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Thermodynamic studies of fluphenazine decanoate solubility in propylene glycol + water mixtures and correlation with the Jouyban–Acree model

Vahid Panahi-Azar[a], Ali Shayanfar[b], Fleming Martínez[c], William E. Acree Jr[d], Abolghasem Jouyban[e,*]

[a] Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Grupo de Investigaciones Farmacéutico-Fisicoquímicas, Departamento de Farmacia, Universidad Nacional de Colombia, A.A. 14490, Bogotá D.C., Colombia
[d] Department of Chemistry, University of North Texas, Denton, TX 76203-5070, USA
[e] Drug Applied Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

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ABSTRACT

Solubilities of fluphenazine decanoate (FD) in binary mixtures of propylene glycol + water (PG + W) at 293.2, 298.2, 303.2, 308.2, and 313.2 K are reported. The combination of Jouyban–Acree model and van't Hoff equation is used to predict the solubility of FD in a given solvent mixture at different temperatures. The thermodynamic properties (enthalpy, entropy and Gibbs energy standard changes of solutions) for FD in PG + W mixtures are calculated from solubility data using the modified version of van't Hoff and Gibbs equations. The results show that Jouyban–Acree model can predict the solubility of FD in PG + W mixtures as a function of temperature over the studied temperature range. The study represents the first time that thermodynamic properties of solutes dissolved in binary solvent mixtures have been described by the Jouyban–Acree model. The calculated values are in good agreement with the measured experimental data.

1. Introduction

Solubility alteration of chemicals is required in many chemical and pharmaceutical applications, including crystallization, separation, decontamination, liquid extraction, and drug formulation. Solvent mixing or cosolvency is one of the most frequent and feasible methods used in the chemical industry. Temperature alteration and solvent mixing are common methods to modify solubility in crystallization studies. For many solutes there is insufficient solubility data. To address this concern considerable effort has been devoted to developing models that enable one to make solubility predictions from a minimum number of experimental input values [1–4].

Fluphenazine decanoate (FD) is an ester prodrug of fluphenazine that is used to treatment of schizophrenia [5]. FD is practically insoluble in water, and very soluble in alcohol, chloroform, cyclohexane and ether [6]. In this study the solubility of FD in binary propylene glycol + water (PG + W) mixtures was determined. PG is a stable, low toxic pharmaceutical cosolvent used in many commercially available oral and parenteral pharmaceutical formulations of poorly soluble drugs [7].

Experimental solubility determination is a time-consuming and costly process [8]. Several mathematical models have been proposed in the published literature to predict the solubility of drugs in cosolvent + water mixtures. The Jouyban–Acree model is one of the models developed by our group. The model provides an accurate mathematical description for how the solute solubility varies with both temperature and solvent composition. The model for representing the solubility of a solute in binary mixture at various temperatures is [9]:

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

where $x_{m,T}^{sat}$ is the solute solubility in the solvent mixtures at temperature T, m_1 and m_2 are the fractions of the PG and W in the absence of the solute, $x_{1,T}^{Sat}$ and $x_{2,T}^{Sat}$ denote 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. A predictive limitation of the Jouyban–Acree model is that the model constants must be known for the given solute dissolved in the binary solvent mixture under consideration in order to compute the J_i constants in Eq. (1). This limitation severely restricts the application of the Jouyban–Acree model in the early drug discovery and development stages as the drug candidate's solubility may not have been measured yet. Predictions, not measurements, are used in early drug

* Corresponding author. Tel.: +98 411 3372254; fax: +98 411 3344798.
E-mail address: ajouyban@hotmail.com (A. Jouyban).

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discovery and development studies to select the more promising drug candidates for future studies.

Quantitative structure–property relationship (QSPR) models have been proposed to predict the numerical values of the model constants. The QSPR model that was recommended for predicting the solubility of drug molecules in binary PG + W mixtures is [9]:

$$\log x_{m,T}^{sat} = m_1 \log x_{1,T}^{sat} + m_2 \log x_{2,T}^{sat} + \left[\frac{37.030 m_1 m_2}{T} + \frac{319.490 m_1 m_2 (m_1 - m_2)}{T}\right]. \quad (2)$$

The required input values for the solubility at different temperatures in mono-solvent can be calculated using van't Hoff:

$$\log x_T^{Sat} = A + \frac{B}{T} \quad (3)$$

with the A and B model constants determined from a linear least square analysis of the measured solute solubility as a function of temperature, ($\log X_T^{Sat}$) [10], or from solubility data measured at two temperatures (e.g. at the lowest and at the highest temperatures studied for each mono-solvent). The Jouyban–Acree and van't Hoff models were combined to enable one to make solubility predictions for drug molecules in mixed solvents as a function of temperature using measured solubility data for the drug dissolved in each solvent at two temperatures [11].

Solubility measurements often employ spectroscopic methods that give the experimental concentration of the solute in the saturated solution as a molar solubility value. The density of the saturated solution is required to convert the measured molar solubility (mole per liter) value to a mole fraction solubility (or vice versa), which is required in many industrial applications, The Jouyban–Acree model also describes the variation of the density of liquid mixtures as a function of both temperature and composition [12]. In recent papers [13,14] we have used trained versions of the Jouyban–Acree model to calculate densities of saturated drug solutions. The model was trained using measured density data for the solute-free binary solvent mixture. The advantage of this latter application of the Jouyban–Acree model is the large reduction in the number of experimental measurements that must be made to just two measurements. One must measure the densities of saturated drug solutions for the two mono-solvents, $\rho_{1,T}^{sat}$ and $\rho_{2,T}^{sat}$. To apply the density version of the Jouyban–Acree model to FD dissolved in binary PG + W mixtures, we first trained the model for binary PG + W mixtures at various temperatures:

$$\log \rho_{m,T} = m_1 \log \rho_{1,T} + m_2 \log \rho_{2,T} + 17.543\left(\frac{m_1 m_2}{T}\right) + 4.755\left(\frac{m_1 m_2 (m_1 - m_2)}{T}\right) - 1.032\left(\frac{m_1 m_2 (m_1 - m_2)}{T}\right)^2 \quad (4)$$

in which $\rho_{m,T}$, $\rho_{1,T}$ and ρ_{2T} are the density of solute free mixtures and solvents 1 and 2 at temperatures T. The experimental density data were collected from the published literature [15]. The calculated interaction terms in Eq. (4) can be used to predict the density of saturated solutions of FD dissolved in binary PG + W mixtures by:

$$\log \rho_{m,T}^{sat} = m_1 \log \rho_{1,T}^{sat} + m_2 \log \rho_{2,T}^{sat} + 17.543\left(\frac{m_1 m_2}{T}\right) + 4.755\left(\frac{m_1 m_2 (m_1 - m_2)}{T}\right) - 1.032\left(\frac{m_1 m_2 (m_1 - m_2)}{T}\right)^2 \quad (5)$$

in which $\rho_{m,T}^{Sat}$ is the density of the saturated solution of the drug in the mixed solvent system, $\rho_{1,T}^{Sat}$ and $\rho_{2,T}^{Sat}$ are the densities of the saturated solutions of the drug in mono-solvents 1 and 2 at temperature of T.

Standard enthalpy (ΔH°), entropy (ΔS°), and Gibbs energy (ΔG°) changes can be calculated using modified version of van't Hoff equation [16–19]. The mean harmonic temperature (T_{hm}) that is used in van't Hoff analysis, is calculated as

$$T_{hm} = \frac{n}{\sum_{i=1}^{n}(1/T)} \quad (6)$$

where n is the number of temperatures studied. Expressed in terms of the mean harmonic temperature, the modified version of van't Hoff equation becomes [16–19]:

$$\log x_T^{Sat} = -\frac{\Delta H^\circ}{R}\left(\frac{1}{T} - \frac{1}{T_{hm}}\right) \quad (7)$$

R is the universal gas constant ($R = 8.314\ \mathrm{J\ K^{-1}\ mol^{-1}}$). The ΔG° and ΔS° values are calculated:

$$\Delta G^\circ = -RT_{hm} \cdot \text{intercept} \quad (8)$$

$$\Delta S^\circ = \frac{\Delta H^\circ - \Delta G^\circ}{T_{hm}} \quad (9)$$

from Eqs. (8) and (9), respectively. The relative enthalpic, ($\%\xi_H$), and entropic ($\%\xi_{TS}$), contributions of the solubility of FD in PG + W mixtures is given by Eqs. (10) and (11), respectively [16,18]:

$$\%\xi_H = 100\frac{\left|\Delta H^\circ\right|}{\left|\Delta H^\circ\right| + \left|T\Delta S^\circ\right|} \quad (10)$$

$$\%\xi_{TS} = 100\frac{\left|T\Delta S^\circ\right|}{\left|\Delta H^\circ\right| + \left|T\Delta S^\circ\right|} \quad (11)$$

To date, the Jouyban–Acree model has been applied to properties such as electrophoretic mobility, instability rate constants, acid dissociation constants, retention factor of analytes in HPLC, solvatochromic parameter, dielectric constant, surface tension, refractive index, ultrasound velocity and viscosity of solvent mixtures [9]. However, there is no report on prediction of thermodynamic properties (ΔH°, ΔS°, ΔG°) for solutes dissolved in binary solvent mixtures.

The objectives of the present study are: (1) to measure the experimental solubility data of FD in PG + W mixtures at different temperatures; (2) to determine the feasibility of predicting the solubility of FD in PG + W mixtures using a combination of Jouyban–Acree model and van't Hoff equation, (3) to further assess the applicability of our proposed method for predicting the density of saturated solutions based on the density of solute free solvent mixtures; (4) to compute the thermodynamic characteristic of FD dissolved in binary PG + W mixtures calculated by van't Hoff equation; and (5) to determine whether the calculated thermodynamic properties for FD dissolved in binary PG + W could be described by the Jouyban–Acree model.

2. Experimental

2.1. Materials

FD (99.4% in mass fraction) was a gift from Chemidaru, PG (99.5% in mass fraction) was purchased from Scharlau Chemie (Spain), ethanol (96% volume fraction) from Jahan Alcohol Teb (Arak, Iran) and used for dilution of the concentrated solutions before spectroscopic analysis, and double-distilled water was used for the preparation of the solutions. All chemicals were used as received from the company without further purifications.