



# Solubility and thermodynamic function of vanillin in ten different environmentally benign solvents



Faiyaz Shakeel<sup>a,b,\*</sup>, Nazrul Haq<sup>a,b</sup>, Nasir A. Siddiqui<sup>c</sup>

<sup>a</sup> Research Center, College of Science, King Saud University, Riyadh 11451, Saudi Arabia

<sup>b</sup> Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

<sup>c</sup> Department of Pharmacognosy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

## ARTICLE INFO

### Article history:

Received 15 December 2014

Received in revised form 19 January 2015

Accepted 20 January 2015

Available online 17 February 2015

### Keywords:

Apelblat model

Environmentally benign solvent

Van't Hoff model

Solubility

Thermodynamics

Vanillin

## ABSTRACT

The solubility of vanillin in ten different environmentally benign solvents namely water, ethanol, ethylene glycol (EG), ethyl acetate (EA), isopropanol (IPA), propylene glycol (PG), polyethylene glycol-400 (PEG-400), Transcutol, butanol-1 and butanol-2 was measured and correlated at  $T = (298–318)$  K. The resulting experimental data were correlated with the modified Apelblat and Van't Hoff models. Both the models showed good correlation of experimental solubility data with calculated ones with root mean square deviations in the range of (0.08–1.55)%. The mole fraction solubility of vanillin was observed highest in PEG-400 ( $4.29 \times 10^{-1}$  at 298 K) followed by Transcutol, EA, butanol-2, ethanol, EG, PG, IPA, butanol-1 and water from  $T = (298–318)$  K. The results of thermodynamic function in terms of dissolution enthalpy, Gibbs energy and dissolution entropy showed endothermic, spontaneous and entropy-driven dissolution of vanillin in all environmentally benign solvents.

© 2015 Elsevier Ltd. All rights reserved.

## 1. Introduction

Chemically, vanillin is 3-methoxy-4-hydroxybenzaldehyde (Fig. 1) which occurs as a white to slightly yellow crystalline needles (Noubigh, Cherif, Provost, & Abderrabba, 2008; Noubigh, Mgaidi, Abderrabba, Provost, & Furst, 2007). Its molecular formula and molar mass have been reported as  $C_8H_8O_3$  and  $152.15 \text{ g mol}^{-1}$ , respectively (Noubigh et al., 2008). It is obtained from the bean or pod of *Vanilla orchid* and showed strong antioxidant activity due to the presence of phenolic group (Kayaci & Uyar, 2012; Kumar, Sharma, & Mishra, 2012; Peng et al., 2010). It is commonly used flavoring agent in food, beverage and pharmaceutical industries (Hundre, Karthik, & Anandharamakrishnan, 2015; Li, Jiang, Mao, & Shen, 1998; Walton, Mayer, & Narbad, 2003). The mole fraction solubility of vanillin in water has been reported as  $1.17 \times 10^{-3}$  at 298 K (Noubigh et al., 2008). The solubility of organic compounds in pure solvents is an important physicochemical parameter in purification, crystallization, separation/extraction, product development and industrial optimization process (Anwer et al., 2014; Noubigh et al., 2008; Shakeel, Anwer, Shazly, & Jamil, 2014; Shakeel, Haq, Alanazi, & Alsarra, 2015). Several environmentally

benign solvents (also known as green solvents) such as Transcutol, ethanol, propylene glycol (PG) and polyethylene glycol-400 (PEG-400) have been investigated for solubilization of various natural bioactive organic compounds (Anwer et al., 2014; Liu, Chen, & Ji, 2014; Shakeel et al., 2014, 2015). The temperature dependent solubility data of vanillin in water and various salt solutions have been reported in literature (Noubigh et al., 2007, 2008). However, the temperature dependent solubility data of vanillin in ethanol, butanol-1, butanol-2, ethylene glycol (EG), ethyl acetate (EA), isopropanol (IPA), PG, PEG-400 and Transcutol are not available in literature. The modified Apelblat and Van't Hoff models are the commonly used mathematical models used to correlate the experimental solubility data with calculated ones (Apelblat & Manzurola, 1999; Liu et al., 2014; Manzurola & Apelblat, 2002). Therefore, in this work, the solubilities of natural vanillin in various environmentally benign solvents such as water, ethanol, butanol-1, butanol-2, EG, EA, IPA, PG, PEG-400 and Transcutol were measured and correlated at  $T = (298–318)$  K and atmospheric pressure of 0.1 MPa using an isothermal method. From solubility data, various thermodynamic functions such as molar enthalpy of dissolution ( $\Delta_{\text{sol}}H^0$ ), molar entropy of dissolution ( $\Delta_{\text{sol}}S^0$ ) and Gibbs free energy ( $\Delta_{\text{sol}}G^0$ ) were also determined using Van't Hoff and Krug analysis. The solubility data of this work could be useful in purification, crystallization, separation/extraction, pre-formulation studies and formulation development of vanillin in food, chemical and pharmaceutical industries.

\* Corresponding author at: Center of Excellence in Biotechnology Research, College of Science, King Saud University, P.O. Box 2460, Riyadh 11451, Saudi Arabia. Tel.: +966 537507318.

E-mail address: [faiyazs@fastmail.fm](mailto:faiyazs@fastmail.fm) (F. Shakeel).

## 2. Experimental

### 2.1. Materials

Vanillin, ethyl alcohol (IUPAC name: ethanol), 1-butyl alcohol (IUPAC name: butanol-1) and 2-butyl alcohol (IUPAC name: butanol-2) were procured from Sigma Aldrich (St. Louis, MO). Transcutol (IUPAC name: diethylene glycol monoethyl ether) was procured from Gattefosse (Lyon, France). EA (IUPAC name: ethyl acetate), EG (IUPAC name: ethane-1,2-diol) and IPA (IUPAC name: 2-propanol) were procured from Winlab Laboratory (Leicestershire, UK). PG (IUPAC name: propane-1,2-diol) and PEG-400 [IUPAC name: poly(oxyethylene)] were procured from Fluka Chemicals (Busch, Switzerland). Chromatographic grade acetonitrile and acetone were procured from Acros Organics (Hamilton, NJ). The water used in this work was high pure chromatographic grade water which was obtained from Milli-Q water purification system (Berlin, Germany). All these materials were of high purity and used without any further purification. The detailed information about all these materials is presented in Table 1.

### 2.2. HPLC analysis of vanillin

The analysis of vanillin in solubility samples was carried out by reversed phase high performance liquid chromatography (RP-HPLC) method. The analysis was carried out at 298 K with Waters HPLC system (Waters, USA) equipped with an isocratic 1515 HPLC pump, 717 autosampler, quaternary pumps, a programmable dual  $\lambda$  UV-visible variable-wavelength absorbance detector (Waters, 2487), column oven and an inline vacuum degasser was used. The column used in this work was Nucleodur 150  $\times$  4.6 mm RP C<sub>8</sub> column having a 5  $\mu$ m packing as a stationary phase. The ternary mixture of acetonitrile:water:acetone (70:20:10% v/v) was used as a mobile phase. The elution of vanillin was performed at a flow rate of 1.0 mL min<sup>-1</sup> at 220 nm. The proposed RP-HPLC method was validated for linearity, accuracy, precision, sensitivity and specificity (unpublished data).

### 2.3. Measurement of vanillin solubility

The mole fraction solubility of vanillin in ten different environmentally benign solvents was measured from  $T = (298\text{--}318)$  K at  $p = 0.1$  MPa using an isothermal method of Higuchi and Connors (Higuchi & Connors, 1965). The excess amount of crystalline vanillin was added in 5 g of each environmentally benign solvent in triplicates. The concentrated suspensions were shaken continuously in a biological shaker (Julabo, PA) at 100 rpm for 72 h. The temperature of shaker was controlled precisely with thermostatic bath equipped with shaker. After 72 h, all the concentrated suspensions were taken out from the shaker and allowed to settle vanillin particles for 2 h (Anwer et al., 2014; Shakeel et al., 2015). The super-

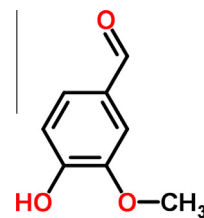


Fig. 1. Molecular structure of vanillin (molar mass: 152.15 g mol<sup>-1</sup>).

natants from each sample were centrifuged at 5000 rpm for 15 min in order to remove fine solid particles. The samples were diluted around 1000 times with respective environmentally benign solvent and subjected for analysis of vanillin content by RP-HPLC method at 220 nm as described in previous section. The proposed RP-HPLC method was observed linear in the concentration range of (0.1–100)  $\mu$ g g<sup>-1</sup> with correlation coefficient of 0.997. The experimental mole fraction solubility ( $x_e$ ) of vanillin in each environmentally benign solvent was calculated using Eq. (1) (Anwer et al., 2014; Shakeel et al., 2015):

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

In which,  $m_1$  and  $m_2$  are the masses of vanillin (g) and respective environmentally benign solvent (g), respectively.  $M_1$  and  $M_2$  are the molar masses of vanillin (g mol<sup>-1</sup>) and respective environmentally benign solvent, respectively.

## 3. Results and discussion

### 3.1. Measured solubility data of vanillin

The measured solubility data of vanillin in ten different environmentally benign solvents from  $T = (298\text{--}318)$  K at atmospheric pressure of 0.1 MPa are listed in Table 2. The temperature-dependent solubility data of vanillin in water are available in literature. The solubility of vanillin in water has been reported as  $1.17 \times 10^{-3}$  at  $T = 298$  K (Noubigh et al., 2008). In the present work, the solubility of vanillin in water was observed as  $1.23 \times 10^{-3}$  at  $T = 298$  K. This value was very close to reported value of vanillin in water which indicated that the results of our work were in good agreement with previous literature. The graphical correlation between experimental and literature solubilities of crystalline vanillin in water is presented in Fig. 2 at  $T = (298\text{--}318)$  K. The results showed good correlation between experimental and literature values of vanillin in water (Fig. 2). Overall, these results indicated good agreement of experimental data of this work with reported solubility data of vanillin in water at  $T = (298\text{--}318)$  K. Generally, the values of  $x_e$  were found to be increased with the rise

Table 1

Sample table for vanillin and environmentally benign solvents used in the experiment.

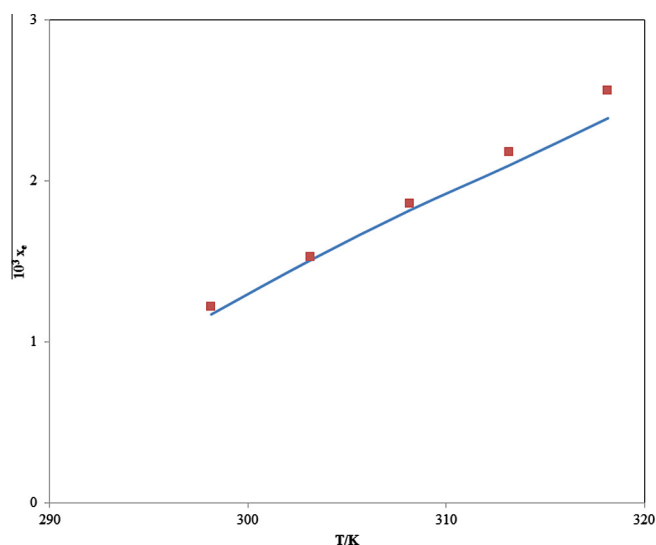
Material	Molecular formula	Molar mass (g mol <sup>-1</sup> )	Purity (mass fraction)	Purification method	Analysis method	Source
Vanillin	C <sub>8</sub> H <sub>8</sub> O <sub>3</sub>	152.15	0.990	None	HPLC	Sigma Aldrich
Ethanol	C <sub>2</sub> H <sub>5</sub> OH	46.06	0.999	None	GC	Sigma Aldrich
Propylene glycol	C <sub>3</sub> H <sub>8</sub> O <sub>2</sub>	76.09	0.995	None	GC	Fluka Chemicals
Transcutol	C <sub>6</sub> H <sub>14</sub> O <sub>3</sub>	134.17	0.999	None	GC	Gattefosse
Polyethylene glycol-400	H(OCH <sub>2</sub> CH <sub>2</sub> ) <sub>n</sub> OH	400.00	0.999	None	GC	Fluka Chemicals
Ethylene glycol	C <sub>2</sub> H <sub>6</sub> O <sub>2</sub>	62.07	0.996	None	GC	Winlab Laboratory
Ethyl acetate	C <sub>4</sub> H <sub>8</sub> O <sub>2</sub>	88.10	0.998	None	GC	Winlab Laboratory
Isopropyl alcohol	C <sub>3</sub> H <sub>8</sub> O	60.10	0.997	None	GC	Winlab Laboratory
Butanol-1	C <sub>4</sub> H <sub>10</sub> O	74.12	0.995	None	GC	Sigma Aldrich
Butanol-2	C <sub>4</sub> H <sub>10</sub> O	74.12	0.995	None	GC	Sigma Aldrich

HPLC: high performance liquid chromatography; GC: gas chromatography.

**Table 2**  
Experimental mole fraction solubilities ( $x_e$ ) of crystalline vanillin in ten different environmentally benign solvents (S) at temperatures  $T = (298–318)$  K and pressure  $p = 0.1$  MPa<sup>a</sup> (values in parentheses are standard deviations).

S	$x_e$				
	$T = 298$ K	$T = 303$ K	$T = 308$ K	$T = 313$ K	$T = 318$ K
Water	$1.23 (0.01) \times 10^{-3}$	$1.54 (0.02) \times 10^{-3}$	$1.87 (0.02) \times 10^{-3}$	$2.19 (0.03) \times 10^{-3}$	$2.56 (0.04) \times 10^{-3}$
Ethanol	$7.94 (0.05) \times 10^{-2}$	$8.33 (0.06) \times 10^{-2}$	$8.61 (0.07) \times 10^{-2}$	$9.03 (0.07) \times 10^{-2}$	$9.36 (0.08) \times 10^{-2}$
PG	$7.15 (0.04) \times 10^{-2}$	$7.45 (0.04) \times 10^{-2}$	$7.75 (0.05) \times 10^{-2}$	$8.09 (0.06) \times 10^{-2}$	$8.55 (0.07) \times 10^{-2}$
PEG-400	$4.29 (0.01) \times 10^{-1}$	$4.42 (0.03) \times 10^{-1}$	$4.52 (0.02) \times 10^{-1}$	$4.66 (0.04) \times 10^{-1}$	$4.77 (0.06) \times 10^{-1}$
Transcutol	$2.38 (0.02) \times 10^{-1}$	$2.46 (0.02) \times 10^{-1}$	$2.54 (0.03) \times 10^{-1}$	$2.61 (0.04) \times 10^{-1}$	$2.68 (0.04) \times 10^{-1}$
EG	$7.54 (0.06) \times 10^{-2}$	$7.93 (0.06) \times 10^{-2}$	$8.34 (0.07) \times 10^{-2}$	$8.71 (0.08) \times 10^{-2}$	$9.09 (0.09) \times 10^{-2}$
IPA	$6.60 (0.03) \times 10^{-2}$	$6.91 (0.04) \times 10^{-2}$	$7.25 (0.04) \times 10^{-2}$	$7.59 (0.05) \times 10^{-2}$	$7.89 (0.06) \times 10^{-2}$
EA	$1.23 (0.01) \times 10^{-1}$	$1.27 (0.01) \times 10^{-1}$	$1.31 (0.02) \times 10^{-1}$	$1.36 (0.02) \times 10^{-1}$	$1.40 (0.03) \times 10^{-1}$
Butanol-1	$6.47 (0.02) \times 10^{-2}$	$6.81 (0.01) \times 10^{-2}$	$7.15 (0.03) \times 10^{-2}$	$7.52 (0.04) \times 10^{-2}$	$7.86 (0.05) \times 10^{-2}$
Butanol-2	$8.79 (0.06) \times 10^{-2}$	$9.20 (0.07) \times 10^{-2}$	$9.64 (0.05) \times 10^{-2}$	$1.00 (0.04) \times 10^{-1}$	$1.04 (0.03) \times 10^{-1}$

<sup>a</sup> The standard uncertainties  $u$  are  $u(T) = 0.14$  K,  $u_r(m) = 0.1\%$ ,  $u(p) = 0.003$  MPa and  $u_r(x_e) = 1.2\%$ .



**Fig. 2.** Comparison of experimental mole fraction solubilities of crystalline vanillin in water with literature values at (298–318) K; symbol represents the experimental solubilities and solid line represents the literature values taken from Noubigh et al. (2008).

in temperature in all environmentally benign solvents investigated. The  $x_e$  values of crystalline vanillin were observed highest in PEG-400 ( $4.29 \times 10^{-1}$  at  $T = 298$  K) followed by Transcutol ( $2.38 \times 10^{-1}$  at  $T = 298$  K), EA ( $1.23 \times 10^{-1}$  at  $T = 298$  K), butanol-2 ( $8.79 \times 10^{-2}$  at  $T = 298$  K), ethanol ( $7.94 \times 10^{-2}$  at  $T = 298$  K), EG ( $7.54 \times 10^{-2}$  at  $T = 298$  K), PG ( $7.15 \times 10^{-2}$  at  $T = 298$  K), IPA ( $6.60 \times 10^{-2}$  at  $T = 298$  K), butanol-1 ( $6.47 \times 10^{-2}$  at  $T = 298$  K) and water ( $1.23 \times 10^{-3}$  at  $T = 298$  K) from  $T = (298–318)$  K (Table 2). The  $x_e$  values of crystalline vanillin in PEG-400, Transcutol and EA were significantly higher than water and other environmentally benign solvents. However, the  $x_e$  values of vanillin in butanol-2, ethanol, EG, PG, IPA and butanol-1 were not significantly different at each temperature investigated. Nevertheless, the  $x_e$  values of vanillin in butanol-2, ethanol, EG, PG, IPA and butanol-1 were significantly higher than water at each temperature investigated. The higher  $x_e$  values of vanillin in organic solvents were probably due to lower polarity of organic solvents as compared to water. Overall, the solubility of vanillin was good in all environmentally benign solvents investigated. Based on these results, crystalline vanillin has been considered as freely soluble in PEG-400, Transcutol, EA, butanol-2, ethanol, EG, PG, IPA and butanol-1 and soluble in water according to the United States Pharmacopoeia (USP) classification of solubility.

### 3.2. Correlation of experimental solubilities with Van't Hoff model

Van't Hoff model was applied to correlate experimental solubilities of vanillin with calculated ones (Liu et al., 2014). According to this model, the mole fraction solubility of crystalline vanillin can be calculated using Eq. (2):

$$\ln x^{\text{idl}} = a + \frac{b}{T} \quad (2)$$

In which,  $x^{\text{idl}}$  is the mole fraction solubility of vanillin calculated by Van't Hoff model. The parameters  $a$  and  $b$  are the Van't Hoff model parameters which were calculated by plotting  $\ln x_e$  as a function of  $1/T$ . For the correlation of  $x_e$  with  $x^{\text{idl}}$ , the root mean square deviations (RMSD) were calculated with the help of Eq. (3) (Shakeel et al., 2015).

$$RMSD = \left[ \frac{1}{N} \sum_{i=1}^N \left( \frac{x^{\text{idl}} - x_e}{x_e} \right)^2 \right]^{\frac{1}{2}} \quad (3)$$

In which,  $N$  represents the number of temperature points. The correlation between  $x_e$  and  $x^{\text{idl}}$  in ten different environmentally benign solvents from  $T = (298–318)$  K is presented in Fig. S1.

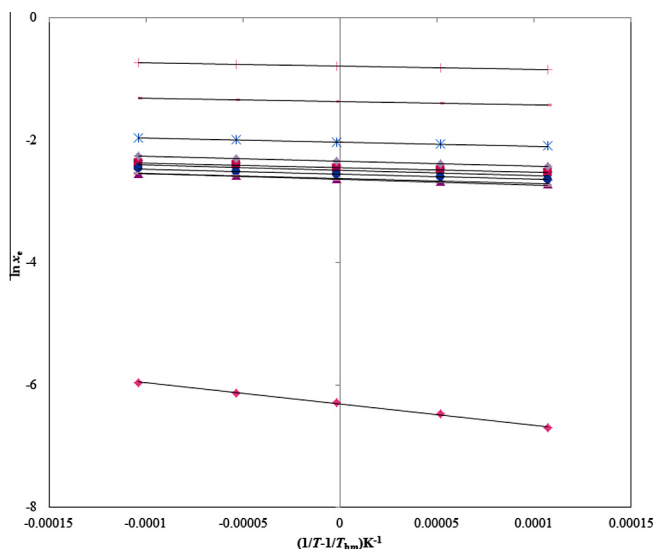
The values of  $a$ ,  $b$ , correlation coefficients ( $R^2$ ) and RMSD in all environmentally benign solvents are listed in Table S1. The RMSD values in ten different environmentally benign solvents were observed in the range of (0.08–1.55) % (Table S1). The highest value of RMSD was observed in water (1.55%). However, the lowest one was observed in butanol-1 (0.08%). The  $R^2$  values for crystalline vanillin in ten different environmentally benign solvents were observed as 0.9920–0.9990. These data indicated good correlation of experimental solubilities of crystalline vanillin with Van't Hoff model.

### 3.3. Correlation of experimental solubilities with the modified Apelblat model

The modified Apelblat model was also used to correlate experimental solubilities of vanillin with calculated ones (Apelblat & Manzurola, 1999; Manzurola & Apelblat, 2002). The solubility of crystalline vanillin can be calculated using Eq. (4) for this model:

$$\ln x^{\text{Apl}} = A + \frac{B}{T} + C \ln(T) \quad (4)$$

In which,  $x^{\text{Apl}}$  is the calculated solubility of vanillin and  $T$  is the absolute temperature (K). The coefficients  $A$ ,  $B$  and  $C$  are the modified Apelblat parameters which were calculated by multivariate



**Fig. 3.** Van't Hoff plots for experimental solubilities of crystalline vanillin in ten different environmentally benign solvents at mean harmonic temperature of 307.98 K;  $\blacklozenge$  water,  $\blacksquare$  ethanol,  $\blacktriangle$  IPA,  $\times$  EG,  $\ast$  EA,  $\bullet$  PG,  $+$  PEG-400,  $-$  Transcutol,  $-$  butanol-1 and  $\blacklozenge$  butanol-2.

non-linear regression analysis of experimental solubilities of vanillin listed in Table 2 (Shakeel et al., 2015). In order to correlate  $x_e$  with  $x^{Apl}$ , the RMSD values were calculated again using Eq. (3).

The values of the modified Apelblat parameters  $A$ ,  $B$ , and  $C$ ,  $R^2$  and RMSD in ten different environmentally benign solvents are presented in Table S2. The RMSD values in ten different environmentally benign solvents were observed in the range of (0.13–0.57) % (Table S2). The  $R^2$  values in ten different environmentally benign solvents were observed as 0.9970–0.9999. These data indicated again good correlation of experimental solubilities of crystalline vanillin with the modified Apelblat model. The correlation between  $x_e$  and  $x^{Apl}$  in ten different environmentally benign solvents from  $T = (298–318)$  K is presented in Fig. S2.

### 3.4. Thermodynamic function of vanillin dissolution

The dissolution enthalpy ( $\Delta_{sol}H^0$ ) for crystalline vanillin in ten different environmentally benign solvents was determined by reported method of Van't Hoff analysis (Holguín, Rodríguez, Cristancho, Delgado, & Martínez et al., 2012; Ruidiaz, Delgado, Martínez, & Marcus, 2010). According to this method, the  $\Delta_{sol}H^0$  values can be calculated at mean harmonic temperature ( $T_{hm}$ ) using Eq. (5):

$$\left( \frac{\partial \ln x}{\partial \left( \frac{1}{T} - \frac{1}{T_{hm}} \right)} \right)_p = - \frac{\Delta_{sol}H^0}{R} \quad (5)$$

In which,  $R$  represents the universal gas constant. The  $T_{hm}$  was 307.98 K in this work. The Van't Hoff plots were constructed

between  $\ln x_e$  and  $1/T - 1/T_{hm}$  using Eq. (5). These plots were found to be linear with  $R^2$  values in the range of 0.992–0.999 as shown in Fig. 3.

The  $\Delta_{sol}H^0$  values of crystalline vanillin in ten different environmentally benign solvents were determined from the slope of Fig. 3. The Gibbs free energy ( $\Delta_{sol}G^0$ ) for the dissolution of vanillin in ten different environmentally benign solvents was calculated at  $T_{hm}$  by Krug analysis using Eq. (6) (Krug, Hunter, & Grieger, 1976):

$$\Delta_{sol}G^0 = -RT_{hm} \times \text{intercept} \quad (6)$$

In which, the intercept for each environmentally benign solvent was determined from Fig. 3.

Finally, the dissolution entropy ( $\Delta_{sol}S^0$ ) for crystalline vanillin in ten different environmentally benign solvents was determined using Eq. (7):

$$\Delta_{sol}S^0 = \frac{\Delta_{sol}H^0 - \Delta_{sol}G^0}{T_{hm}} \quad (7)$$

The results of thermodynamic function in terms of  $\Delta_{sol}H^0$ ,  $\Delta_{sol}G^0$  and  $\Delta_{sol}S^0$  for the dissolution of vanillin in ten different environmentally benign solvents are listed in Table 3.

The  $\Delta_{sol}H^0$  values for vanillin dissolution were observed as positive values in all environmentally benign solvents investigated, indicating an endothermic dissolution behavior of vanillin in all environmentally benign solvents. The  $\Delta_{sol}H^0$  value for vanillin dissolution in water, butanol-1, butanol-2, ethanol, EG, EA, IPA, PG, PEG-400 and Transcutol was observed as 28.73 kJ mol<sup>-1</sup>, 6.85 kJ mol<sup>-1</sup>, 7.69 kJ mol<sup>-1</sup>, 6.45 kJ mol<sup>-1</sup>, 7.36 kJ mol<sup>-1</sup>, 5.23 kJ mol<sup>-1</sup>, 7.11 kJ mol<sup>-1</sup>, 6.92 kJ mol<sup>-1</sup>, 4.14 kJ mol<sup>-1</sup> and 4.65 kJ mol<sup>-1</sup>, respectively. The  $\Delta_{sol}G^0$  values for vanillin dissolution were also observed as positive values in all environmentally benign solvents, indicating spontaneous dissolution of vanillin in all environmentally benign solvents investigated. The  $\Delta_{sol}G^0$  value for vanillin dissolution in water, butanol-1, butanol-2, ethanol, EG, EA, IPA, PG, PEG-400 and Transcutol was observed as 16.15 kJ mol<sup>-1</sup>, 5.99 kJ mol<sup>-1</sup>, 6.75 kJ mol<sup>-1</sup>, 6.26 kJ mol<sup>-1</sup>, 6.37 kJ mol<sup>-1</sup>, 5.20 kJ mol<sup>-1</sup>, 6.72 kJ mol<sup>-1</sup>, 6.53 kJ mol<sup>-1</sup>, 2.02 kJ mol<sup>-1</sup> and 3.51 kJ mol<sup>-1</sup>, respectively. The  $\Delta_{sol}G^0$  and  $\Delta_{sol}H^0$  values for vanillin dissolution were significantly lower in PEG-400, Transcutol and EA as compared to water. However, the  $\Delta_{sol}G^0$  and  $\Delta_{sol}H^0$  values for vanillin dissolution in ethanol, PG, EG, butanol-1, butanol-2 and IPA were not changed significantly. The data of  $\Delta_{sol}G^0$  and  $\Delta_{sol}H^0$  were in good agreement with solubility data of crystalline vanillin. The  $\Delta_{sol}S^0$  values for vanillin dissolution were also observed as positive values in all environmentally benign solvents, indicating an entropy-driven dissolution of vanillin in all environmentally benign solvents. The lower values of  $\Delta_{sol}H^0$  in PEG-400, EA and Transcutol indicated that relatively low energy is required for the solubilization of vanillin in PEG-400, EA and Transcutol as compared to water. The positive values of  $\Delta_{sol}H^0$  for vanillin dissolution were possible due to the stronger interactions between vanillin molecules and the environmentally benign solvent molecules as compared to those between the solvent-solvent and vanillin-vanillin molecules as reported in literature (Shakeel et al., 2014, 2015).

**Table 3**

Thermodynamic parameters along with  $R^2$  values for dissolution of crystalline vanillin in ten different environmentally benign solvents at mean harmonic temperature of 307.98 K (values in parentheses are standard deviations).

Parameters	Water	Ethanol	PG	PEG-400	Transcutol	EG	IPA	EA	Butanol-1	Butanol-2
$\Delta_{sol}H^0$ /kJ mol <sup>-1</sup>	28.73 (0.24)	6.45 (0.08)	6.92 (0.10)	4.14 (0.06)	4.65 (0.07)	7.36 (0.11)	7.11 (0.10)	5.23 (0.05)	6.85 (0.06)	7.69 (0.12)
$\Delta_{sol}G^0$ /kJ mol <sup>-1</sup>	16.15 (0.22)	6.26 (0.07)	6.53 (0.09)	2.02 (0.02)	3.51 (0.04)	6.37 (0.10)	6.72 (0.11)	5.20 (0.08)	5.99 (0.07)	6.75 (0.08)
$\Delta_{sol}S^0$ /J mol <sup>-1</sup> K <sup>-1</sup>	40.82 (0.38)	0.60 (0.00)	1.26 (0.00)	6.88 (0.07)	3.69 (0.02)	3.23 (0.01)	1.22 (0.00)	0.11 (0.00)	2.78 (0.04)	3.03 (0.02)
$R^2$	0.996 (0.01)	0.997 (0.02)	0.992 (0.00)	0.999 (0.01)	0.999 (0.02)	0.999 (0.01)	0.999 (0.00)	0.997 (0.01)	0.999 (0.00)	0.999 (0.02)

#### 4. Conclusion

The solubilities of crystalline vanillin in ten different environmentally benign solvents such as water, ethanol, butanol-1, butanol-2, EG, EA, IPA, PG, PEG-400 and Transcutol were measured at  $T = (298\text{--}318)\text{K}$  using an isothermal method. The mole fraction solubility of vanillin was observed highest in PEG-400 followed by Transcutol, EA, butanol-2, ethanol, EG, PG, IPA, butanol-1 and water at  $T = (298\text{--}318)\text{K}$ . The experimental solubility data of vanillin were correlated well with the modified Apelblat and Van't Hoff models in all environmentally benign at  $T = (298\text{--}318)\text{K}$ . Thermodynamic function of vanillin dissolution was measured by Van't Hoff and Krug analysis. The results of thermodynamic function indicated endothermic, spontaneous and entropy-driven dissolution of crystalline vanillin in all environmentally benign solvents investigated. Based on solubility data of this work, crystalline vanillin has been considered as freely soluble in PEG-400, Transcutol, EA, butanol-2, ethanol, EG, PG, IPA and butanol-1 and soluble in water according to USP classification of solubility. The solubility data of this work could be useful in purification, crystallization, separation/extraction, pre-formulation studies and formulation development of vanillin.

#### 5. Conflict of interest

The authors report no conflict of interest related with this manuscript.

#### Acknowledgment

The authors would like to extend their appreciation to the Deanship of Scientific Research, College of Science Research Center, King Saud University, Riyadh, Saudi Arabia for supporting this project.

#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.foodchem.2015.01.102>.

#### References

- Anwer, M. K., Al-Shdefat, R., Jamil, S., Alam, P., Abdel-Kader, M. S., & Shakeel, F. (2014). Solubility prediction of bioactive compound hesperidin in six pure solvents at (298.15–333.15) K. *Journal of Chemical and Engineering Data*, 59, 2065–2069.
- Apelblat, A., & Manzurola, E. (1999). Solubilities of *o*-acetylsalicylic, 4-aminosalicylic, 3,5-dinitrosalicylic and *p*-toluic acid and magnesium-DL-aspartate in water from  $T = (278\text{--}348)\text{K}$ . *The Journal of Chemical Thermodynamics*, 31, 85–91.
- Higuchi, T., & Connors, K. A. (1965). Phase-solubility techniques. *Advanced Analytical Chemistry and Instrumentation*, 4, 117–122.
- Holguin, A. R., Rodriguez, G. A., Cristancho, D. M., Delgado, D. R., & Martínez, F. (2012). Solution thermodynamics of indomethacin in propylene glycol + water mixtures. *Fluid Phase Equilibria*, 314, 134–139.
- Hundre, S. Y., Karthik, P., & Anandharamakrishnan, C. (2015). Effect of whey protein isolate and  $\beta$ -cyclodextrin wall systems on stability of microencapsulated vanillin by spray-freeze drying method. *Food Chemistry*, 174, 16–24.
- Kayaci, F., & Uyar, T. (2012). Encapsulation of vanillin/cyclodextrin inclusion complex in electrospun polyvinyl alcohol (PVA) nanoweb: Prolonged shelf-life and high temperature stability of vanillin. *Food Chemistry*, 133, 641–649.
- Krug, R. R., Hunter, W. G., & Grieger, R. A. (1976). Enthalpy-entropy compensation. 2. Separation of the chemical from the statistic effect. *Journal of Physical Chemistry*, 80, 2341–2351.
- Kumar, R., Sharma, P. K., & Mishra, P. S. (2012). A review on the vanillin derivatives showing various biological activities. *International Journal of PharmTech Research*, 4, 266–279.
- Li, R., Jiang, Z., Mao, L., & Shen, H. (1998). Adsorbed resin phase spectrophotometric determination of vanillin or/and its derivatives. *Talanta*, 47, 1121–1127.
- Liu, J. Q., Chen, S. Y., & Ji, B. (2014). Solubility and thermodynamic functions of isatin in pure solvents. *Journal of Chemical and Engineering Data*, 59, 3407–3414.
- Manzurola, E., & Apelblat, A. (2002). Solubilities of L-glutamic acid, 3-nitrobenzoic acid, acetylsalicylic, *p*-toluic acid, calcium-L-lactate, calcium gluconate, magnesium-DL-aspartate, and magnesium-L-lactate in water. *The Journal of Chemical Thermodynamics*, 34, 1127–1136.
- Noubigh, A., Cherif, M., Provost, E., & Abderrabba, M. (2008). Solubility of gallic acid, vanillin, syringic acid and protocatechuic acid in aqueous sulfate solutions from (293.15–318.15) K. *Journal of Chemical and Engineering Data*, 53, 1675–1678.
- Noubigh, A., Mgaidi, A., Abderrabba, M., Provost, E., & Furst, W. (2007). Effects of salts on the solubility of phenolic compounds: Experimental measurements and modeling. *Journal of the Science of Food and Agriculture*, 87, 783–788.
- Peng, H., Xiong, H., Li, J., Xie, M., Liu, Y., Bai, C., et al. (2010). Vanillin cross-linked chitosan microspheres for controlled release of resveratrol. *Food Chemistry*, 121, 23–28.
- Ruidiaz, M. A., Delgado, D. R., Martínez, F., & Marcus, Y. (2010). Solubility and preferential solvation of indomethacin in 1,4-dioxane + water solvent mixtures. *Fluid Phase Equilibria*, 299, 259–265.
- Shakeel, F., Anwer, M. K., Shazly, G. A., & Jamil, S. (2014). Measurement and correlation of solubility of bioactive compound silymarin in five different green solvents at 298.15–333.15 K. *Journal of Molecular Liquids*, 195, 255–258.
- Shakeel, F., Haq, N., Alanazi, F. K., & Alsarra, I. A. (2015). Thermodynamics of solubility of isatin in (PEG 400 + water) mixed solvent systems at  $T = (298.15\text{--}338.15)\text{K}$ . *The Journal of Chemical Thermodynamics*, 82, 156–160.
- Walton, N. J., Mayer, M. J., & Narbad, A. (2003). Molecules of interest vanillin. *Phytochemistry*, 63, 505–515.