Journal of Molecular Liquids 240 (2017) 447–453

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Solubility measurement, thermodynamics and molecular interactions of flufenamic acid in different neat solvents

Sultan Alshehri, Faiyaz Shakeel *

Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

ARTICLE INFO

Article history:
Received 4 April 2017
Received in revised form 17 May 2017
Accepted 22 May 2017
Available online 24 May 2017

Keywords:
Activity coefficient
Anti-inflammatory drug
Dissolution thermodynamics
Flufenamic acid
Neat solvent
Solubility

ABSTRACT

The solubility data of poorly soluble anti-inflammatory drug flufenamic acid (FFA) are scarce in literature. Therefore, in the current study, the solubility of FFA in eleven different neat solvents including "water, methanol, ethanol, isopropanol (IPA), ethylene glycol (EG), propylene glycol (PG), 1-butanol, 2-butanol, dimethyl sulfoxide (DMSO), polyethylene glycol-400 (PEG-400) and Transcutol®" was measured and correlated at temperatures "$T = 298.2$ K to 318.2 K" and pressure "$p = 0.1$ MPa". The solubilities of FFA in mole fraction were measured using a static equilibrium method and correlated with "van't Hoff and Apelblat equations". The mole fraction solubilities of FFA were obtained maximum in DMSO (2.86×10^{-1}), followed by Transcutol (2.78×10^{-1}), 2-butanol (1.79×10^{-1}), 1-butanol (1.77×10^{-1}), IPA (1.44×10^{-1}), ethanol (1.12×10^{-1}), methanol (6.29×10^{-2}), PEG-400 (6.16×10^{-2}), EG (1.20×10^{-2}), PG (1.81×10^{-2}) and water (1.60×10^{-6}) at "$T = 318.2$ K" and similar trends were also recorded at each temperature studied. Activity coefficients were also calculated in order to evaluate the molecular interactions between solute and solvent molecules and results showed higher solute-solvent molecular interactions in FFA-DMSO, FFA-Transcutol, FFA-2-butanol, FFA-1-butanol, FFA-IPA and FFA-ethanol in comparison with other solute-solvent combinations. "Apparent thermodynamic analysis" showed an "endothermic and entropy-driven dissolution" of FFA in all neat solvents studied.

1. Introduction

Flufenamic acid [FFA] (Fig. 1; IUPAC name: *2-[[3-(trifluoromethyl) phenyl]-amino]benzoic acid*; molecular formula: $C_{14}H_{10}F_3NO_2$; molar mass: 281.23 g mol^{-1} and CAS registry number: 530-78-9) has been recommended for the treatment of pain and inflammation associated with various kind of diseases and administered both topically as well as orally [1–3]. It belongs to the anthranilic class of non-steroidal anti-inflammatory drugs (NSAIDs) [2]. It has been reported as a potent NSAID which is a weakly acidic compound ($pK_a = 3.9$) with high value of octanol/water partition coefficient (log $P = 4.88$) [3]. Due to high value of its octanol/water partition coefficient, it is practically insoluble in water which is the main barrier of formulation development of FFA especially in terms of liquid dosage forms. The solubility data of poorly soluble drug molecules in "aqueous and organic solvents" have great importance in various industrial processes such as "purification, recrystallization, drug discovery process and formulation development" [4–9]. Hence, it is important to measure the solubility of FFA properly in these solvents in order to obtain complete physicochemical information of such drugs. The mole fraction solubility of FFA in water at temperature $T = 295.2$ K has been reported as 4.29×10^{-7} [3,10]. The solubility of FFA in light mineral oil at $T = 305.2$ K has also been reported [11]. The solubility of FFA in polyethylene glycol-400 (PEG-400) at ambient room temperature ($T = 298.2$ K) was also reported by Rytting et al. [12]. Lee et al. reported the solubility of FFA in hexane, methyl benzene and ethanol at $T = 298.2$ K and atmospheric pressure [13]. Surov et al. and Perlovich et al. reported the solubility data of FFA in hexane and 1-octanol at $T = 293.2$ K to 315.2 K under atmospheric pressure [2,14]. Domanska et al. also reported the solubility data of FFA in ethanol and 1-octanol at $T = 298.8$ K to 322.3 K under atmospheric pressure [15]. However, the solubility data of FFA in other neat solvents including methanol, isopropanol (IPA), 1-butanol, 2-butanol, Transcutol®, ethylene glycol (EG), propylene glycol (PG) and dimethyl sulfoxide (DMSO) have not been reported so far. Hence, in this study, the solubility of FFA in eleven different neat solvents including water, methanol, ethanol, IPA, 1-butanol, 2-butanol, Transcutol, EG, PG, PEG-400 and DMSO were measured and correlated at "$T = 298.2$ K to 318.2 K" and "$p = 0.1$ MPa". "Apparent thermodynamic analysis" on solubility data of FFA was also performed by "van't Hoff and Krug et al. analysis" in order to obtain dissolution behavior of FFA [16–18]. Studied temperature ranges were chosen randomly at the interval of 5.0 K in order to obtain good estimate of data. This temperature range was chosen in such a manner that the higher temperature should not exceed the fusion/melting temperature of drug. The activity coefficients were calculated to

* Corresponding author at: Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.
E-mail address: faiyazs@fastmail.fm (F. Shakeel).

http://dx.doi.org/10.1016/j.molliq.2017.05.105
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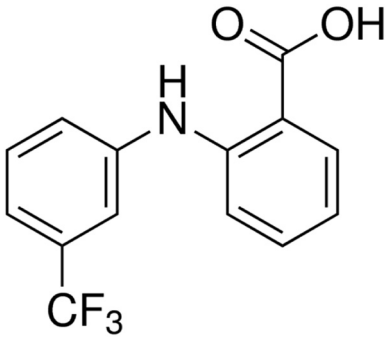

Fig. 1. Molecular structure of FFA (molar mass: 281.23 g mol^{-1}).

evaluate the molecular solute-solvent interactions. The solubility data of this study would be useful in "purification, recrystallization, drug discovery and formulation development" of FFA.

2. Experimental

2.1. Materials

FFA and Transcutol® [IUPAC name: 2-(2-ethoxyethoxy) ethanol] were obtained from "Sigma Aldrich (St. Louis, MO)" and "Gattefosse (Lyon, France)", respectively. Methyl alcohol (IUPAC name: methanol), ethyl alcohol (IUPAC name: ethanol), IPA (IUPAC name: isopropanol), 1-butyl alcohol (IUPAC name: 1-butanol) and 2-butyl alcohol (IUPAC name: 2-butanol) were obtained from "Scharlau Chemicals (Madrid, Spain)". EG (IUPAC name: 1,2-ethanediol), PG (IUPAC name: 1,2-propanediol), PEG-400 (IUPAC name: polyethylene glycol-400) and DMSO (IUPAC name: dimethyl sulfoxide) were obtained from "Anova Chem (Hurden, Switzerland)". Purified water (specific conductivity was <1.0 μS cm^{-1}) was obtained from "Milli-Q water purification unit". The information of these materials are presented in Supplementary Table 1 (Table S1).

2.2. High performance liquid chromatographic (HPLC) analysis of FFA

The analysis of FFA was performed using "reversed-phase (RP)-HPLC" technique which was coupled with "ultra-violet (UV)" detector. All analysis of FFA were carried out at "$T = 298.2$ K" using "Waters HPLC system (Waters, USA)". The column used for the analysis of FFA was "Nucleodur (150 × 4.6 mm, 5 μm) RP C_8 column". The binary mixture of methanol and ethanol (80:20% v/v) was used as the mobile phase for the analysis of FFA. The elution of FFA was performed at a flow rate of 1.0 mL min^{-1} at 245 nm. The volume of injection was set at 20 μL. The stock solution of FFA was prepared in the concentration of 100 μg g^{-1}. From this stock solution, the serial dilutions were prepared on mass/mass basis in order to obtain the concentration in the range of (1 to 80) μg g^{-1}. The calibration curve was plotted between the concentration of FFA (μg g^{-1}) and peak area. The calibration curve of FFA was obtained linear in the concentration range of (1 to 80) μg g^{-1} with coefficient of determination (R^2) of 0.9999. The equation for regression line was obtained as peak area = 11,757 * concentration − 9368.8. The proposed analytical methodology was developed in the laboratory and validated well in terms of linearity, accuracy, precision, reproducibility, sensitivity and robustness with satisfactory results.

2.3. Solid state characterization of FFA

The solid state characterization of FFA was performed using "Differential Scanning Calorimetry (DSC)". DSC analysis on pure and recovered FFA was performed in order to investigate the solid state characterization and polymorphic transformations of FFA. DSC analysis was performed on both pure and recovered FFA. FFA was recovered from equilibrated sample by the evaporation of solvent. DSC analysis was performed using "DSC 8000 instrument (Perkin Elmer, USA)" equipped with chiller and autosampler. The calibration was performed using pure indium in the range of 283.2 K to 773.2 K. A mass of 3.0 mg of pure and recovered FFA was accurately weighed and taken into the aluminium pan which was hermetically sealed. DSC thermograms of pure and recovered FFA were obtained under a nitrogen purge of 20 mL min^{-1} at a heating rate of 10 K min^{-1} in the temperature range of 298.2 K to 523.2 K.

2.4. Measurement of FFA solubility

The solubility of pure FFA in eleven different neat solvents was measured using a static equilibrium method [19]. The solubility of pure FFA in mole fraction in each neat solvent was measured at "$T = 298.2$ K to 318.2 K" and "$p = 0.1$ MPa". The excess quantity of pure FFA was added in known quantities of each neat solvent in triplicates manner. Each solute-solvent mixture was vortexed for about 10 min transferred to the "OLS 200 Grant Scientific Biological Shaker (Grant Scientific, Cambridge, UK)" at 100 rpm for 72 h. The precision in temperature of "OLS 200 Grant Scientific Biological Shaker" was ±0.25 K. After 72 h, each solute-solvent mixture was taken out from the shaker and allowed to settle the particles of FFA for 24 h [8]. After 24 h settling of the particles of FFA, the top cleared layer was withdrawn carefully, diluted suitably with mobile phase and subjected for the analysis of FFA content by RP-HPLC method at 245 nm. The concentration of FFA (μg g^{-1}) in each sample was determined by calibration curve of FFA discussed in above section. Then, the experimental solubilities of FFA (x_e) in mole fraction were calculated using Eq. (1) [9,20]:

$$x_e = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

Here, the symbols m_1 and m_2 are the masses of pure FFA and respective neat solvent (g), respectively. The symbols M_1 and M_2 are the molar masses of pure FFA and respective neat solvent (g mol^{-1}), respectively.

3. Results and discussion

3.1. Solid state characterization of FFA

The DSC thermogram of pure FFA is shown in Fig. 2. DSC thermogram of recovered FFA is not shown because it was similar with pure FFA. DSC thermogram of pure FFA showed a very sharp crystalline peak at the fusion temperature (T_{fus}) of 407.77 K with fusion enthalpy (ΔH_{fus}) of 29.85 kJ mol^{-1} (Fig. 2). A sharp crystalline peak at T_{fus} of 407.58 K with ΔH_{fus} of 29.65 kJ mol^{-1} was also recorded for recovered FFA, indicating that FFA was not transformed to polymorphic state during equilibrium. The sharp crystalline peaks of pure and recovered FFA indicated that FFA was in crystalline form. A single crystalline peak for pure and recovered FFA indicated that they do not show the evidence of polymorphic transformations. The T_{fus} value of FFA has been reported as 405.30 K which was also recorded by Perkin Elmer DSC instrument [2]. The T_{fus} value of 407.77 K obtained in this work was very similar to its reported value. Therefore, DSC results of this study were in good agreement with reported results.

3.2. Experimental solubilities of FFA and its literature comparison

The x_e values of pure FFA measured by a "static equilibrium method" in eleven different neat solvents at "$T = 298.2$ K to 318.2 K" and "$p = 0.1$ MPa" are presented in Table 1. The mole fraction solubility of FFA in water at "$T = 295.2$ K" has been reported as 4.29×10^{-7} [3,10]. The mole fraction solubility of FFA in water at "$T = 298.2$ K" was recorded as 5.83×10^{-7} in this study. The mole fraction solubility of FFA in water obtained in this study was in good agreement with reported one.