Solubility of caffeic acid in CO_2 + ethanol: Experimental and predicted data using Cubic Plus Association Equation of State

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GRAPHICAL ABSTRACT
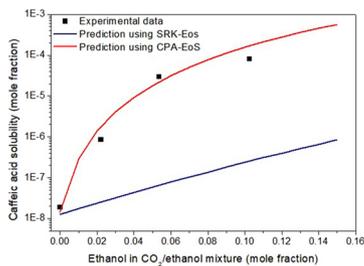
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ABSTRACT

This work evaluated the solubility of caffeic acid (CA) in mixtures of supercritical carbon dioxide ($scCO_2$) and ethanol at different temperatures (313, 323 and 333 K), pressures (20, 30 and 40 MPa) and concentrations of ethanol (2.2, 5.4 and 10.2 mol%). The Soave-Redlich-Kwong and Cubic Plus Association (CPA) equations of state were used to correlate the binary mixture data and to predict the ternary system data. CA solubility in ethanol is approximately 10^6 times higher than its solubility in pure $scCO_2$. By using 10.2 mol% ethanol in $scCO_2$, CA solubility increased 30,000 times at 313 K and 20 MPa. Both models provided reasonable descriptions of the experimental data for the binary systems. However, CPA-EoS can better describe the strong interactions between acid molecules and ethanol, and can predict that the addition of small amounts of ethanol to $scCO_2$ provides a large increase in CA solubility.

1. Introduction

Caffeic acid, or 3,4-dihydroxycinnamic acid (CA), is an abundant phenolic acid that represents between 75% and 100% of the total content of hydroxycinnamic acids in many fruits [1]. CA is rarely found in its free form. For instance, the ester formed by caffeic and quinic acids is one of the chlorogenic acids found in fruits (blueberries, kiwis, plums, cherries, apple, ciders), vegetables, wine, olive oil, and, in high

concentrations, in coffee [1,2]. Thus, this compound is present in significant amounts in the human diet. The CA structure (Fig. 1) is characterized by having a benzene ring, a carboxylic acid group and two hydroxyl groups in the molecule, conferring it antioxidant properties [3]. Besides its antioxidant activity, CA presents as well anti-ischemia, anti-thrombosis, anti-hypertension, anti-fibrosis, anti-virus and anti-tumor properties [4–6].

The production of natural extracts rich in phenolic compounds, such

Nomenclatures

Abbreviations

AARD	Average absolute relative deviation
ALD	Average logarithmic deviation
AG	Association group
CA	Caffeic acid
CPA	Cubic plus association
COSMO-SAC	Conductor-like screening model - segment activity coefficient
EoS	Equation of state
OF	Objective function
PR	Peng-Robinson
SAFT	Statistical associating fluid theory
SRK	Soave-Redlich-Kwong
scCO2	Supercritical carbon dioxide

List of symbols

a	Energy parameter in the physical term
a_0, c_1	Parameters for calculating a
b	Co-volume parameter in the physical term
C_p	Heat capacity
g	Radial distribution function
H	Enthalpy
k_{ij}	Binary interaction parameter
N	Number of experimental data
P	Pressure
R	Gas constant
T	Temperature
V	Molar volume
X_{Ai}	Fraction of molecule not bonded at site a
y, x	Mole fractions

Greek symbols

β	Association volume
ε	Association energy
Δ	Association strength
ρ	Molar density
η	Reduced fluid density
ϕ	Coefficient of fugacity
ω	Acentric factor

Subscripts

A,B	Molecules sites
atm	Atmospheric condition
C	Critical properties
cal	Calculated
exp	Experimental
i,j	Pure component indexes
m	Melting
f	Fusion

Superscript

vap	Vapor

as CA, is interesting for food, chemical and pharmaceutical industries. Extractions using supercritical carbon dioxide (scCO$_2$) as a solvent have some advantages over traditional extraction techniques. Mainly, it is a flexible and selective process that provides clean extracts, i.e. free of toxic residues. Furthermore, carbon dioxide is cheap, available in high purity, non-toxic, non-flammable and "Generally Recognized as Safe" (GRAS) for food applications.

Knowledge on the solubility of phenolic compounds in scCO$_2$ is very important for design and optimization of processes aiming to obtain natural extracts rich in phenolic compounds using supercritical technology. However, CA presents low solubility in scCO$_2$ (approximately 10^{-8} and 10^{-9} in mole fraction [7]) and consequently low extraction yields are obtained using this solvent. The low solubility of CA in scCO$_2$ is associated with the high polarity of this compound. Thus, its extraction from vegetable sources using scCO$_2$ should be performed in the presence of polar co-extractants to increase the solvent polarity. Ethanol is one of the most used cosolvents because it is also considered a "green solvent" [8]. It is thus important to know the CA solubility in CO$_2$/ethanol mixtures. Other phenolic compounds with antioxidant properties had their solubility previously reported in CO$_2$ + ethanol, such as quercetin, curcumin, catechin, epicatechin, resveratrol and ferulic, *trans*-cinnamic and gallic acids [9–18].

The thermodynamic modeling of these systems makes possible the

prediction of data for multicomponent systems and at different conditions of temperature and pressure from those experimentally studied. Cubic state equations, such as Peng-Robinson (PR-EoS) and Soave-Redlich-Kwong (SRK-EoS), are the most commonly used to describe systems under high pressures. However, the prediction of the phase equilibrium of systems containing phenolic compounds, scCO$_2$ and ethanol using these equations does not provide good results [17], because the presence of polar cosolvents may induce specific interactions, such as hydrogen bonding between the solute and the cosolvent, which a cubic equation of state cannot properly take into account [19]. Most of the prior works on solubility of biomolecules in mixtures of CO$_2$ and cosolvent correlated the data by fitting binary interaction parameters to the experimental data of the ternary system [20,21]. Only Ting et al. [22] and Yang and Zhong [23] attempted the prediction of solubility data of ternary systems.

One promising model for polar and associating solvents is the Cubic-Plus-Association Equation of State (CPA-EoS), which consists in the combination of a cubic equation (Soave-Redlich-Kwong) and the association term proposed by Wertheim and widely used in SAFT-type (Statistical Associating Fluid Theory) equations of state [24]. Compared with SAFT, CPA-EoS is a simpler yet accurate model for associating mixtures, while keeping the well-known advantages of cubic equations of state. The CPA-EoS has already been successfully used to describe the CA solubility in water and other biomolecules in organic solvents [25–27] and in the liquid-vapor equilibrium modeling of the CO$_2$/ethanol/water system [28].

This work addresses the measurement of the solubility data of caffeic acid in mixtures of supercritical carbon dioxide and ethanol and evaluates the ability of Cubic-Plus-Association Equation of State (CPA-EoS) to predict the behavior of these systems.
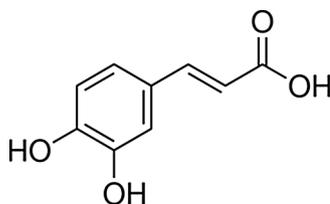

Fig. 1. Caffeic acid chemical structure.

2. Experimental

2.1. Chemicals

Caffeic acid with purity $\geq$ 98% (CAS Number 331-39-5, Sigma-Aldrich, USA), carbon dioxide 99.5% w/w (White Martins Gases Industriais, Brazil) and ethanol 99.5% (Synth, Brazil) were used.

2.2. Solubility measurements

2.2.1. Caffeic acid – ethanol system

Solubility measurements of caffeic acid in ethanol were performed in triplicate using a jacketed glass cell coupled to a thermostatic bath (Polystat, Cole Parmer, USA). The system was assembled adding excess solute to a fixed volume of solvent. The mixture was stirred for 1 h with a magnetic stirrer and then allowed to equilibrate and phase separate for 24 h. A syringe was used to collect a representative sample of the upper phase far away from the solid-liquid interface. Then the solution was weighted (Accurate Analytical Balance with precision $+/-$ 0.0001 g, model XT 220A, Sweden), concentrated in a rotary vacuum evaporator (Marconi rotary evaporator, model MA-120, Brazil) and kept in an oven (Marconi, model MA030/12, Brazil) under vacuum (Marconi vacuum pump model MA057/1, Brazil) at 323 K until constant mass. Solubility in mass fraction was calculated by the ratio of the solute mass and the solution mass collected by syringe.

2.2.2. Caffeic acid–CO₂–ethanol system

The solubility of caffeic acid in CO_2 - ethanol mixtures was measured by a dynamic method in a supercritical extraction unit, as detailed in studies published recently [29,30]. The investigation was conducted in triplicate at different conditions of temperature (313, 323 and 333 K), pressure (20, 30 and 40 MPa), and amounts of ethanol (2 mol%, 5 mol% and 10 mol% on a solute free-basis).

An extractor with 100 mL capacity (32 cm length) was manually packaged with caffeic acid mixed with glass beads (5 cm diameter). Measured in the end of the process (atmospheric conditions), the CO_2 flow rate was around 0.4 L/min and the ethanol flow rate varied according to the desired mixture at 0.02, 0.05 and 0.1 mL/min. In previous tests, the CO_2 flow rate 0.4 L/min was found to be low enough to ensure that solid-supercritical fluid phase equilibrium was achieved during solubility measurements. Considering the local atmospheric conditions as 298 K and 0.095 MPa, the values for the density of ethanol and carbon dioxide were assumed as 0.78 g/mL and 1.65 g/L, respectively.

The valve where occurs the expansion from high to ambient pressure and a session of pipe through which the extract flows until it is collected in the collector flask are both heated since they are submerged within a thermostatic bath working at the same temperature of the solubility measurements. The samples were collected in a flask at ambient temperature for obtaining the mixtures of ethanol + caffeic acid. CO_2 gas was led to a gas flowmeter to control the CO_2 flow and to a volume totalizer to measure the total amount of carbon dioxide used in the experiment.

The CO_2 amount used for each measurement depended on the proportion CO_2/ethanol mixture evaluated to guarantee sufficient sample mass to be well quantified: 5, 10 and 20 L of CO_2 were used for the solubility measurements with ethanol concentrations of 10, 5 and 2.5 mol% ethanol, respectively.

The samples were concentrated in a rotary vacuum evaporator (Marconi, model MA-120, Brazil) and kept in an oven (Marconi, model MA030/12, Brazil) under vacuum (Marconi, model MA057/Brazil) at 323 K until constant weight. The samples were stored at 247 K until quantification.

2.3. Quantification of caffeic acid

The quantification of caffeic acid was performed by spectrophotometry (UV-VIS spectrophotometer Aquamate Orion 8000, Thermo Scientific, USA) at 217 nm. For that purpose, calibration curves with solutions of known concentrations of caffeic acid varying from 0.001 to 0.01 mg/mL were prepared (R^2 > 0.99).

3. Thermodynamic modeling

The CA solubilities in CO_2, ethanol, and CO_2 + ethanol were calculated using the equation of equilibrium based on the equality of solute fugacity in the solid and solution (light) phases. Assuming a pure solid phase and no significant temperature dependence on the difference between the heat capacity of the pure liquid and solid (ΔC_p), Eq. (1) [31] is obtained.

$$y_{CA} = \frac{\phi_{pure\ CA}^{liquid}}{\phi_{CA}^{liquid}} \exp\left[-\frac{\Delta H}{R}\left(\frac{1}{T} - \frac{1}{T_m}\right) + \frac{\Delta C_p}{R}\left[\frac{T_m}{T} - 1 - \ln\left(\frac{T_m}{T}\right)\right] \right.$$
$$\left. - \left[\frac{(P - P_{atm})\Delta V_{CA}}{RT}\right] \right]$$
(1)

where y_{CA} is the solute mole fraction solubility; R is the gas constant; T is the absolute temperature; T_m is the melting temperature; ϕ is the coefficient of fugacity; ΔH is the phase transition enthalpy; $\Delta C_{p,CA} = C_{p,CA}^{liquid} - C_{p,CA}^{solid}$ and $\Delta V_{CA} = V_{CA}^{liquid} - V_{CA}^{solid}$.

Fugacity coefficients were calculated from the Soave-Redlich-Kwong or the Cubic Plus Association equations of state. In both cases, the binary interaction parameters were estimated by minimizing an objective function (OF) (Eq. (2)) which evaluates the difference between the experimental and calculated values of solubility.

$$OF(k_{ij}) = AARDy\ (\%) = \frac{100}{N}\sum_{j=1}^{N}\left[\frac{|y_{cal} - y_{exp}|}{y_{exp}}\right]_j$$
(2)

3.1. Soave-Redlich-Kwong Equation of State (SRK-EoS)

The SRK-EoS has the following form:

$$P = \frac{RT}{V - b} - \frac{a}{V\ (V + b)}$$
(3)

where V is molar volume; a and b are the pure component parameters of energy and co-volume, respectively. A Soave-type temperature dependency of the energy parameter is used:

$$a(T) = a_0[1 + c_1(1 - \sqrt{T/T_c})]^2$$
(4)

The a and b parameters are calculated by using the critical properties and the acentric factor (ω) of the pure components, as presented in Table 1. For mixtures, the parameters were calculated using the classical van der Waals one-fluid mixing rules, with one binary interaction parameter k_{ij}.

$$a = \sum_i \sum_j a_{ij}y_iy_j \quad a_{ij} = \sqrt{a_ia_j}\ (1 - k_{ij})$$
(5)

Table 1
Pure component physical properties.

| Compound	M (g/mol)	T_C(K)	P_C(MPa)	ω	T_m (K)	ΔH_f (J/mol)
CO₂	44.01	304.13[a]	7.377[a]	0.223[a]		
Ethanol	46.07	513.92[a]	6.137[a]	0.643[a]		
Caffeic acid	180.16	993.05[b]	5.809[b]	1.056[c]	469[c]	13638.78[c]

[a] Multiflash™ database [35].
[b] Murga et al. [7].
[c] Saldaña et al. [36].

Table 2
CA solubility in ethanol (mole fraction) at atmospheric pressure.

T/K	$x_{CA} \times 10^2$
293.15	1.41 ± 0.05
298.15	1.51 ± 0.08
303.15	1.58 ± 0.03
308.15	1.73 ± 0.05
313.15	1.86 ± 0.05
318.15	2.13 ± 0.05
323.15	2.3 ± 0.1
328.15	2.5 ± 0.2
333.15	2.8 ± 0.1
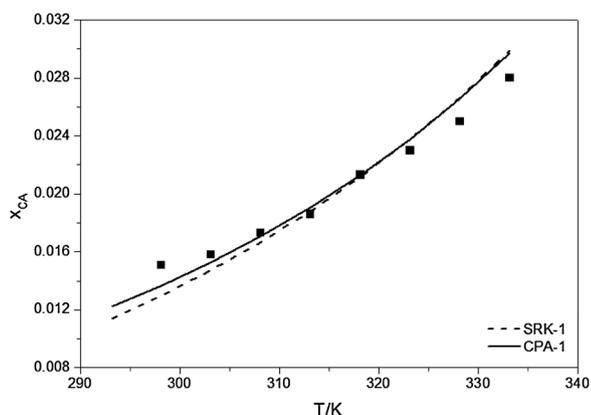
Fig. 2. Thermodynamic modeling of the CA solubility in ethanol (x_{CA}) at atmospheric pressure using SRK-1 and CPA-1 models.

Table 3
Mole fraction CA solubility in CO_2 and ethanol mixtures (y_{CA}).

Y_{et} (%)[a]	T/K[b]	P/MPa[b]	$y_{CA} \times 10^6$
2.23 ± 0.01	313.15	20	0.58 ± 0.08
		30	0.8 ± 0.2
		40	1.7 ± 0.4
	323.15	20	1.9 ± 0.2
		30	0.86 ± 0.06
		40	0.92 ± 0.09
	333.15	20	1.2 ± 0.2
		30	4.8 ± 0.9
		40	2.6 ± 0.3
5.37 ± 0.03	313.15	20	6 ± 1
		30	14 ± 1
		40	37 ± 5
	323.15	20	22 ± 2
		30	30 ± 3
		40	36 ± 2
	333.15	20	11 ± 2
		30	59 ± 3
		40	54 ± 3
10.2 ± 0.1	313.15	20	60 ± 2
		30	69 ± 5
		40	77 ± 4
	323.15	20	66 ± 5
		30	80 ± 1
		40	90 ± 5
	333.15	20	44 ± 3
		30	84 ± 4
		40	91 ± 4

[a] Y_{et}: mole percentage of ethanol on a solute free-basis.
[b] Uncertainties of temperature and pressure measurements are 0.5 K and 0.1 MPa, respectively.
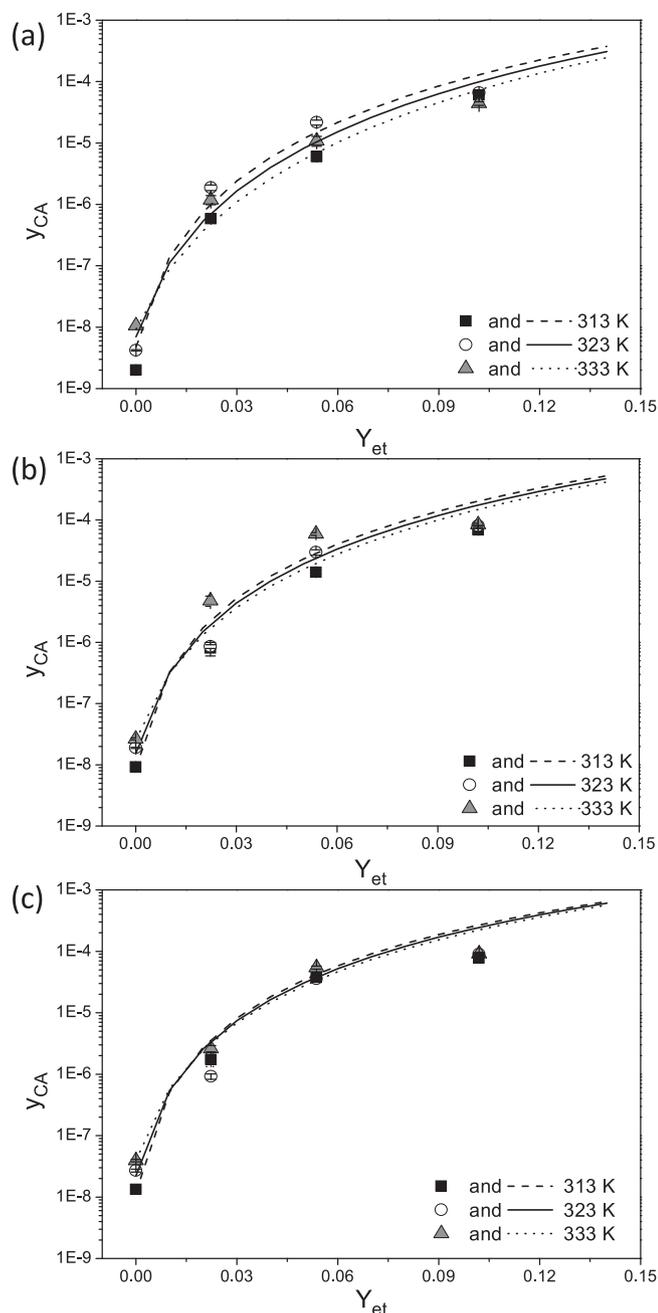
$$b = \sum_i b_i y_i \tag{6}$$
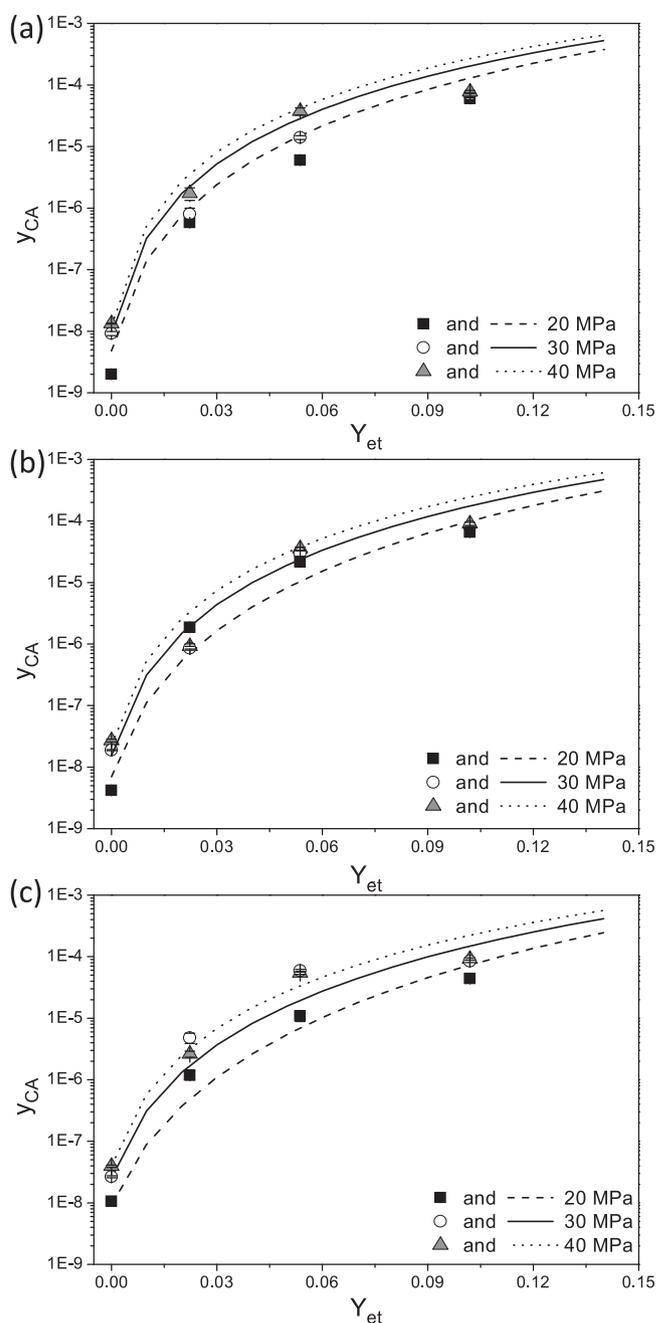
Fig. 3. Prediction of CA solubility in CO_2/ethanol mixtures (y_{CA}) from CPA-1: (a) 313 K; (b) 323 K; (c) 333 K. Experimental data of CA solubility in pure $scCO_2$ were obtained from Murga et al. [7]. Y_{et}: ethanol mole fraction on a solute free-basis; Symbols: experimental data; Lines: predicted data.

3.2. Cubic Plus Association Equation of State (CPA-EoS)

As mentioned previously, the CPA equation of state results from the combination of the SRK equation and the Wertheim association term [24]. In CPA, each associative compound is conceptualized as having one or more sites through which it may bond to other molecules, and the EoS can thus be described as follows:

$$P = \frac{RT}{V - b} - \frac{a}{V(V + b)} + \frac{RT}{2V}\left(1 + \frac{1}{V}\frac{\partial \ln(g)}{\partial \rho_i}\right) \sum_i x_i \sum_{A_j} \left(1 - X_{A_i}\right) \tag{7}$$

where i and j are used to index the molecules, and the capital letters A and B are used to index the bonding sites on a particular molecule i; x is

Fig. 4. Prediction of CA solubility in CO_2/ethanol mixtures (y_{CA}) from CPA-1: (a) 20 MPa; (b) 30 MPa; (c) 40 MPa. Experimental data of CA solubility in pure $scCO_2$ were obtained from Murga et al. [7]. Y_{et}: ethanol mole fraction on a solute free-basis; Symbols: experimental data; Lines: predicted data.

the mole fraction; ρ is the molar density; g is a radial distribution function and X_{Ai} is the mole fraction of component i not bonded at site A;
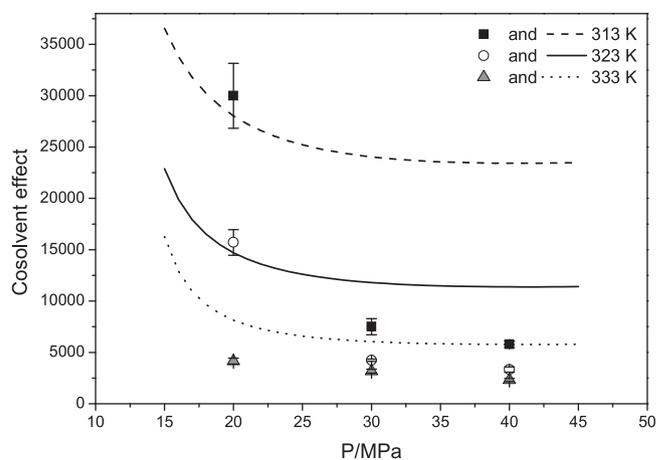
The X_{Ai} is calculated by solving the following set of equations:

$$X_{Ai} = \frac{1}{1 + \rho \sum_j x_j \sum X_{Bj} \Delta^{AiBj}}$$

(8)

where $\Delta^{Ai}B_j$ is the association strength between two sites belonging to two different molecules.

$$\Delta^{AiBj} = g(\rho) \left[\exp\left(\frac{\varepsilon^{AiBj}}{RT} \right) - 1 \right] b_{ij} \beta^{AiBj}$$

(9)

The simplified hard-sphere radial distribution function (g) was used

Fig. 5. Cosolvent effect on CA solubility in $scCO_2$ with 10.2 mol% ethanol. The lines represent the cosolvent effect calculated according to CPA-1.

[32]:

$$g(\rho) = \frac{1}{1 - 1,9\eta}$$

(10)

$$\eta = \frac{1}{4} b\rho$$

(11)

Apart from the three pure component parameters (a_0, c_1 and b) for non-associating components, two more parameters, related to the associative contribution of the compound, are required: the energy of association between the sites of molecule (ε) and the parameter of association volume (β). These five parameters are obtained simultaneously from fitting the equation to vapor pressure and liquid density data of pure compounds.

For mixtures, the classical van der Waals mixing rule are used (Eqs. (5) and (6)) for the a and b parameters. For the association parameters several combining rules have been suggested [33]. The Elliot combining rule and CR-2 [34] are the most used. For many mixtures, both of these combining rules provide accurate descriptions of the phase equilibria. In this work the CR-2 (Eqs. (12) and (13)) was used for the mixtures studied.

$$\beta^{A_iB_j} = \sqrt{\beta^{A_i} \beta^{B_j}}$$

(12)

$$\varepsilon^{A_iB_j} = \frac{1}{2} \left(\varepsilon^{A_i} + \varepsilon^{B_j} \right)$$

(13)

It is not rare to find Eq. (1) in a simplified form, in which only the term with ΔH is considered, since the other terms may be neglected when compared to that one. In this way, for comparison purposes and in order to evaluate the influence of ΔC_p and ΔV on the modeling performance, two different approaches for SRK (SRK-1 and SRK-2) and four approaches based on the CPA model (CPA-1 to CPA-4) were tested. Details on the differences will be presented and discussed in Section 4.3.

4. Results and discussion

4.1. Caffeic acid – ethanol system

One of the objectives of this work is to predict CA solubility in CO_2 + ethanol. For this analysis, it is important to obtain experimental phase equilibrium data for all the binary systems involved in the ternary mixture. For this reason, phase equilibrium measurements were conducted for the system caffeic acid – ethanol.

CA solubility in ethanol was measured at nine temperatures in the range from 293 K to 333 K, as shown in Table 2 and Fig. 2. CA solubility doubles by increasing the temperature from 293 K to 333 K. Zhang et al.

Table 4

CPA parameters of pure components.

Compound	a_0 (J m³/mol)	$b \times 10^5$ (m³/mol)	c_1	Associative Group (AG)	Number of AG	ε (J/mol)	$\beta \times 10^{-3}$	AARD P (%)
CO_2	0.35[a]	2.72[a]	0.76[a]					
Ethanol	0.86716[b]	4.91[b]	0.7369[b]	OH	1	21532[b]	8.0[b]	
Caffeic acid	3.8896[c]	15.6[c]	1.9534[c]	OH and COOH	3	19090.37[d]	27.88[d]	7.8

[a] Oliveira et al. [42].
[b] Folas et al. [43].
[c] Mota et al. [25].
[d] Fitted from vapor pressure data of caffeic acid reported by Chen et al. [44].

Table 5

Binary interaction parameters from SRK-EoS and CPA-EoS for CA (1) − CO_2 (2) − ethanol (3) system.

| Pair ij	$k_{ij} = A + B \times (T/K)$				AARD (%)		Data reference
	SRK-1		CPA-1		SRK	CPA	
	A	$B \times 10^4$	A	$B \times 10^4$			
12	0.167	− 0.170	0.084	− 2.12	20.0[a]	28.7[a]	Murga et al. [7]
13	0.0149	− 1.45	− 0.0424	3.70	6.9[a]	5.0[a]	This work
23	0.2199	4.13	0.0407	3.01	2.9[b]	14.8[b]	Lim et al. [45]

[a] AARD y.
[b] AARD P.

Table 6

Different model approaches evaluated, based in Eq. (1).

Model	$\Delta C_{p,CA}$ (J/mol K)	ΔV_{CA} (m³/mol)	ALD[a]
SRK-1 and CPA-1	0	0	0.288[b]
SRK-2 and CPA-2	50	2.549×10^{-5}	0.321[b]
CPA-3	50	0	0.314[b]
CPA-4	0	2.549×10^{-5}	0.297[b]

[a] $ALD = \sum_{j=1}^{N} \frac{1}{N} \left| \log \frac{y_i^{calc}}{y_i^{expt}} \right|$.

[b] ALD for prediction of phase equilibrium data in ternary system CO_2–ethanol – caffeic acid using CPA model.
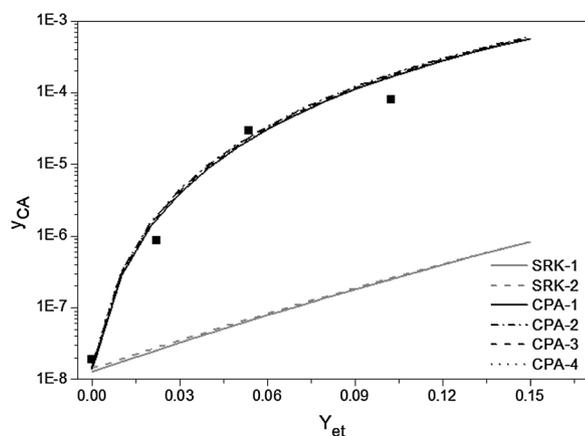
Fig. 6. Comparison between SRK and CPA model for prediction of ternary system caffeic acid − CO_2 – ethanol at 323.15 K and 30 MPa.

[37] evaluated CA solubility in ethanol/water mixtures, and the solubility at 298 K and 90.05% ethanol was 0.0621 in mass fraction (0.016 in mole fraction). This value is consistent with those obtained in this work, since Zhang et al. [37] shows that CA solubility should not increase when adding more ethanol in the ethanol/water mixture. Recently, Ji et al. [38] also evaluated the solubility of caffeic acid in ethanol. The average absolute deviation between their data and the results presented in this work is approximately 25%. In addition, CA solubility in water present lower values than the solubility in ethanol, varying from 5×10^{-5} to 3×10^{-4} in mole fraction for temperatures within the range 288 K to 323 K [26], and CA solubility in ethanol is approximately 10^6 times higher than CA solubility in scCO₂ [7]. All these results attest the importance of using cosolvents, such as ethanol, to obtain extracts with high CA content.

Although CA solubility in ethanol is much greater than in scCO₂ + ethanol mixtures, the use of pure ethanol as solvent could be not recommended mainly in order to obtain extracts enriched in specific compounds, since ethanol is not a selective solvent and it extracts a large group of components. In this context, supercritical extraction with CO_2 stands out for being a selective and flexible process allowing the increase of the solvent́s polarity by adding ethanol to the supercritical fluid in a gradual way. Besides that, the use of pure ethanol requires a high cost step after extraction for the ethanol separation.

4.2. Caffeic acid − CO_2 − ethanol system

The CA solubility in CO_2 and ethanol mixtures was evaluated at three values for temperatures (313, 323 and 333 K), pressures (20, 30 and 40 MPa) and concentrations of ethanol (2.2, 5.4 and 10.2 mol%), as shown in Table 3. There are no available data in the literature for this mixture. The lowest CA solubility values were obtained at 313 K and 20 MPa, for all the proportions of ethanol studied. However, the conditions of temperature and pressure that presented the greatest solubility varied according to the amount of ethanol in the CO_2/ethanol mixture. For example, using 2.2 mol% ethanol the highest CA solubility was found at 333 K and 30 MPa. On the other hand, with 10.2 mol% ethanol in the CO_2/ethanol mixture the greatest values were found at higher pressures (40 MPa).

Although the CA solubility in the mixture CO_2 + ethanol was still much lower than in pure ethanol, the solubility of CA in scCO₂ + 10.2% ethanol reached values 10^5 times higher than its solubility in pure scCO₂ (313 K and 20 MPa) [7]. As mentioned in previous works, the increase in solubility using cosolvent occurs mainly due to the strong hydrogen bonds formed between the solute and the alcohol molecules [19,39–41]. However, the increase in the density of the solvent mixture with the addition of cosolvent in the system and the dipole–dipole type interactions can also be responsible for this behavior [40].

Other phenolic compounds for which the solubility in CO_2 + ethanol was previously reported did not present such a huge increase in solubility when adding ethanol. This is probably due to the fact that CA solubility in scCO₂ is rather small and caffeic acid is a fairly polar compound.

Although the highest solubility values were observed at the higher temperature and pressure conditions, the influence of temperature and pressure decreases when the quantity of cosolvent in the mixture is increased. The dependencies of the solubility with temperature and pressure are shown in Figs. 3 and 4, in which the proximity of the solubility data is noteworthy when using 10.2 mol% ethanol. Similar

behavior was also found for solubility of urea [41] and ferulic acid [17].

The experimental data suggests a logarithmic dependency of the solubility data with ethanol concentration. The increase in CA solubility due to the increase in the concentration of ethanol from 5.4 mol% to 10.2 mol% is not as important as the increase from 0 to 2.2 mol% ethanol. Then, an increase on ethanol concentration above 10.2 mol% should not promote a significant further increase on the CA solubility. Thus, the use of greater amounts of ethanol should be avoided, since this ethanol addition would increase the extract production cost, because of the purification step associated with the necessity of cosolvent evaporation after extraction.

Fig. 4. The ratio of the solubility in the ternary system (CO_2/ethanol mixture) and the solubility in a binary system ($scCO_2$) under the same conditions of temperature and pressure provides the cosolvent effect (Eq. (14)).

$$cosolvent \quad effect = \frac{y_{CA}^{CO_2 + Ethanol}}{y_{CA}^{CO_2}} \tag{14}$$

As a consequence of the results aforementioned, i.e. solubility values less dependent on temperature and pressure at larger concentrations of ethanol, the cosolvent effect is lower for high pressure and temperature values when approximately 10 mol% of ethanol is used as cosolvent (Fig. 5). In addition, a significant increase of up to 30,000 times in the solubility of caffeic acid in $scCO_2$ was observed by adding 10.2 mol% ethanol at 313 K and 20 MPa (cosolvent effect = 30,000).

For systems containing 2.2 and 5.4 mol% ethanol (**Fig. A.1** of the Appendix A. Supplementary data), the highest cosolvent effect were 290 and 3075, respectively. Although the highest cosolvent effect was also observed at 323 K and 20 MPa by using 2.2 mol%, there was no clear trend for the influence of temperature and pressure on the solubility data.

In general, the cosolvent effect values were not well predicted even using Cubic Plus Association equation of state. It probably occurs due to the low accuracy to predict the effects of temperature and pressure on CA solubility in $scCO_2$ + ethanol. Indeed cosolvent effect is a sensitive parameter and strongly affected as a consequence of the deviations observed between experimental and calculated solubility values.

4.3. Thermodynamic modeling

The melting temperature (T_m) and enthalpy of fusion (ΔH_f) required by Equation 1, are presented in Table 1. While for SRK equation, a_0, c_1 and b are calculated from the critical properties, CPA parameters for pure components (a_0, c_1, b, ε and β) are obtained by **fitting** vapor pressure and/or liquid density data of the pure compounds. For the solvents CO_2 and ethanol, these parameters were obtained from literature, as indicated in Table 4. The association term in CPA was characterized by the nature and number of associating groups, each of these being defined by an association scheme, as proposed by Huang and Radosz [46]. CO_2 was here considered as a non-associating compound and the two-site (2B) scheme was used for carboxylic acid groups and for alcohols.

For caffeic acid a group-contribution scheme can be applied for the association term, as reported in studies on polifunctional phenolics solubility [25,26,47]. 2 B association scheme was thus adopted for each hydroxyl or carboxyl group contained in the molecule. CPA pure component parameters were fitted to vapor pressure data [44] using as initial estimation the values reported by Mota et al. [25].It was not possible to use the parameters from Mota et al. [25] because in our work the parameters ε and β were not fitted for each type of associative group of the molecule.

The values for k_{ij}, the binary interaction parameters (BIP) (Equation 5), were estimated by fitting the experimental data with the SRK and CPA EoS. Their values are reported in Table 5. Experimental data from Murga et al. [7] and Lim et al. [45] were used to estimate the BIP

between CO_2 and caffeic acid and CO_2 and ethanol, respectively.

A good description of the binary systems was achieved with low average absolute relative deviations (AARD). The largest AARD was obtained for caffeic acid − CO_2 system (28.7%), however **Fig. A.2** of the Appendix A shows that the deviation between these experimental and calculated points are high at low pressures, near to the critical point.

As previously mentioned, different approaches for SRK (SRK-1 and SRK-2) and CPA (CPA-1 to CPA-4) models were evaluated, in which different values of ΔC_p and ΔV were considered, as shown in Table 6. The ΔV value adopted was estimated assuming that the liquid molar volume is about 20% higher than the solid molar volume reported by Moncada et al. [48], as suggested by Goodman et al. [49]. The ΔC_p adopted value was of 50 J/mol K. However, no significant influence of this term on the results was observed.

No fitting was performed for the ternary mixtures. These were predicted using the BIP's from the binary mixtures. Although the SRK model was as good at fitting the binary systems as the CPA-EoS, the prediction of ternary system was not successful. The comparison between the results for the prediction of the ternary system (caffeic acid − CO_2–ethanol) using CPA-EoS and SRK-EoS are shown in Fig. 6. It was observed that SRK-EoS greatly underestimates the solubility values independently of ΔC_p and ΔV values adopted.

As expected, the predicted CA solubility using CPA-EoS was much closer to solubility experimental data than that of the SRK-EoS prediction. Unlike SRK, CPA takes into account the associative interactions such as hydrogen bonding, which take place between the caffeic acid and ethanol.

Fig. 6 also shows that similar results were obtained using the various approaches with CPA-EoS. Comparing the average logarithmic deviation (*ALD*) between the experimental and calculated data (Table 6), the best results were obtained with CPA-1 (*ALD* = 0.28). In addition to providing the lowest ALD value, CPA-1 is more suitable mainly because it allows to use the simplified form of Eq. (1).

Comparing the predictions from CPA with those from SAFT and PR + COSMOSAC, which were previously reported [22,23], all the three presented reasonable results. Ting et al. [22] evaluated PR + COSMOSAC for the prediction of solubility of different solutes in CO_2 + cosolvents and 0.48 was the minimum *ALD* value obtained. However CPA, besides a slightly better description of the experimental data, also provides most of the advantages of cubic equations of state, such as simplicity of application, low computational overhead and good correlation for phase equilibria data at high pressures. The results by PR + COSMOSAC are also of interest because the prediction of the ternary system requires only the melting temperature and enthalpy of fusion of the solute.

In general, the CPA-EoS predictions provide a good description of the dependence of caffeic acid solubility with the concentration of ethanol, for the temperature and pressure ranges here evaluated, as shown in Figs. 3 and 4. Both experimental and calculated data for the ternary system showed that the effect of pressure becomes less significant with the increase of ethanol content in the CO_2/ethanol mixture, as shown in Fig. 3 where both experimental and predicted data become closer to each other at higher concentrations of ethanol.

However, mainly at higher pressures, according to the CPA predictions, the effect of temperature on CA solubility is not relevant. This behavior is shown in Fig. 4**b** and **c**, by the overlapping lines.

As observed for the experimental data, CPA predicted the higher cosolvent effect at lower temperatures and pressure when CO_2/ethanol (90:10 mol/mol) was used as solvent (Fig. 5). However, for other proportions of CO_2 and ethanol, the prediction of the cosolvent effect indicated the opposite behavior (**Fig. A.1** of the Appendix A).

Finally, although accurate trends for prediction of the CA solubility in CO_2/ethanol were obtained, there was some divergences between the behavior of calculated and experimental data when the influence of temperature and pressure on cosolvent effect were analyzed.

5. Conclusions

Experimental data on the solubility of caffeic acid in ethanol and mixtures of supercritical carbon dioxide and ethanol were reported in this work for the first time in the open literature. As expected, the importance of the use of cosolvent to obtain natural extracts by supercritical technology was confirmed, with an increase of up to 30,000 times observed in the solubility of caffeic acid when 10 mol% of ethanol was added to $scCO_2$.

The use of concentrations higher than 10 mol% of ethanol should be analyzed, in terms of cost benefit, due to the small increase in the solubility of CA on these conditions. When compared with SRK-EoS, the CPA model showed an excellent prediction of the solubility of caffeic acid in supercritical carbon dioxide in the presence of ethanol.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.supflu.2018.04.008.

References

[1] C. Manach, Polyphenols: food sources and bioavailability, Am. J. Clin. Nutr. 79 (2004) 727–747.

[2] M.N. Clifford, Chlorogenic acids and other cinnamates?nature, occurrence and dietary burden, J. Sci. Food Agric. 79 (1999) 362–372, http://dx.doi.org/10.1002/(SICI)1097-0010(19990301)79.

[3] S.E. Soares, Phenolic acids as antioxidants, Rev. Nutr. 15 (2002) 71–81.

[4] J.H. Chen, C.T. Ho, Antioxidant activities of caffeic acid and its related hydroxycinnamic acid compounds, J. Agric. Food Chem. 45 (1997) 2374–2378, http://dx.doi.org/10.1021/jf970055t.

[5] R. Jiang, K. Lau, P. Hon, T.C.W. Mak, K. Woo, Chemistry and biological activities of caffeic acid derivatives from Salvia miltiorrhiza, Curr. Med. Chem. 12 (2005) 237–246.

[6] I. Gülçin, Antioxidant activity of caffeic acid (3, 4-dihydroxycinnamic acid), Toxicology 217 (2006) 213–220, http://dx.doi.org/10.1016/j.tox.2005.09.011.

[7] R. Murga, M.T. Sanz, S. Beltrán, J.L. Cabezas, Solubility of three hydroxycinnamic acids in supercritical carbon dioxide, J. Supercrit. Fluids 27 (2003) 239–245.

[8] F.P. Byrne, S. Jin, G. Paggiola, T.H.M. Petchey, J.H. Clark, T.J. Farmer, A.J. Hunt, C. Robert McElroy, J. Sherwood, Tools and techniques for solvent selection: green solvent selection guides, Sustain. Chem. Process. 4 (2016) 1–24, http://dx.doi.org/10.1186/s40508-016-0051-z.

[9] H. Sovová, Solubility of ferulic acid in supercritical carbon dioxide with ethanol as cosolvent, J. Chem. Eng. Data 46 (2001) 1255–1257.

[10] A. Berna, A. Cháfer, J.B. Montón, S. Subirats, High-pressure solubility data of system ethanol (1) + catechin (2) + CO2 (3), J. Supercrit. Fluids 20 (2001) 157–162.

[11] A. Berna, A. Cháfer, J.B. Montón, High-pressure solubility data of the system resveratrol (3) + ethanol (2) + CO2 (1), J. Supercrit. Fluids 19 (2001) 133–139.

[12] A. Chafer, T. Fornari, A. Berna, R.P. Stateva, Solubility of quercetin in supercritical CO2 + ethanol as a modifier: measurements and thermodynamic modelling, J. Supercrit. Fluids 32 (2004) 89–96.

[13] A. Cháfer, A. Berna, J.B. Montón, R. Muñoz, High-pressure solubility data of system ethanol (1) + epicatechin (2) + CO2 (3), J. Supercrit. Fluids 24 (2002) 103–109.

[14] T. Fornari, A. Cháfer, R.P. Stateva, A. Berna, Trans-cinnamic acid solubility enhancement in the presence of ethanol as a supercritical CO2 cosolvent, J. Chem. Eng. Data 54 (2009) 2263–2268.

[15] A. Cháfer, T. Fornari, R.P. Stateva, A. Berna, J. García-Reverter, Solubility of the natural antioxidant gallic acid in supercritical CO2 + ethanol as a cosolvent, J. Chem. Eng. Data 52 (2007) 116–121, http://dx.doi.org/10.1021/je060273v.

[16] L.C. Paviani, M.R.S. Chiari, T.R. Crespo, F.A. Cabral, Thermodynamic modeling of phase equilibrium behavior of curcumin − CO2 − ethanol, III Iberoam, Conf. Supercrit. Fluids (2013) 1–7.

[17] R.G. Bitencourt, F.A. Cabral, A.J.A. Meirelles, Ferulic acid solubility in supercritical carbon dioxide, ethanol and water mixtures, J. Chem. Thermodyn. 103 (2016) 285–291, http://dx.doi.org/10.1016/j.jct.2016.08.025.

[18] S. Zhan, S. Li, Q. Zhao, W. Wang, J. Wang, Measurement and correlation of curcumin solubility in supercritical carbon dioxide, J. Chem. Eng. Data 62 (2017) 1257–1263, http://dx.doi.org/10.1021/acs.jced.6b00798.

[19] S.S.T. Ting, D.L. Tomasko, S.J. Macnaughton, N.R. Foster, Chemical physical interpretation of cosolvent effects in supercritical fluids, Ind. Eng. Chem. Res. 32 (1993) 1482–1487, http://dx.doi.org/10.1021/ie00019a023.

[20] Z. Huang, Y.C. Chiew, M. Feng, H. Miao, J.H. Li, L. Xu, Modeling aspirin and naproxen ternary solubility in supercritical CO2/alcohol with a new Peng-Robinson EOS plus association model, J. Supercrit. Fluids 43 (2007) 259–266, http://dx.doi.org/10.1016/j.supflu.2007.05.011.

[21] S.N. Reddy, G. Madras, Modeling of ternary solubilities of solids in supercritical carbon dioxide in the presence of cosolvents or cosolutes, J. Supercrit. Fluids 63 (2012) 105–114, http://dx.doi.org/10.1016/j.supflu.2011.11.016.

[22] Y.S. Ting, C.M. Hsieh, Prediction of solid solute solubility in supercritical carbon dioxide with organic cosolvents from the PR + COSMOSAC equation of state, Fluid Phase Equilib. 431 (2017) 48–57, http://dx.doi.org/10.1016/j.fluid.2016.10.008.

[23] H. Yang, C. Zhong, Modeling of the solubility of aromatic compounds in supercritical carbon dioxide-cosolvent systems using SAFT equation of state, J. Supercrit. Fluids 33 (2005) 99–106, http://dx.doi.org/10.1016/j.supflu.2004.05.008.

[24] G.M. Kontogeorgis, E.C. Voutsas, I.V. Yakoumis, D.P. Tassios, An equation of state for associating fluids, Ind. Eng. Chem. Res. 35 (1996) 4310–4318.

[25] F.L. Mota, A.J. Queimada, S.P. Pinho, E.A. Macedo, Aqueous solubility of some natural phenolic compounds, Ind. Eng. Chem. Res. 47 (2008) 5182–5189, http://dx.doi.org/10.1021/ie071452o.

[26] F.L. Mota, A.J. Queimada, S.P. Pinho, E.A. Macedo, Water solubility of drug-like molecules with the cubic-plus-association equation of state, Fluid Phase Equilib. 298 (2010) 75–82, http://dx.doi.org/10.1016/j.fluid.2010.07.004.

[27] F.L. Mota, A.J. Queimada, S.P. Pinho, E.A. Macedo, Solubility of drug-like molecules in pure organic solvents with the CPA EoS, Fluid Phase Equilib. 303 (2011) 62–70.

[28] C. Perakis, E. Voutsas, K. Magoulas, D. Tassios, Thermodynamic modeling of the vapor-liquid equilibrium of the water/ethanol/CO2 system, Fluid Phase Equilib. 243 (2006) 142–150, http://dx.doi.org/10.1016/j.fluid.2006.02.018.

[29] R.G. Bitencourt, C.L. Queiroga, Í. Montanari Junior, F.A. Cabral, Fractionated extraction of saponins from Brazilian ginseng by sequential process using supercritical CO2, ethanol and water, J. Supercrit. Fluids 92 (2014) 272–281, http://dx.doi.org/10.1016/j.supflu.2014.06.009.

[30] R.G. Bitencourt, C.L. Queiroga, G.H.B. Duarte, M.N. Eberlin, L.K. Kohn, C.W. Arns, F.A. Cabral, Sequential extraction of bioactive compounds from Melia azedarach L. in fixed bed extractor using CO2, ethanol and water, J. Supercrit. Fluids 95 (2014) 355–363, http://dx.doi.org/10.1016/j.supflu.2014.09.027.

[31] J.M. Prausnitz, R.N. Lichtenthaler, E.G. de Azevedo, Molecular Thermodynamics of Fluid-phase Equilibria, Third, Pearson Education, 1999.

[32] G.M. Kontogeorgis, I.V. Yakoumis, H. Meijer, E. Hendriks, T. Moorwood, Multicomponent phase equilibrium calculations for water–methanol–alkane mixtures, Fluid Phase Equilib. 158–160 (1999) 201–209, http://dx.doi.org/10.1016/S0378-3812(99)00060-6.

[33] G.M. Kontogeorgis, M.L. Michelsen, G.K. Folas, S. Derawi, N. Von Solms, E.H. Stenby, Ten Years with the CPA (Cubic-Plus-Association) equation of state. Part 2. Cross-associating and multicomponent systems, Ind. Eng. Chem. Res. 45 (2006) 4855–4868, http://dx.doi.org/10.1021/ie051305v.

[34] E.C. Voutsas, I.V. Yakoumis, D.P. Tassios, Prediction of phase equilibria in water/alcohol/alkane systems, Fluid Phase Equilib. 158–160 (1999) 151–163, http://dx.doi.org/10.1016/S0378-3812(99)00131-4.

[35] KBC Advanced Technologies, Multiflash Version 6.1, (2018) London, United Kingdom.

[36] M.D.A. Saldaña, B. Tomberli, S.E. Guigard, S. Goldman, C.G. Gray, F. Temelli, Determination of vapor pressure and solubility correlation of phenolic compounds in supercritical CO2, J. Supercrit. Fluids 40 (2007) 7–19.

[37] L. Zhang, X. Gong, Y. Wang, H. Qu, Solubilities of protocatechuic aldehyde, caffeic acid, D-galactose, and D-raffinose pentahydrate in ethanol-water solutions, J. Chem. Eng. Data 57 (2012).

[38] W. Ji, Q. Meng, L. Ding, F. Wang, J. Dong, G. Zhou, B. Wang, Measurement and correlation of the solubility of caffeic acid in eight mono and water + ethanol mixed solvents at temperatures from (293.15–333.15) K, J. Mol. Liq. 224 (2016) 1275–1281, http://dx.doi.org/10.1016/j.molliq.2016.10.110.

[39] M. Sauceau, J.-J. Letourneau, B. Freiss, D. Richon, J. Fages, Solubility of efflucimibe in supercritical carbon dioxide with or without a co-solvent, J. Supercrit. Fluids 31 (2004) 133–140, http://dx.doi.org/10.1016/j.supflu.2003.11.004.

[40] Z. Huang, Y.C. Chiew, W.-D. Lu, S. Kawi, Solubility of aspirin in supercritical carbon dioxide/alcohol mixtures, Fluid Phase Equilib. 237 (2005) 9–15, http://dx.doi.org/10.1016/j.fluid.2005.08.004.

[41] O.J. Catchpole, S.J. Tallon, P.J. Dyer, J.-S. Lan, B. Jensen, O.K. Rasmussen, J.B. Grey, Measurement and modelling of urea solubility in supercritical CO2 and CO2 + ethanol mixtures, Fluid Phase Equilib. 237 (2005) 212–218, http://dx.doi.org/10.1016/j.fluid.2005.09.004.

[42] M.B. Oliveira, A.J. Queimada, G.M. Kontogeorgis, J.A.P. Coutinho, Evaluation of the CO2 behavior in binary mixtures with alkanes, alcohols, acids and esters using

the Cubic-Plus-Association Equation of State, J. Supercrit. Fluids 55 (2011) 876–892, http://dx.doi.org/10.1016/j.supflu.2010.09.036.

[43] G.K. Folas, J. Gabrielsen, M.L. Michelsen, E.H. Stenby, G.M. Kontogeorgis, Application of the Cubic-Plus-Association (CPA) equation of state to cross-associating systems, Ind. Eng. Chem. Res. 44 (2005) 3823–3833, http://dx.doi.org/10.1021/ie048832j.

[44] X. Chen, V. Oja, W.G. Chan, M.R. Hajaligol, Vapor pressure characterization of several phenolics and polyhydric compounds by Knudsen effusion method, J. Chem. Eng. Data 51 (2006) 386–391, http://dx.doi.org/10.1021/je050293h.

[45] J.S. Lim, Y.Y. Lee, H.S. Chun, Phase equilibria for carbon dioxide-ethanol-water system at elevated pressures, J. Supercrit. Fluids 7 (1994) 219–230, http://dx.doi.org/10.1016/0896-8446(94)90009-4.

[46] S. Huang, M. Radosz, Equation of State for small, large, polydisperse, and associating molecules, Ind. Eng. Chem. Res. 29 (1990) 2284–2294, http://dx.doi.org/10.1021/ie00107a014.

[47] A.J. Queimada, F.L. Mota, S.P. Pinho, E.A. Macedo, Solubilities of biologically active phenolic compounds: measurements and modeling, J. Phys. Chem. B 113 (2009) 3469–3476.

[48] J. Moncada, C.A. Cardona, Y.A. Pisarenko, Solubility of some phenolic acids contained in citrus seeds in supercritical carbon dioxide: comparison of mixing rules, influence of multicomponent mixture and model validation, Theor. Found. Chem. Eng. 47 (2013) 381–387, http://dx.doi.org/10.1134/S0040579513040234.

[49] B.T. Goodman, W.V. Wilding, J.L. Oscarson, R.L. Rowley, A note on the relationship between organic solid density and liquid density at the triple point, J. Chem. Eng. Data 49 (2004) 1512–1514, http://dx.doi.org/10.1021/je034220e.