Industrial Crops & Products 116 (2018) 56–63

Contents lists available at ScienceDirect

Industrial Crops & Products

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

Solubility determination and thermodynamic data of apigenin in binary {Transcutol® + water} mixtures

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ARTICLE INFO

Keywords:
Activity coefficient
Bioflavonoid
Cosolvency model
Dissolution thermodynamics
Molecular interactions
Solvation

ABSTRACT

Solubility and thermodynamic data of apigenin (APG) in binary {2-(2-ethoxyethoxy)ethanol (Transcutol®) + water} mixtures were obtained in this work. The mole fraction solubilities (x_e) of APG in binary {Transcutol® + water} mixtures were measured at temperature $T = 298.15$ K to318.15 K and atmospheric pressure $p = 0.1$ MPa. Solubility values of APG determined in this study were fitted well with four different computational models namely "van't Hoff, Apelblat, Yalkowsky and Jouyban-Acree" models with root mean square deviations of < 4.0%. The maximum x_e value of APG was recorded in neat Transcutol® (0.382 at $T = 318.15$ K). However, the minimum x_e value of APG was recorded in neat water (1.01×10^{-6} at $T = 298.15$ K). The values of activity coefficients were also determined for the evaluation of solute-solvent molecular interactions and results suggested higher solute-solvent molecular interaction in APG-Transcutol in comparison with other combinations studied. Apparent thermodynamic analysis suggested endothermic and entropy-driven dissolution of APG in all binary {Transcutol® + water} mixtures studied. Enthalpy-entropy compensation analysis suggested enthalpy-driven mechanism as the main mechanism for solvation behavior of APG.

1. Introduction

Apigenin (APG) (Fig. 1; IUPAC name: 5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one; molecular formula: $C_{15}H_{10}O_5$; molar mass: 270.24 g mol^{-1} and CAS registry number: 520-36-5) occurs as a light yellow crystalline powder (Xiao et al., 2011; Zhang et al., 2012). It is poorly soluble bioflavonoid which is commonly present in most of the fruits and vegetables (Peterson and Dwyer, 1995; Shukla and Gupta, 2010; Shakeel et al., 2017a). It shows several biological activities including antioxidant, anti-inflammatory and anticancer activities in animal models (Takahashi et al., 1998; Gates et al., 2007; Tong et al., 2007; Gates et al., 2009; Funakoshi-Tago et al., 2011; Horvathova et al., 2013). It has been reported as poorly soluble in water due to which its dissolution rate and bioavailability are poor (Shakeel et al., 2017a). Various formulation approaches were evaluated for solubility, dissolution rate and bioavailability enhancement of APG in literature (Al Shaal et al., 2011; Arsic et al., 2011; Das et al., 2013; Ding et al., 2013; Zhai et al., 2013; Zhao et al., 2013; Zhang et al., 2013; Shen et al., 2014; Huang et al., 2016; Zhao et al., 2016; Jangdey et al., 2017; Telange et al., 2017). Different bioflavonoids isolated from various plant sources have weak solubilization capacity in an aqueous media including water (Shakeel et al., 2016, 2017a). Therefore, the solubilities of these bioflavonoids in "aqueous-cosolvent" binary mixtures have significant importance in the development of their dosage forms for human use (Shakeel et al., 2015a, 2016). The solubilization power of Transcutol® has been proved recently in solubility improvement of several weakly soluble natural drugs including "isatin, vanillin and reserpine" (Shakeel et al., 2015a, 2015b, 2015c). Transcutol® is used as an excipient in various pharmaceutical/food products and up to 10% concentration has been reported as safe for these formulations (Ether, 2013). The main side effects of Transcutol® in humans are central nervous system disorders, respiratory disorders and skin irritation (Ether, 2013). The solubility data and thermodynamics of APG in twelve different neat solvents including "water, methanol, ethanol, isopropanol, ethylene glycol, propylene glycol, 1-butanol, 2-butanol, ethyl acetate (EA), polyethylene glycol-400, dimethyl sulfoxide and Transcutol®" at temperatures $T = 298.15$ K to 318.15 K and atmospheric pressure $p = 0.1$ MPa have been reported in literature (Shakeel et al., 2017a). The solubility data of APG in seven different neat solvents namely "water, methanol, ethanol, 1-propanol, 1-butanol, acetone and EA" at $T = 288.2$ K to 328.2 K and atmospheric pressure were also recorded (Xiao et al., 2011). The solubility data of APG in

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https://doi.org/10.1016/j.indcrop.2018.02.047
Received 27 November 2017; Received in revised form 10 February 2018; Accepted 14 February 2018

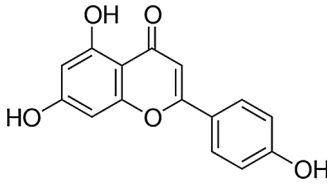

Fig. 1. Molecular structure of APG.

binary (ethanol + water) mixtures at T = 273.2 K to 323.2 K" and atmospheric pressure were also determined (Xiao et al., 2010). However, the solubility data and thermodynamics of APG in binary {Transcutol® + water} mixtures have not been reported. Hence, aim of this study was to determine the solubilities of APG in binary {Transcutol® + water} mixtures (including neat solvents) by a static equilibrium method at T = 298.15 K to 318.15 K under atmospheric pressure. Dissolution thermodynamic parameters of APG were also calculated using apparent thermodynamic analysis.

2. Materials and methods

2.1. Materials

Apigenin "(mass fraction purity > 0.99 by HPLC)" and Transcutol® "[IUPAC name: 2-(2-ethoxyethoxy)ethanol and mass fraction purity of > 0.99 by GC]" were obtained from "Beijing Mesochem Technology Co. Pvt. Ltd. (Beijing, China)" and "Gattefosse (Lyon, France)", respectively. Chromatographic grade acetonitrile "(mass fraction purity of > 0.99 by GC)" was obtained from "Sigma Aldrich (St. Louis, MO, USA)". 0.05 M ammonium phosphate buffer for chromatographic analysis was obtained in the laboratory. The water used in this study was deionized water and obtained from "Milli-Q water purification unit". The information of materials is given in Table 1.

2.2. Determination of APG solubility in binary {Transcutol® + water} mixtures

The solubility of APG with respect to mass fraction value of Transcutol® (m = 0.0 to 1.0; m is the mass fraction of Transcutol® in binary {Transcutol® + water} mixtures) in binary {Transcutol® + water} mixtures including neat solvents was measured at T = 298.15 K to 318.15 K under atmospheric pressure. The solubility of APG in mole fraction was determined using a static equilibrium method reported in literature (Higuchi and Connors, 1965). In order to perform these experiments, the excess quantity of crystalline APG was added in known amount of each {Transcutol® + water} mixture including neat solvents. Each experiment was conducted in triplicates manners. The resultant mixtures were vortexed for 5 min and transferred to the "OLS 200 Grant Scientific Biological Shaker (Grant Scientific, Cambridge, UK)" which was shaken at a speed of 100 rpm for 72 h (Shakeel et al., 2017a). After 72 h, each sample was withdrawn carefully from the shaker and allowed to settle APG particles for 24 h in order to obtain complete settling of particles (Shakeel et al., 2015c, 2017a). The supernatants were then withdrawn carefully from each sample, diluted and subjected for the quantification of APG content by validated ultra-performance liquid chromatography-ultra violet (UPLC-UV) method at 336 nm (Shakeel et al., 2017a). Mixture of 0.05 M ammonium formate buffer: acetonitrile (72:28% v/v) was used as mobile phase for UPLC analysis of APG. The "experimental mole fraction solubilities (x_e)" of APG were then determined using Eqs. (1) and (2) (Shakeel et al., 2013; Sunsandee et al., 2013):

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

$$x_e = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (2)$$

Here, m_1 is the mass of APG (g) and m_2 and m_3 represent the masses of Transcutol® (g) and water (g), respectively. M_1 represent the molar mass of APG (g mol^{-1}) and M_2 and M_3 represent the molar masses of Transcutol® (g mol^{-1}) and water (g mol^{-1}), respectively. Eq. (1) is applicable for the calculation of x_e values of APG in neat solvents (Transcutol® and water) and Eq. (2) is applicable for the calculation of x_e values of APG in {Transcutol® + water} mixtures.

3. Results and discussion

3.1. Experimental solubility data of APG with literature comparison

The x_e values of APG in binary {Transcutol® + water} mixtures (including neat solvents) at T = 298.15 K to 318.15 K under atmospheric pressure are furnished in Table 2. The solubilities of APG in mole fraction in neat water and neat Transcutol® at various temperatures and atmospheric pressure have been reported in literature (Xiao et al., 2011; Shakeel et al., 2017a). However, the solubilities of APG in mole fraction in binary {Transcutol® + water} mixtures at various temperatures are not available in literature. The solubility of APG in mole fraction in water at T = 298.2 K has been reported as 1.03×10^{-6} (Xiao et al., 2011) and 1.04×10^{-6} (Shakeel et al., 2017a). Solubility of APG in mole fraction in water at T = 298.2 K was obtained as 1.01×10^{-6} in the present study. The solubility of APG in mole fraction in neat Transcutol® at T = 298.2 K has been reported as 0.334 by Shakeel et al. (Shakeel et al., 2017a). But solubility of APG in mole fraction in neat Transcutol® at T = 298.2 K was obtained as 0.336 in the present study. Solubilities of APG in mole fraction in neat water and neat Transcutol® obtained in this work were similar to those reported in literature. The graphical correlation between experimental and reported solubilities of APG in neat water and neat Transcutol® at T = 298.15 K to 318.15 K are also presented in supplementary Figs. 1 and 2 (Figs. S1 and S2), respectively. Figs. S1 and S2 showed good correlation/curve fitting of experimental solubilities with reported ones in both neat solvents at T = 298.15 K to 318.15 K. These results suggested good agreement of experimental solubility data of APG with reported ones.

Generally, the x_e values of APG at constant pressure i.e. atmospheric pressure were recorded as increasing with the rise in temperature and increase in the m value of Transcutol® in binary {Transcutol® + water} mixtures. The solubility enhancement of bioactive compounds with the rise in temperature has been reported very well in literature (Shakeel et al., 2015a, 2015b). Therefore, our results were obtained in similar trend as reported previously with respect to temperature. Maximum x_e

Table 1
Materials information and their sources.

Materials	Molecular formula	Molar mass (g mol^{-1})	CAS Registry no.	Purification method	Mass fraction purity	Analysis method	Source
APG	$C_{15}H_{10}O_5$	270.24	520 − 36-5	None	> 0.99	HPLC	Beijing MesochemTechnology
Transcutol®	$C_6H_{14}O_3$	134.17	111 − 90-0	None	> 0.99	GC	Gattefosse
Acetonitrile	C_2H_3N	41.05	75 − 05-8	None	> 0.99	GC	Sigma Aldrich
Water	H_2O	18.07	7732 − 18-5	None	–	–	Milli-Q

Apigenin (APG), high performance liquid chromatography (HPLC) and gas chromatography (GC).