solubility data in solvent mixtures for training process is a limitation for the model when the solubility predictions are the goal of the computations in early drug discovery studies.

Experimental solubilities of acetaminophen and ibuprofen in PEG 600 (1)–water (3) mixtures and the experimental solubilities of acetaminophen in PG (2)–water (3) mixtures were reported in previous studies [27,28]. In this study, the experimental solubilities of these drugs in PEG 600 (1)–PG (2) and PEG 600 (1)–PG (2)–water (3) mixtures and ibuprofen solubility data in PG (2)–water (3) mixtures at 25 °C are reported and the applicability of the Jouyban–Acree model to predict the measured solubility data is shown. In addition, the applicability of the Jouyban–Acree model for predicting the density of the saturated solutions by employing the density of solute-free solutions of mixed solvents is shown.

2. Experimental

2.1. Materials

Acetaminophen and ibuprofen were gifts from Daana Pharmaceutical Company (Iran). The purity of the drugs was checked by determining their melting points and comparing their measured solubilities in mono-solvents with the corresponding data from the literature [29,30]. PG was purchased from Merck (Germany), PEG 600 was a gift from Daana Pharmaceutical Company (Iran) and double distilled water was used for preparation of the solutions.

2.2. Apparatus and procedures

The binary solvent mixtures were prepared by mixing the appropriate grams of the solvents with the uncertainty of 0.1 g. The solubilities of acetaminophen and ibuprofen in the solvent mixtures were determined by equilibrating excess amounts of drugs at 25 °C using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature controlling system maintained constant within ±0.2 °C (Nabziran, Tabriz, Iran). Because of the high viscosity of PEG 600, after sufficient length of time (>98 h), the saturated solutions of the drugs were centrifuged at 13,000 rpm for 15 min, diluted with water for acetaminophen and methanol for ibuprofen, then assayed at 243 nm and 222 nm, respectively, using a UV–Vis spectrophotometer (Beckman DU-650, Fullerton, USA). Concentrations of the diluted solutions were determined from the calibration curves. Each experimental data point represents the average of at least three repetitive experiments with the measured molar solubilities being reproducible to within ±2.8%. Densities of the saturated solutions and the solvent mixtures in the absence of the solute were measured by a 5 ml pycnometer as a single measurement.

3. Theory and calculations

In the numerical analysis I, the experimental solubility data of each drug in binary solvents were fitted to Eq. (1), the model constants were computed and the back-calculated solubilities were used to compute the MRD values. In the next analysis, the obtained model constants were included in Eq. (2), and then it was used to calculate the solubility of each drug in ternary solvent mixtures. In order to provide better calculations, the ternary interaction terms of Eq. (3) were calculated using a linear regression analysis.

In a previous study [22], the generally trained version of the Jouyban–Acree model has been reported for PG (1)–water (2) binary mixtures:

$$\log C_{m,T}^{\mathrm{Sat}} = w_1 \log C_{1,T}^{\mathrm{Sat}} + w_2 \log C_{2,T}^{\mathrm{Sat}} + \frac{w_1 w_2}{T}[37.030 + 319.490(w_1 - w_2)]. \quad (4)$$