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Solubility of fluphenazine decanoate in aqueous mixtures of polyethylene glycols 400 and 600 at various temperatures

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ABSTRACT

The solubility of fluphenazine decanoate (FD) in aqueous binary mixtures of polyethylene glycols 400 (PEG 400) and 600 (PEG 600) at 298.0–318.0 K and atmospheric pressure along with some thermodynamic properties are reported. The previously trained version of the Jouyban–Acree model for PEG 400 + water, a recently proposed general cosolvency model employing partial solubility parameters, and a combination of the model with van't Hoff equation were used to predict the solubility of FD in PEG 400 + water and PEG 600 + water at different temperatures. The results show that the Jouyban–Acree model can be used for solubility prediction of FD in aqueous mixtures of PEG 400 and PEG 600 at different temperatures. Densities of solute free aqueous mixtures of PEG 400 and PEG 600 along with their FD-saturated solutions are also reported.

1. Introduction

High hydrophobicity and low aqueous solubility is frequently observed characteristics of hits, lead compounds, development candidates and marketed drugs. Nearly 40% of currently marketed drugs and up to 75% of drug candidates currently under development investigations are poorly soluble drugs [1] and low aqueous solubility is still a challenging area in the pharmaceutical industry [2,3]. Any computational method to predict and even estimate the aqueous solubility of a drug could assist the medicinal chemist to identify low water soluble hits will be a useful tool to save money in drug discovery studies. Available prediction tools to compute the aqueous solubility of drugs are reviewed [4] and recently a new simple relationship was proposed to predict the aqueous solubility of drugs [5]. The proposed model employs simple computational descriptors and trained using the aqueous solubility of official drugs and was validated using a prediction data set of 75 aqueous solubility data of pharmaceuticals which were not included in the training process of the model. Although the model produced better predictions in comparison with other similar models, however, more accurate models to predict the aqueous solubility is highly in demand in the pharmaceutical industry. The common application of high-throughput screening procedures in non-aqueous and/or mixed solvent systems plays an important role in drug discovery investigations. In addition, the mixed solvent systems are used in drug development studies including formulation of liquid dosage forms for oral and/or parenteral uses, optimizing separation parameters in analytical methods such as liquid chromatography or capillary electrophoresis especially in combination with temperature.

Cosolvency or solvent mixing is a common method for solubilization of low aqueous soluble drugs and polyethylene glycols (PEGs) are used frequently in the pharmaceutical, chemical, cosmetic, and food industries [6]. Due to the significant lack of solubility data for many solute-solvent combinations and in order to facilitate the prediction of the solubility data in a given solvent composition and to provide some evidences for better understanding the solubility phenomenon, a number of mathematical models have been presented [7]. These models vary from the simplest log-linear model of Yalkowsky [8] to the more complicated equation of state of Ruckenstein and Shulgin [9]. Most of pharmaceutical scientists prefer to use log-linear model since it requires the aqueous solubility of the drug and its logarithm of partition coefficient which could be easily computed using available software such as ACD-Lab [10]. However, the model produces relatively high prediction error. To provide more accurate predictions for solubility of drugs in

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Table 1
Details of materials used in this work.

Chemical name	Source	Purity
Fluphenazine decanoate	Chimidaru Pharm. Co.	0.994 in mass fraction
Polyethylene glycol 400	Daana Pharm. Co.	0.95 in mass fraction
Polyethylene glycol 600	Daana Pharm. Co.	0.95 in mass fraction
Ethanol (for dilution purposes)	Jahan Alcohol Teb	0.935 in mass fraction
Water	Lab made	Conductivity of <1.5 microSiemense

mixed solvents at various temperatures, the Jouyban–Acree model was proposed which requires the solubility data in the mono-solvents as input data and its computations are straightforward.

Fluphenazine decanoate (FD), CAS number of 5002-47-1, is a long acting phenothiazine drug used to treat schizophrenia. Aqueous solubility of FD is low, however it is soluble in ethanol, acetone, benzene and ether [11]. The solubilities of FD in propylene glycol + water and PEG 200 + water mixtures at various temperatures were reported in previous reports [12,13]. In this work, the solubility data of FD in PEG 400 + water and PEG 600 + water mixtures at different temperatures are reported along with densities of their solute free and saturated solutions. The predicted solubilities using previously trained models also were used to compare their prediction capabilities. In addition, the solubilization powers of PEGs 200, 400 and 600 were discussed in terms of available quantitative scales.

2. Experimental

2.1. Materials

FD (purity of 0.994 in mass fraction) was a gift from Chimidaru, PEGs 400 and 600 (0.95 in mass fraction) were purchased from Daana Pharmaceutical company (Tabriz, Iran) and ethanol (0.935 in mass fraction), used for dilution of the solutions for spectrophotometric analysis, was purchased from Jahan Alcohol Teb (Arak, Iran). Double-distilled water was used in the preparation of solvent mixtures. Summary of details of the used materials is listed in Table 1.

2.2. Solubility determination procedures

PEGs + water mixtures were prepared by mixing appropriate masses of the solvents with the uncertainty of 0.1 g. Various solubility determination methods could be found in the literature [14] and the saturation shake-flask method of Higuchi and Connors [15] was used in this work. Briefly, the solubility of FD was determined by equilibrating an excess amount of the solid with the binary solvent mixtures using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature-controlling system having an uncertainty of 0.2 K (Nabziran, Tabriz, Iran) for 3 days. After the attainment of equilibrium at 298 K the solubility and density measurements were performed, and the unused samples containing excess solid were then equilibrated at the next higher temperature (i.e. 303 K) for 2 days. The procedure was repeated until all five temperatures had been studied. The solutions were filtered using hydrophilic Durapore filters (0.45 μm, Millipore, Ireland) and the filtrate was diluted with ethanol. The absorbance of the diluted solutions were recorded at 317 nm using a UV–vis spectrophotometer (Beckman DU-650, Fullerton, USA) and the concentrations of FD were calculated based on the Beer–Lambert law calibration curve constructed from the measured absorbance of standard solutions of known FD concentration. Calibration graph was constructed using the molar absorptivity (ranging from 25446.11 $\varepsilon/(\mathrm{L\,mol^{-1}\,cm^{-1}})$ to 27418.67 $\varepsilon/(\mathrm{L\,mol^{-1}\,cm^{-1}})$) of FD standard solutions. The relative standard uncertainty of solubility experiments were 0.02. Each experimental data point is an average of at least three experimental measurements. Densities of the saturated solutions were determined using a 5 mL pycnometer as a single determination with the uncertainty of 0.002 g cm^{-3}. Densities of the solute free PEG 400 + water and PEG 600 + water mixtures at various temperatures were measured in triplicates. Details of the relative standard deviations (RSDs) for repeated measurements are reported in Table 2.

2.3. Computational method

The Jouyban–Acree model for representing the solubility of a solute in binary solvent mixture at various temperatures [7] is

$$\log x_{m,T}^{sat} = m_1 \cdot \log x_{1,T}^{sat} + m_2 \cdot \log x_{2,T}^{sat} + \frac{m_1.m_2}{T} \cdot \sum_{i=0}^{2} J_i.(m_1 - m_2)^i \quad (1)$$

in which $x_{m,T}^{sat}$ is the solute's mole fraction solubility in the binary solvent mixtures at temperature T (expressed as K), m_1 and m_2 are the initial mass fractions of the solvent 1 (PEG 400 or 600) and solvent 2 (water) in the absence of the solute, $x_{1,T}^{sat}$ and $x_{2,T}^{sat}$ denote the mole fraction solubility of the solute in the mono-solvents 1 and 2, respectively, and J_i represent the constants of the model computed by regression analysis. To provide a predictive version of the Jouyban–Acree model for predicting the solubility of drugs in PEG 400 + water mixtures at different temperatures, the following model was proposed [16]:

$$\log x_{m,T}^{sat} = m_1 \cdot \log x_{1,T}^{sat} + m_2 \cdot \log x_{2,T}^{sat} + \left(\frac{m_1 m_2}{T}\right)[394.82 - 355.28(m_1 - m_2) + 388.89(m_1 - m_2)^2] \quad (2)$$

which is applicable to the solubility prediction of drugs in other PEGs + water mixtures at various temperatures [17] since there is no variable representing the effects of cosolvent nature and solute nature on the solubility phenomenon. Recently, a general model which is a combination of the Jouyban–Acree model and partial solubility parameters was proposed for predicting the solubility of drugs in various cosolvent + water mixture as [18]:

$$\begin{aligned}\log x_{m,T} = {} & m_1 \log x_{1,T} + m_2 \log x_{2,T} \\ & + \left(\frac{m_1 m_2}{T}\right)\{0.606\,\delta_{ps}(\delta_{p1} - \delta_{p2})^2 + 0.013\,\delta_{hs}(\delta_{h1} - \delta_{h2})^2\} \\ & + \left(\frac{m_1 m_2 (m_1 - m_2)}{T}\right)\{-8.696\,\delta_{ds}(\delta_{d1} - \delta_{d2})^2 \\ & + 0.376\,\delta_{ps}(\delta_{p1} - \delta_{p2})^2 + 0.013\,\delta_{hs}(\delta_{h1} - \delta_{h2})^2\} \\ & + \left(\frac{m_1 m_2 (m_1 - m_2)^2}{T}\right)\{9.277\,\delta_{ds}(\delta_{d1} - \delta_{d2})^2 - 0.461\,\delta_{ps}(\delta_{p1} - \delta_{p2})^2 \\ & + 0.017\,\delta_{hs}(\delta_{h1} - \delta_{h2})^2\}\end{aligned} \quad (3)$$

in which δ_{ds}, δ_{ps} and δ_{hs} are the partial solubility parameters of the solutes, δ_d, δ_h and δ_p are the partial solubility parameters of solvents and subscripts 1 and 2 denote cosolvent (PEGs 400 or 600 in this work) and water, respectively. The partial solubility parameters represent the effects of cosolvent and solute natures on the solubility.