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Solubility of anti-inflammatory drug lornoxicam in ten different green solvents at different temperatures

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ABSTRACT

In this work, the solubility of poorly water soluble anti-inflammatory drug lornoxicam (LOX) in ten different green solvents such as water, ethanol, 1-butanol, 2-butanol, ethylene glycol (EG), ethyl acetate (EA), isopropanol (IPA), propylene glycol (PG), polyethylene glycol-400 (PEG-400) and 2-(2-ethoxyethoxy) ethanol was measured at $T = (298.15$ to $323.15)$ K and $p = 0.1$ MPa using an isothermal method. The measured solubility data of LOX were correlated with Apelblat and Van't Hoff models with root mean square deviations in the range of 0.33 to 3.70%. The mole fraction solubility of LOX was observed highest in PEG-400 (8.55×10^{-3}) followed by 2-(2-ethoxyethoxy) ethanol, EG, EA, PG, 2-butanol, 1-butanol, IPA, ethanol and water at $T = 298.15$ K. Thermodynamic analysis indicated an endothermic and spontaneous dissolution behavior of LOX in all green solvents.

1. Introduction

The IUPAC name of lornoxicam (LOX) is 6-chloro-4-hydroxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide as shown in Fig. 1 [1,2]. It is commercially available as orange to yellow crystalline powder [2]. It is a newly launched non-steroidal anti-inflammatory drug (NSAID) which is used in the treatment of pains associated with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and postoperative dental pain [3–5]. It is marketed in the form of tablets and injections and its dose is relatively low as compared to other NSAIDs [3]. It has been reported as practically insoluble in water which results in poor in vivo absorption and bioavailability upon oral administration [1,3]. The solubility data of solid solutes in pure solvents could be useful in purification, crystallization, drug development process and formulation development [6–8]. The commonly used environmentally benign solvents (green solvents) for solubility enhancement of poorly water soluble drugs are ethanol, propylene glycol (PG) and polyethylene glycol-400 (PEG-400) [8–10]. Recently, 2-(2-ethoxyethoxy) ethanol (Transcutol) has also been investigated as a potential green solvent for solubility enhancement of various poorly water soluble drugs [11,12]. Various approaches such as cosolvency, solid dispersion and complexation have been investigated for solubility and dissolution enhancement of LOX in literature [3,13–15].

Moreover, the solubility of LOX in various pure solvents such as water, ethanol, ethyl acetate (EA), PG and PEG-400 at 298.15 K has also been reported in literature [3]. However, the temperature dependent solubility data of LOX in water, ethanol, ethylene glycol (EG), EA, 1-butanol, 2-butanol, isopropyl alcohol (IPA), PG, PEG-400 and 2-(2-ethoxyethoxy) ethanol are not available in literature. Therefore, in this work, the solubilities of crystalline LOX were measured at $T = (298.15$ to $323.15)$ K and $p = 0.1$ MPa using an isothermal method. From solubility data of crystalline LOX, various thermodynamic parameters for LOX dissolution were also determined using Van't Hoff and Krug et al. analysis approaches.

2. Experimental

2.1. Materials

LOX, 1-butyl alcohol (IUPAC name: 1-butanol), 2-butyl alcohol (IUPAC name: 2-butanol) and ethyl alcohol (IUPAC name: ethanol) were obtained from Sigma Aldrich (St. Louis, MO). EG (IUPAC name: ethane-1,2-diol), EA (IUPAC name: ethyl acetate) and IPA (IUPAC name: 2-propanol) were obtained from Winlab Laboratory (Leicestershire, UK). PG (IUPAC name: propane-1,2-diol) and PEG-400 [IUPAC name: poly(ethylene glycol)-400] were obtained from Fluka Chemicals (Busch, Switzerland). Transctol [IUPAC name: 2-(2-ethoxyethoxy) ethanol] was obtained from Gattefosse (Lyon, France). The water used in this work was chromatographic grade/high pure deionized water which was collected from Milli-Q water purification unit (Berlin,

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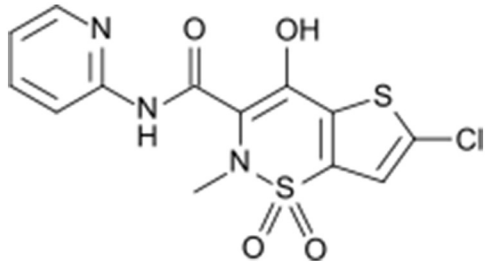

Fig. 1. Molecular structure of LOX (molar mass: 371.81 g·mol^{-1}).

Germany). The general information regarding all these materials is listed in Table 1.

2.2. Determination of LOX solubility

The solubility of LOX in ten different green solvents was determined at T = (298.15 to 323.15) K and p = 0.1 MPa using an isothermal method [16]. The excess amount of crystalline LOX was added in known amount of each green solvent. The experiments were carried out in triplicates. The samples were shaken continuously in a biological shaker bath (Julabo, PA) equipped with a thermostatic bath which was used to control the temperature. The speed of shaker was maintained at 100 rpm and experiments were performed for 72 h [8,9]. After 72 h, the samples were taken out from the biological shaker and allowed to settle LOX particles for 2 h [11,12]. The supernatants were taken, centrifuged (at 5000 rpm for 10 min) to remove fine solid particles, diluted with 0.05 M sodium hydroxide solution and subjected for analysis of LOX content using a UV–Visible spectrophotometer at a maximum wavelength of 376 nm [13]. The proposed spectrophotometric method was found to be linear in the concentration range of 1 to 25 μg·g^{-1} with correlation coefficient (R^2) of 0.999. The experimental mole fraction solubility (x_e) of LOX was calculated as reported in literature [6,7].

3. Results and discussion

3.1. Solubility data of LOX

The solubility data of LOX in ten different green solvents at T = (298.15 to 323.15) K and p = 0.1 MPa are presented in Table 2. Temperature-dependent solubility data of LOX in water, ethanol, 1-butanol, 2-butanol, EG, EA, IPA, PG, PEG-400 and 2-(2-ethoxyethoxy) ethanol have not been reported in literature. Nevertheless, the solubility of LOX in many of these solvents such as water, ethanol, PG, PEG-400 and EA at T = 298.15 K has been reported in literature [3]. The mole fraction solubility of LOX in water, ethanol, PG, PEG-400 and EA at T = 298.15 K has been reported as 2.74×10^{-6}, 8.18×10^{-6}, 3.27×10^{-5}, 8.64×10^{-3} and 8.79×10^{-5}, respectively [3]. In this work, the mole fraction solubility of LOX in water, ethanol, PG, PEG-400 and EA at T = 298.15 K was observed as 2.91×10^{-6}, 8.43×10^{-6}, 3.17×10^{-5}, 8.55×10^{-3} and 8.39×10^{-5}, respectively. These results were in accordance with previously published report. In general, the mole fraction solubility of LOX was found to be increasing with the rise in temperature in all green solvents. The mole fraction solubilities of crystalline LOX were observed highest in PEG-400 (8.55×10^{-3} at T = 298.15 K) followed by 2-(2-ethoxyethoxy) ethanol (3.17×10^{-4} at T = 298.15 K), EG (2.24×10^{-4} at T = 298.15 K), EA (8.39×10^{-5} at T = 298.15 K), PG (3.17×10^{-5} at T = 298.15 K), 2-butanol (2.99×10^{-5} at T = 298.15 K), 1-butanol (1.36×10^{-5} at T = 298.15 K), IPA (9.05×10^{-6} at T = 298.15 K), ethanol (8.43×10^{-6} at T = 298.15 K) and water (2.91×10^{-6} at T = 298.15 K) at room temperature (Table 2). The solubilities of crystalline LOX in PEG-400 were significantly higher than other green solvents investigated. This observation was possible due to higher molar mass of PEG-400.

3.2. Correlation of measured solubilities of LOX with Apelblat equation

According to this equation, the solubility of crystalline LOX was calculated using Eq. (1) [17,18]:

$$\ln x^{\mathrm{Apl}} = A + \frac{B}{T} + C \ln(T). \tag{1}$$

In which, x^{Apl} is the solubility of crystalline LOX calculated by Apelblat equation and T is the absolute temperature (K). The coefficients A, B and C are the Apelblat parameters and these coefficients were calculated by multivariate regression analysis of experimental solubilities of LOX [11]. The correlation between x_e and x^{Apl} was made by the calculation of the root mean square deviations (*RMSD*) which was calculated using Eq. (2) [11].

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

In which, the symbol N is the number of data points used in the experiment. The graphical correlation between x_e and x^{Apl} in ten different green solvents at T = (298.15 to 323.15) K is presented in Fig. S1. The resulting data of Apelblat correlation in ten different green solvents are listed in Table S1. The *RMSD* values in ten different green solvents were recorded in the range of 0.26 to 1.88% (Table S1). The R^2 values for crystalline LOX in ten different green solvents were recorded in the range of 0.9981 to 0.9999. These results indicated good correlation of experimental solubility data of crystalline LOX with Apelblat model.

Table 1
General information regarding LOX and green solvents.

Material	Molecular formula	Molar mass (g·mol^{-1})	Purity (mass fraction)	Analysis method	Source
LOX	$C_{13}H_{10}ClN_3O_4S_2$	371.82	>0.980	HPLC	Sigma Aldrich
Ethanol	C_2H_5OH	46.07	0.999	GC	Sigma Aldrich
Ethylene glycol	$C_2H_6O_2$	62.07	0.996	GC	Winlab Laboratory
Ethyl acetate	$C_4H_8O_2$	88.11	0.998	GC	Winlab Laboratory
Propylene glycol	$C_3H_8O_2$	76.09	0.995	GC	Fluka Chemicals
Polyethylene glycol-400	$H(OCH_2CH_2)_nOH$	400	0.999	GC	Fluka Chemicals
2-Propanol	C_3H_8O	60.10	0.997	GC	Winlab Laboratory
1-Butanol	$C_4H_{10}O$	74.12	0.990	HPLC	Sigma Aldrich
2-Butanol	$C_4H_{10}O$	74.12	0.990	HPLC	Sigma Aldrich
2-(2-Ethoxyethoxy) ethanol	$C_6H_{14}O_3$	134.17	0.999	GC	Gattefosse
Water	H_2O	18.01	–	–	Milli-Q Purification Unit

High performance liquid chromatography (HPLC); gas chromatography (GC).