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Thermodynamics of the solubility of reserpine in {{2-(2-ethoxyethoxy)ethanol + water}} mixed solvent systems at different temperatures

Faiyaz Shakeel [a,*], Nazrul Haq [a], Nasir A. Siddiqui [b], Fars K. Alanazi [c], Ibrahim A. Alsarra [c]

[a] Research Center, College of Science, King Saud University, Riyadh 11451, Saudi Arabia
[b] Department of Pharmacognosy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia
[c] Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

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ABSTRACT

Thermodynamics of solubility of the bioactive compound reserpine in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems was investigated in this study. The solubility of reserpine was determined from T = (298.15 to 338.15) K at atmospheric pressure using the reported method of Higuchi and Connors. Values of the measured solubility of reserpine were correlated with the ideal and Yalkowsky models. The root mean square deviations (RMSD) were observed to be less than 0.020 by an ideal model. However, the RMSD values were observed as less than 0.050 by the Yalkowsky model. The mole fraction solubility of reserpine was observed highest in pure 2-(2-ethoxyethoxy)ethanol ($7.69 \cdot 10^{-4}$ at T = 298.15 K) and lowest in pure water ($9.71 \cdot 10^{-7}$ at T = 298.15 K) at each temperature investigated. The results of the Van't Hoff and Krug analysis (thermodynamic studies) indicated endothermic and spontaneous dissolution of reserpine in all {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems.

1. Introduction

Reserpine (3,4,5-trimethoxybenzoyl methyl reserpate, figure 1) is a natural bioactive compound which occurs as a white to off-white crystalline powder [1,2]. It is an active phytoconstituent of *Rauwolfia serpentia* which is used as an antihypertensive and antipsychotic drug [3–5]. It has been reported as a poorly water-soluble compound in water and most of the organic solvents [6]. Weak water-solubility of drugs is the main barrier for their formulation development [7,8]. Recently, 2-(2-ethoxyethoxy)ethanol (Transcutol®) has been investigated as an efficient co-solvent for solubility enhancement of several poorly water-soluble drugs [9–15]. Various attempts via co-precipitation, solid dispersion and co-solvency approach have been made in order to enhance solubility and dissolution rate enhancement of reserpine [7,8,16–18]. However, the thermodynamics of solubility of reserpine in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems have not been reported in literature. Therefore, in this work, values of the solubility of reserpine in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems were determined from T = (298.15 to 338.15) K at atmospheric pressure of 0.1 MPa using the reported shake flask method [19]. Various thermodynamic parameters for the dissolution of reserpine were also determined using Van't Hoff and Krug analysis.

2. Experimental

2.1. Materials

Reserpine (mass fraction purity of 0.990) was procured from Sigma Aldrich (St. Louis, MO). Transctol® (IUPAC name: 2-(2-ethoxyethoxy)ethanol and mass fraction purity of 0.999) was procured from Gattefosse (Lyon, France). The water used in this study was high pure deionised water which was obtained from Milli-Q water purification unit (Millipore Corporation, Berlin, Germany). The detailed information regarding these materials is listed in table 1. Because, all these materials were of high purity, these were used without any further purification.

2.2. Measurement of reserpine solubility

The solubility of reserpine against mass fraction of 2-(2-ethoxyethoxy)ethanol (m = 0.0 to 1.0) in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems was measured from T = (298.15 to 338.15) K and atmospheric pressure of 0.1 MPa using

* Corresponding author. Tel.: +966 537507318.
E-mail address: faiyazs@fastmail.fm (F. Shakeel).

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the reported method of Higuchi and Connors [19]. Hence, the excess amount of reserpine was added in known amounts (5 g) of {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems. The concentrated suspensions of reserpine in each {2-(2-ethoxyethoxy)ethanol + water} mixed solvent system were vortexed for 5 min and shaken continuously in a biological shaker (Julabo, PA) at 100 rpm for 72 h [12–14]. Experiments were performed in triplicate. The temperature was controlled with a thermostatic bath equipped with biological shaker. After 72 h, all the samples were taken out from the biological shaker and allowed the solute particles to settle for 2 h [9–11]. The samples were centrifuged at 5000 rpm for 15 min in order to remove fine particles. The supernatants from each sample were taken, diluted and subjected for the quantification of reserpine content using UV–Visible spectrophotometer at 268 nm [17]. The proposed spectrophotometric method was observed linear over the concentration range of (2 to 20) $\mu g \cdot g^{-1}$. The accuracy of the method was observed to be (98.60 to 100.40)%. The experimental mole fraction solubility (x_e) of reserpine in each co-solvent mixture was calculated as reported in literature [10,11].

3. Results and discussion

3.1. Measured solubility data of reserpine

The measured values of the solubility of reserpine in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems at five different temperatures from (298.15 to 338.15) K and atmospheric pressure are listed in table 2. The mole fraction solubility of reserpine in pure water (m = 0.0), pure 2-(2-ethoxyethoxy)ethanol (m = 1.0) and {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems is not available in the literature. However, it has been reported as practically insoluble in water at room temperature (298.15 K) according to the Unites States Pharmacopoeia (USP) [6]. In the present work, the mole fraction solubility of reserpine in water at T = 298.15 K was found to be $9.74 \cdot 10^{-7}$. According to this value, reserpine was considered as practically insoluble in water. This observation was in good agreement with USP [6]. In general, the x_e values of reserpine increased with increase in temperature and mass fraction of 2-(2-ethoxyethoxy)ethanol in {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems. The x_e values of reserpine were observed highest in pure 2-(2-ethoxyethoxy)ethanol ($7.69 \cdot 10^{-4}$ at T = 298.15 K) at each temperature investigated. However, the lowest x_e values were observed in pure water ($9.71 \cdot 10^{-7}$ at T = 298.15 K) at each temperature investigated. The highest x_e values of reserpine in pure 2-(2-ethoxyethoxy)ethanol were probably due to the lower polarity of 2-(2-ethoxyethoxy)ethanol as compared to the higher polarity of water. The influence of mass fraction of 2-(2-ethoxyethoxy)ethanol on mole fraction solubility of reserpine at different temperatures is shown in figure 2. The solubility of bioactive reserpine was found to increase with increase in mass fraction of 2-(2-ethoxyethoxy)ethanol in {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems at each temperature investigated (figure 2). These results are in accordance with previously published solubility values of other poorly water-soluble drugs such as paracetamol, diclofenac sodium, glibenclamide, risperidone, tadalafil, isoniazid analogue and thiosemicarbazone derivative in {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems [9–15].

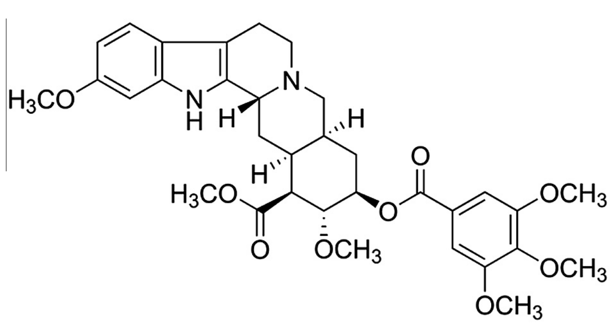

FIGURE 1. Molecular structure of reserpine (molar mass: 608.68).

3.2. Correlation of experimental solubility with an ideal model

According to this model, the mole fraction solubility of reserpine in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems can be calculated using equation (1) [20]:

$$\ln x^{idl} = a + \frac{b}{T}. \tag{1}$$

Here, x^{idl} is the ideal model solubility of reserpine and T is the absolute temperature (K). Parameters a and b are the ideal model parameters which were determined by plotting ln x_e against $1/T$. For the correlation of x_e with x^{idl}, the root mean square deviations ($RMSD$) were calculated with the help of equation (2).

$$RMSD = \left[\frac{1}{N}\sum_{i=1}^{N}\left(\frac{x^{idl} - x_e}{x_e}\right)^2\right]^{\frac{1}{2}}, \tag{2}$$

in which, N is the number of experimental temperature points. The graphical correlations between x_e and x^{idl} of reserpine in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems are presented in figure S1.

The values of a and b, correlation coefficients (R^2) and $RMSD$ in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems are presented in table S1. The $RMSD$ values in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems were recorded as (0.007 to 0.018). The R^2 values for reserpine were observed to lie within the range of (0.9950 to 0.9990) (table S1). These results indicate a good correlation of measured solubility of reserpine with an ideal model.

3.3. Correlation of experimental solubility with the Yalkowsky model

According to this model, the solubility of reserpine in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems can be calculated with the help of equation (3) [21]:

$$\text{Log}\, x^{Yal} = \log S_2 + (\log S_2 - \log S_1)m_1, \tag{3}$$

in which, x^{Yal} is the Yalkowsky model solubility of reserpine in {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems; S_1 and S_2 represent the solubility of reserpine in pure solvent 1 (2-(2-ethoxyethoxy)ethanol) and pure solvent 2 (water), respectively; and m_1 is the mass fraction of pure solvent 1 in the absence of reserpine. For correlation of experimental solubility with the Yalkowsky model, $RMSD$ values were calculated again using the previous equation (2).

The log x^{Yal} values of reserpine along with $RMSD$ values in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems at different temperatures are listed in table S2. The $RMSD$ values in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems were recorded as (0.010 to 0.044). These results also indicate a good correlation of measured solubility with the Yalkowsky model.

3.4. Thermodynamic parameters for reserpine dissolution

The dissolution enthalpy ($\Delta_{sol}H^{o}$) for reserpine in various {2-(2-ethoxyethoxy)ethanol + water} mixed solvent systems was