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Thermodynamics and solubilization behavior of (2Z)-*N*-cyclohexyl-2-(3-hydroxybenzylidine) hydrazine carbothioamide in polyethylene glycol-400 + water mixtures at (298.15 to 338.15) K

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ABSTRACT

Dissolution thermodynamics of (2Z)-*N*-cyclohexyl-2-(3-hydroxybenzylidine) hydrazine carbothioamide (CHBH) in various polyethylene glycol-400 (PEG-400) + water mixtures from (298.15 to 338.15) K were studied and correlated. The experimental solubilities were correlated with the modified Apelblat and Yalkowsky models. The root mean square deviations (RMSD) were observed as (0.88–4.28)% for the modified Apelblat model and (2.10–8.25)% for Yalkowsky model. The mole fraction solubility (7.12×10^{-2} at 298.15 K) and mass fraction solubility (5.32×10^{-2} kg kg^{-1} at 298.15 K) of CHBH were observed highest in pure PEG-400. However, the lowest mole fraction (3.83×10^{-7} at 298.15 K) and mass fraction solubility (5.90×10^{-6} kg kg^{-1} at 298.15 K) of CHBH were observed in pure water. Thermodynamic studies showed endothermic and spontaneous dissolution of CHBH in all co-solvent mixtures.

1. Introduction

(2Z)-*N*-cyclohexyl-2-(3-hydroxybenzylidine) hydrazine carbothioamide (CHBH) is a newly synthesized derivative of thiosemicarbazone (TSC) [1]. The molecular structure of CHBH is presented in Fig. 1 (molar mass: 277.38 g mol^{-1} and molecular formula: $C_{14}H_{19}N_3OS$). TSC derivatives have been investigated with wide variety of therapeutic applications including anticancer, anticonvulsant and antimalarial potential [2–5]. Unfortunately, TSC derivatives developed in literature showed poor aqueous solubility which is the main barrier for formulation development of TSC derivatives [2,5]. Co-solvency approach is a simple and commonly used method for solubility and stability enhancement of poorly soluble compounds [6]. Co-solvents such as ethanol, propylene glycol (PG) and polyethylene glycol-400 (PEG-400) are the commonly used co-solvents for solubility enhancement of poorly water-soluble compounds [6–11]. The modified Apelblat model is the commonly used thermodynamics-based mathematical model for the correlation of experimental solubilities with calculated ones and to investigate the influence of temperature on mole fraction solubility of solute [12–14]. However, the log-linear model of Yalkowsky is also one of the simple co-solvency models used to correlate experimental solubilities of solute with calculated ones and to investigate the influence of co-solvent mixtures on mole fraction solubility of solute [15]. The temperature dependent solubility data and dissolution thermodynamics of CHBH in various pure solvents such as water, ethanol, PG, PEG-400, ethylene glycol, isopropyl alcohol, ethyl acetate and 2-(2-ethoxyethoxy) ethanol and various 2-(2-ethoxyethoxy) ethanol + water co-solvent mixtures at (298.15–338.15) K have been reported in literatures [1,16]. However, the temperature dependent solubility data and dissolution thermodynamics of CHBH in various PEG-400 + water mixtures have not been reported in literature. Therefore, in the present investigation, the dissolution thermodynamics of CHBH in various PEG-400 + water mixtures from (298.15 to 338.15) K were studied. The experimental solubilities of CHBH were measured using an isothermal method [17]. The experimental solubilities of CHBH were correlated with the modified Apelblat and Yalkowsky models.

2. Experimental

2.1. Materials

CHBH [IUPAC name: (2Z)-*N*-cyclohexyl-2-(3-hydroxybenzylidine) hydrazine carbothioamide] (mass fraction purity of 0.994)

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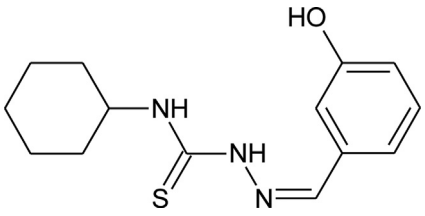

Fig. 1. Molecular structure of CHBH.

was synthesized in the laboratory of Pharmaceutical Chemistry, King Saud University, Riyadh, Saudi Arabia [1]. PEG-400 [IUPAC name: poly(oxyethene)] (mass fraction purity of 0.999) was purchased from Fluka Chemicals (Busch, Switzerland). The water used in this study was deionized water and obtained from ELGA water purification system (Wycombe, Bucks, UK). The compound CBHB was purified by recrystallization with absolute ethanol. The purity of CHBH was determined using gas chromatography method. All other materials were of high purity and used without any further purification.

2.2. Measurement of CHBH solubility

The solubility of CHBH against mass fraction of PEG-400 (m = 0.0–1.0) in various PEG-400 + water mixtures was measured from (298.15 to 338.15) K at atmospheric pressure of 0.1 MPa using an isothermal method [17]. The excess amount of solute was added in known amounts of each co-solvent mixture in triplicate. These mixtures were transferred to an isothermal biological shaker (Julabo, PA) at 100 rpm for 72 h [1,16]. After 72 h, all co-solvent mixtures were taken out from the shaker and allowed to settle solute particles for the period of 2 h [16]. The supernatants from each sample were diluted with respective solute free co-solvent mixture. The quantification of CHBH content in each sample was performed by UV–vis spectrophotometer (SP1900, Axiom, Germany) at 320 nm as reported previously [1]. The standard uncertainty for the temperatures $u(T)$ was observed as ±0.09 K. However, the relative standard uncertainty in solubility $u_r(x_e)$ was found to be 1.1%. The experimental mole fraction solubilities (x_e) of CHBH were calculated using reported formula [7,8].

3. Results and discussion

3.1. Solubility data of CHBH

The mole fraction and mass fraction solubilities (S_m) of CHBH in various PEG-400 + water mixtures from (298.15 to 338.15) K and atmospheric pressure are listed in Table 1. The solubilities of CHBH were found to be increasing with increase in temperature in all PEG-400 + water mixtures at (298.15 to 338.15) K. The values of x_e and S_m in pure water have been reported as 3.90×10^{-7} and 6.00×10^{-6} kg kg^{-1} at 298.15 K, respectively [1]. However, the values of x_e and S_m in pure PEG-400 have been reported as 7.10×10^{-2} and 5.30×10^{-2} kg kg^{-1} at 298.15 K, respectively [1]. In the current study, the values of x_e and S_m in pure water were observed as 3.83×10^{-7} and 5.90×10^{-6} kg kg^{-1} at 298.15 K, respectively. Moreover, the values of x_e and S_m in pure PEG-400 were observed as 7.12×10^{-2} and 5.32×10^{-2} kg kg^{-1} at 298.15 K, respectively. These results indicated that our results were in good agreement with previously published solubility data of CHBH [1]. Overall, the values of x_e and S_m of CHBH were observed highest in pure PEG-400 (m = 1.0) as compared to water (m = 0.0) and other co-solvent mixtures at (298.15 to 338.15) K (Table 1). The solubilities of CHBH in pure PEG-400 were significantly higher than its solubilities in water from (298.15 to 338.15) K that could be due to the higher polarity and lower molar mass of water as compared to pure PEG-400 [7,9]. Similar type of results were also obtained for isoniazid analog (a poorly water-soluble compound) in PG + water and PEG-400 + water co-solvents mixtures which indicated good agreement of our results with previous literatures [8,10]. Based on these results, CHBH has been considered as practically insoluble in water and soluble in PEG-400. Hence, PEG-400 could be used as a physiologically compatible co-solvent in preformulation studies and formulation development of CHBH.

3.2. Correlation of experimental solubilities with the modified Apelblat model

The modified Apelblat model was used to investigate the influence of temperature on mole fraction solubility of CHBH [12–14]. According to this model, the mole fraction solubility of solute is temperature dependent and can be expressed using Eq. (1) [13,14]:

$$\ln x = A + \frac{B}{T} + C\ln(T) \quad (1)$$

In which, x and T are the calculated solubilities of CHBH and absolute temperature (K), respectively. The parameters A, B and C are the modified Apelblat parameters which were determined by multivariate regression analysis of experimental mole fraction solubilities of CHBH [1,16]. The calculated solubilities (x) of CHBH were back calculated using these parameters. The percentage of root mean square deviations (% RMSD) between x_e and x were calculated using Eq. (2) [10].

Table 1
Experimental mole fraction (x_e) and mass fraction solubilities (S_m) (kg kg^{-1} of solvent) of CHBH against mass fraction of PEG-400 (m) in various PEG-400 + water mixtures at temperatures T = (298.15 to 338.15) K and pressure p = 0.1 MPa[a].

m	x_e					S_m/kg kg^{-1}				
	T = 298.15 K	T = 308.15 K	T = 318.15 K	T = 328.15 K	T = 338.15 K	T = 298.15 K	T = 308.15 K	T = 318.15 K	T = 328.15 K	T = 338.15 K
0.0	3.83×10^{-7}	5.91×10^{-7}	8.96×10^{-7}	1.38×10^{-6}	1.90×10^{-6}	5.90×10^{-6}	9.10×10^{-6}	1.38×10^{-5}	2.12×10^{-5}	2.93×10^{-5}
0.1	1.39×10^{-6}	2.01×10^{-6}	2.83×10^{-6}	4.16×10^{-6}	5.67×10^{-6}	1.93×10^{-5}	2.80×10^{-5}	3.94×10^{-5}	5.80×10^{-5}	7.90×10^{-5}
0.2	4.58×10^{-6}	6.26×10^{-6}	8.99×10^{-6}	1.36×10^{-5}	1.77×10^{-5}	5.70×10^{-5}	7.80×10^{-5}	1.12×10^{-4}	1.70×10^{-4}	2.20×10^{-4}
0.3	1.55×10^{-5}	2.18×10^{-5}	2.91×10^{-5}	3.91×10^{-5}	5.10×10^{-5}	1.70×10^{-4}	2.40×10^{-4}	3.20×10^{-4}	4.30×10^{-4}	5.60×10^{-4}
0.4	5.01×10^{-5}	6.73×10^{-5}	8.83×10^{-5}	1.26×10^{-4}	1.52×10^{-4}	4.77×10^{-4}	6.40×10^{-4}	8.40×10^{-4}	1.20×10^{-3}	1.45×10^{-3}
0.5	1.74×10^{-4}	2.19×10^{-4}	2.86×10^{-4}	3.65×10^{-4}	4.47×10^{-4}	1.40×10^{-3}	1.76×10^{-3}	2.30×10^{-3}	2.94×10^{-3}	3.60×10^{-3}
0.6	5.62×10^{-4}	6.99×10^{-4}	8.66×10^{-4}	1.12×10^{-3}	1.34×10^{-3}	3.70×10^{-3}	4.60×10^{-3}	5.70×10^{-3}	7.40×10^{-3}	8.80×10^{-3}
0.7	2.07×10^{-3}	2.35×10^{-3}	2.74×10^{-3}	3.07×10^{-3}	3.42×10^{-3}	1.06×10^{-2}	1.20×10^{-2}	1.40×10^{-2}	1.57×10^{-2}	1.75×10^{-2}
0.8	6.29×10^{-3}	7.40×10^{-3}	8.86×10^{-3}	1.09×10^{-2}	1.33×10^{-2}	2.30×10^{-2}	2.71×10^{-2}	3.25×10^{-2}	4.00×10^{-2}	4.90×10^{-2}
0.9	2.17×10^{-2}	2.48×10^{-2}	2.79×10^{-2}	3.13×10^{-2}	3.44×10^{-2}	4.80×10^{-2}	5.50×10^{-2}	6.20×10^{-2}	7.00×10^{-2}	7.70×10^{-2}
1.0	7.12×10^{-2}	7.76×10^{-2}	8.37×10^{-2}	9.33×10^{-2}	1.00×10^{-1}	5.32×10^{-2}	5.84×10^{-2}	6.34×10^{-2}	7.14×10^{-2}	7.75×10^{-2}

[a] The standard uncertainties u are $u(T)$ = 0.09 K, $u(m)$ = 0.1%, $u(p)$ = 0.0003 Mpa and $u_r(x_e)$ = 1.11%.