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Solubility and thermodynamics of ferulic acid in different neat solvents: Measurement, correlation and molecular interactions

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ABSTRACT

In the present investigation, the solubility of a bioactive compound ferulic acid (FA) in various neat solvents namely "water, methanol, ethanol, isopropanol (IPA), ethylene glycol (EG), propylene glycol (PG), 1-butanol, 2-butanol, ethyl acetate (EA), dimethyl sulfoxide (DMSO), polyethylene glycol-400 (PEG-400) and Transcutol®" was measured, correlated and evaluated for molecular interactions. The solubilities of FA in mole fraction were measured at temperatures "$T = 298.2$ K to 318.2 K" and pressure "$p = 0.1$ MPa". The experimental solubilities of FA were correlated with "Van't Hoff and Apelblat models" with root mean square deviation values of <2.0%. The solubilities of FA in mole fraction were recorded maximum in PEG-400 (1.91×10^{-1}) followed by DMSO (6.47×10^{-2}), Transcutol (5.92×10^{-2}), PG (3.59×10^{-2}), methanol (3.15×10^{-2}), ethanol (3.08×10^{-2}), EG (2.71×10^{-3}), IPA (2.55×10^{-2}), 2-butanol (2.47×10^{-2}), 1-butanol (2.38×10^{-2}), EA (1.98×10^{-2}) and water (1.36×10^{-4}) at "$T = 318.2$ K" and similar trend was also obtained at each temperature level. Generally, FA showed good solubilization potential in each neat solvent except in water. The activity coefficients of FA in each neat solvent were also determined in order to evaluate the molecular interactions between FA and solvent molecules. Higher solute-solvent interactions were seen in "PEG-400, DMSO and Transcutol" based on activity coefficients results. "Apparent thermodynamic analysis" showed an "endothermic and entropy-driven dissolution" of FA in each neat solvent.

1. Introduction

Ferulic acid (FA) (Fig. 1; IUPAC name: *4-hydroxy-3-methoxycinnamic acid*; molecular formula: $C_{10}H_{10}O_4$; molar mass: 194.18 g mol^{-1} and CAS registry number: 1325-24-6) is available commercially as a white to off-white crystalline powder [1,2]. It is a phenolic compound which is present in different parts of plants including fruits, grains, vegetables and leaves [2–6]. It had significant applications in biomedical, pharmaceutical and food industries [1,7]. It has been reported as a potent phenolic compound against the variety of diseases and evaluated as a potent antioxidant [7–11], antimicrobial [12], anti-inflammatory [7], anti-allergic [6], cardioprotective [1,7] and anticancer compound [1,6,7]. Antioxidant activity of FA has been documented well in literature [8–11]. The solubility and thermodynamic data of phenolic compounds are scarce in literature. The solubility and thermodynamic data of such compounds in "aqueous and organic solvents" have great importance in their "extraction/separation, purification, recrystallization, drug discovery and formulation development" [13–18]. Therefore, it is necessary to obtain the solubility and thermodynamic data of FA in different neat solvents which could be useful for its industrial applications. The solubility data of FA in different neat solvents such as "water, ethanol, methanol, chloroform, dichloromethane (DCM), methyl acetate (MA), ethyl acetate (EA) and butyl acetate (BA)" at temperatures $T =$ 273.15 K to 333.15 K and atmospheric pressure have been reported by Cairong et al. [19]. The solubility data of FA in water, ethanol, supercritical CO_2 and their mixtures at $T = 293$ K to 333 K and atmospheric pressure have also been reported by Bitencourt et al. [1]. The solubility data of FA in various (ethyl lactate + water) mixtures at $T = 298$ K and atmospheric pressure have also been reported [2]. The solubility data of FA in pure ethyl lactate at $T = 298.2$ K to 343.2 K and atmospheric pressure have also been reported [20]. The solubility data of FA in various aqueous solution at $T = 288.15$ K to 323.15 K and water have also been reported in literature [21,22]. Moreover, the solubility data of FA in supercritical CO_2 alone and in the presence of ethanol at various temperatures have also been reported in literature [1,23,24]. Nevertheless, the solubility data of FA in neat solvents including isopropyl alcohol (IPA), ethylene glycol (EG), propylene glycol (PG), polyethylene glycol-400 (PEG-400), 1-butanol, 2-butanol, Transcutol® and dimethyl sulfoxide (DMSO) have not been reported so far. Therefore, in the current research work, the solubility of FA in twelve different neat solvents including

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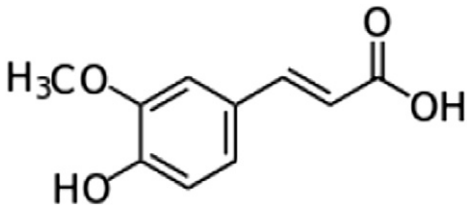

Fig. 1. Molecular structure of FA (molar mass: 194.18 g mol^{-1}).

water, methanol, ethanol, Transcutol, PEG-400, PG, EG, IPA, 1-butanol, 2-butanol, EA and DMSO were determined and correlated at $T = 298.2$ K to 318.2 K and $p = 0.1$ MPa. "Apparent thermodynamic analysis" on experimental solubility data of FA was performed by Van't Hoff and Krug et al. analysis for the evaluation dissolution behavior of FA. Activity coefficients of FA were also determined in order to evaluate the molecular interactions between FA and respective neat solvent. The solubility data of this work would be helpful in various industrial processes namely "extraction/separation, purification, recrystallization, drug discovery and formulation development" of FA.

2. Experimental

2.1. Materials

FA (form I), ethyl alcohol (IUPAC name: ethanol), EG (IUPAC name: 1,2-ethanediol), PG (IUPAC name: 1,2-propanediol) and PEG-400 (IUPAC name: polyethylene glycol-400) were obtained from "Sigma Aldrich (St. Louis, MO)". Transcutol® [IUPAC name: 2-(2-ethoxyethoxy) ethanol] was obtained from "Gattefosse (Lyon, France)". Methyl alcohol (IUPAC name: methanol), EA (IUPAC name: ethyl ethanoate) and DMSO (IUPAC name: dimethyl sulfoxide) were obtained from "*E*-Merck (Darmstadt, Germany)". 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)". Water was obtained from "Milli-Q water purification unit". The information about all these materials is listed in Supplementary Table 1.

2.2. HPLC analysis of FA

The quantification of FA was performed using "reversed phase high performance liquid chromatography (RP-HPLC)" coupled with ultra-violet (UV) detector. All quantifications were performed at $T = 298.15$ K using "HPLC system (Waters, USA)". The column used for the quantification of FA was Nucleodur (150 × 4.6 mm, 5 μm) RP C_8 column. Ternary mixture of acetonitrile:methanol:ethanol (6:2:1% v/v) was used as the mobile phase. The elution of FA was carried out at a flow rate of 1.0 mL min^{-1} at the wavelength of 322 nm. The injection volume was set at 20 μL. The stock solution of FA (100 μg g^{-1}) was prepared and serial dilutions were made on mass/mass basis in order to get the concentration in the range of (0.5 to 50) μg g^{-1}. The calibration curve was constructed between the concentration of FA and measured peak area. The calibration curve of FA was found to be linear in the concentration range of (0.5–50) μg g^{-1} with coefficient of determination (R^2) value of 0.9992. The regressed equation for calibration curve of FA was obtained as $y = 7454.80x - 369.47$; in which x is the concentration of FA and y is the measured peak area of FA.

2.3. Solid state characterization of FA

The solid state characterization of FA was investigated by "Differential Scanning Calorimetry (DSC)" in order to evaluate its thermal parameters and polymorphic states. This analysis was performed on starting material (pure FA) and equilibrated solid material. The equilibrated FA was recovered from equilibrium sample (water) by evaporation of solvent. DSC analysis on pure and equilibrated FA was carried out using "DSC-60 instrument (Shimadzu, Kyoto, Japan)". The accurately weighed 5.0 mg of pure and equilibrated FA was placed into aluminium pan which was hermetically sealed. Indium was used as the reference standard. DSC thermogram of pure and equilibrated FA was recorded under a nitrogen purge of 40 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. Determination of FA solubility

The solubility of pure FA in various neat solvents including water, methanol, ethanol, IPA, EG, PG, 1-butanol, 2-butanol, EA, DMSO, PEG-400 and Transcutol was determined using a static equilibrium method as reported in literature [25]. The solubility of pure FA in each neat solvent was determined at $T = 298.2$ K to 318.2 K and $p = 0.1$ MPa. The excess quantity of pure FA was added in known quantities of each neat solvent in triplicates manner. Each mixture of FA and respective neat solvent was vortexed for about 10 min and transferred to the "OLS 200 Grant Scientific Biological Shaker (Grant Scientific, Cambridge, UK)" at shaking speed of 100 rpm for 72 h. The precision in temperature of Grant Scientific Biological shaker was ±0.20 K. After equilibrium reached, each FA-solvent mixture was taken out from the shaker and allowed to settle FA particles for the period of 24 h [18]. After 24 settling of FA particles, the supernatants from each sample were taken, diluted suitably with mobile phase (wherever applicable) and subjected for the analysis of FA content by the proposed HPLC-UV method at 322 nm. The concentration of FA (μg g^{-1}) in solubility samples was determined by calibration plot of FA discussed in Section 2.2 HPLC analysis of FA. Then, the experimental solubilities of FA (x_e) in mole fraction were determined using Eq. (1) [26,27]:

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

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

3. Results and discussion

3.1. Solid state characterization of FA by DSC analysis

The solid state characterization of pure and equilibrated FA was carried out using DSC analysis in order to evaluate various thermal parameters and polymorphic states of FA. The representative DSC spectra of pure FA are presented in Fig. 2. The DSC spectra of equilibrated FA are not presented because these spectra were almost similar to pure FA. The DSC thermogram of pure FA showed a very sharp crystalline endothermic peak at the fusion temperature (T_{fus}) of 448.0 K with fusion enthalpy (ΔH_{fus}) and fusion entropy (ΔS_{fus}) of 15.01 kJ mol^{-1} and 33.50 J mol^{-1} K^{-1}, respectively. However, the DSC analysis of equilibrated FA presented a very sharp crystalline endothermic peak at T_{fus} value of 447.7 K with ΔH_{fus} and ΔS_{fus} values of 16.24 kJ mol^{-1} and 36.27 J mol^{-1} K^{-1}, respectively. The DSC results of pure and equilibrated FA were similar which indicated that form I of FA was not changed to form II during equilibrium. It has been reported that FA exists in two polymorphic states i.e. form I and form II. The form I of FA shows an endothermic peak at T_{fus} of 448.15 K and form II shows three endothermic peaks at T_{fus} of 378.15 K, 421.15 K and 455.15 K [1]. In the current research work, an endothermic peak of pure FA was recorded at T_{fus} of 448 K which was nearly same with its reported value. These results indicated that FA used in this work was form I of FA and does not exist in different polymorphic forms.