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PII: S0896-8446(18)30112-8  
DOI: <https://doi.org/10.1016/j.supflu.2018.04.008>  
Reference: SUPFLU 4248

To appear in: *J. of Supercritical Fluids*

Received date: 12-2-2018  
Revised date: 5-4-2018  
Accepted date: 8-4-2018

Please cite this article as: Raphaela G.Bitencourt, André M.Palma, João A.P.Coutinho, Fernando A.Cabral, Antonio J.A.Meirelles, Solubility of caffeic acid in CO<sub>2</sub>+ethanol: Experimental and predicted data using Cubic Plus Association Equation of State, The Journal of Supercritical Fluids <https://doi.org/10.1016/j.supflu.2018.04.008>

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## Solubility of caffeic acid in CO<sub>2</sub> + ethanol: experimental and predicted data using Cubic Plus Association Equation of State

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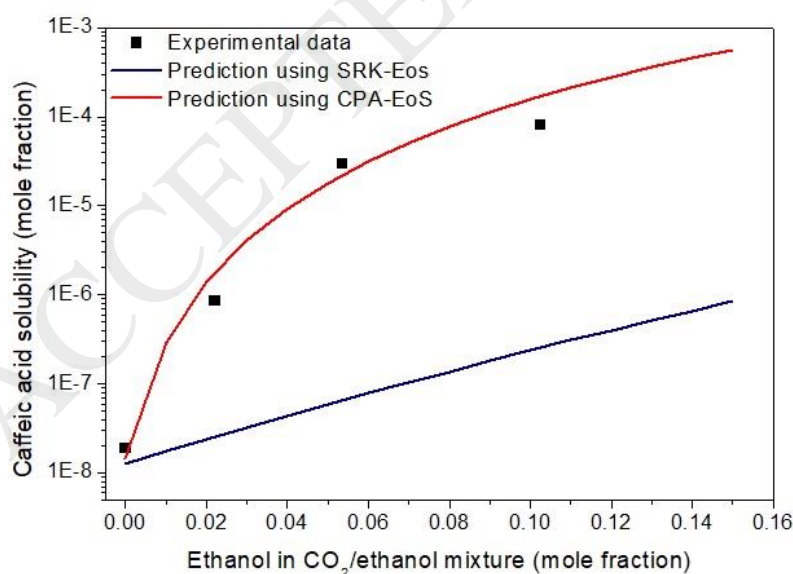
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### Graphical abstract



## Highlights

- CA solubility in CO<sub>2</sub> + ethanol at 20–40 MPa, 313–333 K and 2-10 mol% ethanol
- Comparison between thermodynamic modeling using SRK and CPA equations
- By adding 10.2 mol% ethanol to scCO<sub>2</sub>, CA solubility increased up to 30,000 times
- The use of more than 10 mol% ethanol in CO<sub>2</sub>/ethanol mixture is not recommended
- CPA model showed good ability to predict the ternary system data

## Abstract

This work evaluated the solubility of caffeic acid (CA) in mixtures of supercritical carbon dioxide (scCO<sub>2</sub>) 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<sup>6</sup> times higher than its solubility in pure scCO<sub>2</sub>. By using 10.2 mol% ethanol in scCO<sub>2</sub>, 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<sub>2</sub> provides a large increase in CA solubility.

## Abbreviations

### Nomenclatures

*AARD* - Average Absolute Relative Deviation

$$AARD P(\%) = \frac{100}{N} \sum_{j=1}^N \left[ \frac{|P_{cal} - P_{exp}|}{P_{exp}} \right]_j$$

$$AARD y(\%) = \frac{100}{N} \sum_{j=1}^N \left[ \frac{|y_{cal} - y_{exp}|}{y_{exp}} \right]_j$$

*ALD* - Average Logarithmic Deviation -  $ALD = \sum_{j=1}^N \frac{1}{N} \left| \log \frac{y_i^{calc}}{y_i^{exp}} \right|$

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

scCO<sub>2</sub> - supercritical carbon dioxide

### List of symbols

*a* - energy parameter in the physical term

*a*<sub>0</sub>, *c*<sub>1</sub> - parameters for calculating *a*

*b* - co-volume parameter in the physical term

*C*<sub>*p*</sub> - 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

$\beta$  - association volume

$\mathcal{E}$  - association energy

$\Delta$  - association strength

$\rho$  - molar density

$\eta$  - reduced fluid density

$\varphi$  - coefficient of fugacity

$\omega$  - 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

**Keywords:** 3,4-dihydroxycinnamic acid; supercritical carbon dioxide; cosolvent; phase equilibrium; thermodynamic modeling; Soave-Redlich-Kwong.

## 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].

**Fig. 1.**

The production of natural extracts rich in phenolic compounds, such as CA, is interesting for food, chemical and pharmaceutical industries. Extractions using supercritical carbon dioxide (scCO<sub>2</sub>) 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  $\text{scCO}_2$  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  $\text{scCO}_2$  (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  $\text{scCO}_2$  is associated with the high polarity of this compound. Thus, its extraction from vegetable sources using  $\text{scCO}_2$  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  $\text{CO}_2$ /ethanol mixtures. Other phenolic compounds with antioxidant properties had their solubility previously reported in  $\text{CO}_2$  + 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,  $\text{scCO}_2$  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  $\text{CO}_2$  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<sub>2</sub>/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.

## 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 - CO<sub>2</sub> - ethanol system

The solubility of caffeic acid in CO<sub>2</sub> - 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> gas was led to a gas flowmeter to control the CO<sub>2</sub> flow and to a volume totalizer to measure the total amount of carbon dioxide used in the experiment.

The CO<sub>2</sub> amount used for each measurement depended on the proportion CO<sub>2</sub>/ethanol mixture evaluated to guarantee sufficient sample mass to be well quantified: 5, 10 and 20 L of CO<sub>2</sub> 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<sub>2</sub>, ethanol, and CO<sub>2</sub> + 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 ( $\Delta C_p$ ), **Equation 1** [31] is obtained.

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

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;  $\varphi$  is the coefficient of fugacity;  $\Delta H$  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 ( $OF$ ) (**Equation 2**) which evaluates the difference between the experimental and calculated values of solubility.

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

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

The SRK-EoS has the following form:

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

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:

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

The  $a$  and  $b$  parameters are calculated by using the critical properties and the acentric factor ( $\omega$ ) 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  $k_{ij}$ .

$$a = \sum_i \sum_j a_{ij} y_i y_j \quad a_{ij} = \sqrt{a_i a_j} (1 - k_{ij}) \quad (5)$$

$$b = \sum_i b_i y_i \quad (6)$$

### 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:

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

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 the mole fraction;  $\rho$  is the molar density;  $g$  is a radial distribution function and  $X_{A_i}$  is the mole fraction of component  $i$  not bonded at site  $A$ ;

The  $X_{A_i}$  is calculated by solving the following set of equations:

$$X_{A_i} = \frac{1}{1 + \rho \sum_j x_j \sum_{B_j} X_{B_j} \Delta^{A_i B_j}} \quad (8)$$

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

$$\Delta^{A_i B_j} = g(\rho) \left[ \exp\left(\frac{\varepsilon^{A_i B_j}}{RT}\right) - 1 \right] b_{ij} \beta^{\varepsilon^{A_i B_j}} \quad (9)$$

The simplified hard-sphere radial distribution function ( $g$ ) was used [32]:

$$g(\rho) = \frac{1}{1 - 1.9\eta} \quad (10)$$

$$\eta = \frac{1}{4} b\rho \quad (11)$$

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 ( $\varepsilon^{A_i B_j}$ ) and the site volume ( $b_{ij}$ ).

$\varepsilon$ ) and the parameter of association volume ( $\beta$ ). 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 (**Equations 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 (**Equations 12 and 13**) was used for the mixtures studied.

$$\beta^{A_i B_j} = \sqrt{\beta^{A_i} \beta^{B_j}} \quad (12)$$

$$\varepsilon^{A_i B_j} = \frac{1}{2} (\varepsilon^{A_i} + \varepsilon^{B_j}) \quad (13)$$

It is not rare to find **Equation 1** in a simplified form, in which only the term with  $\Delta H$  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  $\Delta C_p$  and  $\Delta V$  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  $\text{CO}_2$  + 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. [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  $5 \times 10^{-5}$  to  $3 \times 10^{-4}$  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 scCO<sub>2</sub> [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 scCO<sub>2</sub> + 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<sub>2</sub> stands out for being a selective and flexible process allowing the increase of the solvent's 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.

**Fig. 2.**

#### 4.2. Caffeic acid - CO<sub>2</sub> - ethanol system

The CA solubility in CO<sub>2</sub> 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<sub>2</sub>/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<sub>2</sub>/ethanol mixture the greatest values were found at higher pressures (40 MPa).

Although the CA solubility in the mixture CO<sub>2</sub> + ethanol was still much lower than in pure ethanol, the solubility of CA in scCO<sub>2</sub> + 10.2% ethanol reached values 10<sup>5</sup> times higher than its solubility in pure scCO<sub>2</sub> (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<sub>2</sub> + 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 scCO<sub>2</sub> 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 **Fig. 3** and **Fig. 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. 3.**

**Fig. 4.**

The ratio of the solubility in the ternary system (CO<sub>2</sub>/ethanol mixture) and the solubility in a binary system (scCO<sub>2</sub>) under the same conditions of temperature and pressure provides the cosolvent effect (**Equation 14**).

$$co - solvent \ effect = \frac{y_{CA}^{CO_2 + Ethanol}}{y_{CA}^{CO_2}} \quad (14)$$

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<sub>2</sub> was observed by adding 10.2 mol% ethanol at 313 K and 20 MPa (cosolvent effect = 30,000).



**Fig. 5**

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<sub>2</sub> + 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 ( $\Delta H_f$ ) 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 ( $a_0$ ,  $c_1$ ,  $b$ ,  $\mathcal{E}$  and  $\beta$ ) are obtained by fitting vapor pressure and/or liquid density data of the pure compounds. For the solvents CO<sub>2</sub> 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<sub>2</sub> 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]. 2B 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  $\epsilon$  and  $\beta$  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<sub>2</sub> and caffeic acid and CO<sub>2</sub> 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<sub>2</sub> 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  $\Delta C_p$  and  $\Delta V$  were considered, as shown in **Table 6**. The  $\Delta V$  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  $\Delta C_p$  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<sub>2</sub> – 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  $\Delta C_p$  and  $\Delta V$  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 **Equation 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<sub>2</sub> + 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.

$${}^a ALD = \sum_{j=1}^N \frac{1}{N} \left| \log \frac{y_i^{calc}}{y_i^{exp}} \right|; {}^b ALD \text{ for prediction of phase equilibrium data in ternary}$$

system CO<sub>2</sub> – ethanol – caffeic acid using CPA model.

**Fig. 6.**

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 **Fig. 3** and **Fig. 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<sub>2</sub>/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. 4b** and **Fig. 4c**, by the overlapping lines.

As observed for the experimental data, CPA predicted the higher cosolvent effect at lower temperatures and pressure when CO<sub>2</sub>/ethanol (90:10 mol/mol) was used as solvent (**Fig. 5**). However, for other proportions of CO<sub>2</sub> 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<sub>2</sub>/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<sub>2</sub>.

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.

### Acknowledgments

In Brazil, this work was financially supported by CAPES, FAEPEX (Project number 2781/2017, 519.292), FAPESP (Project number 2010/16665-3 and 2014/21252-0) and CNPq (Project numbers 406856/2013-3, 305870/2014-9, 303734/2016-7 and 406963/2016-9). In Portugal, this work was developed within the scope of the project CICECO-Aveiro Institute of Materials, POCI-01-0145- FEDER-007679 (FCT Ref. UID/CTM/50011/2013), financed by national funds through the FCT/MEC and when appropriate co-financed by FEDER under the PT2020 Partnership Agreement.

The authors acknowledge KBC Advanced Technologies Limited for providing Multiflash software for the CPA calculations.

André M. Palma acknowledges KBC for his PhD grant and Raphaela G. Bitencourt thanks CNPq (140345/2014-0) for her scholarship.

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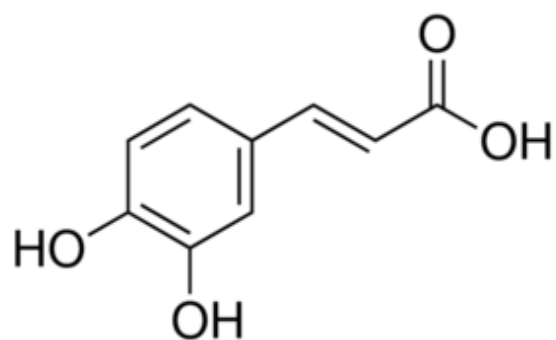


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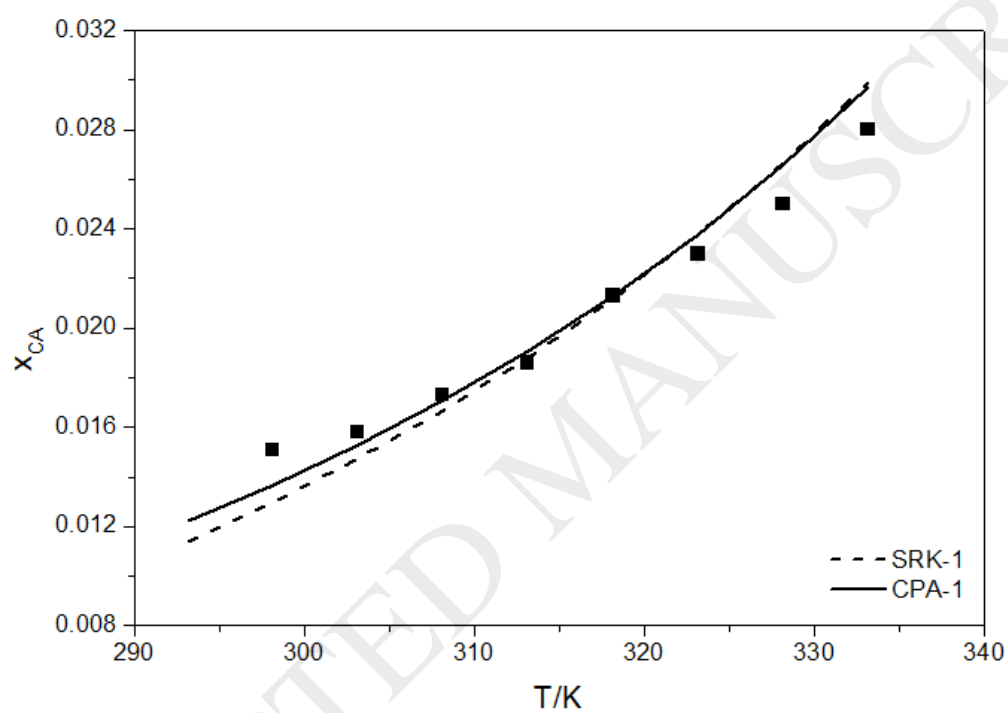
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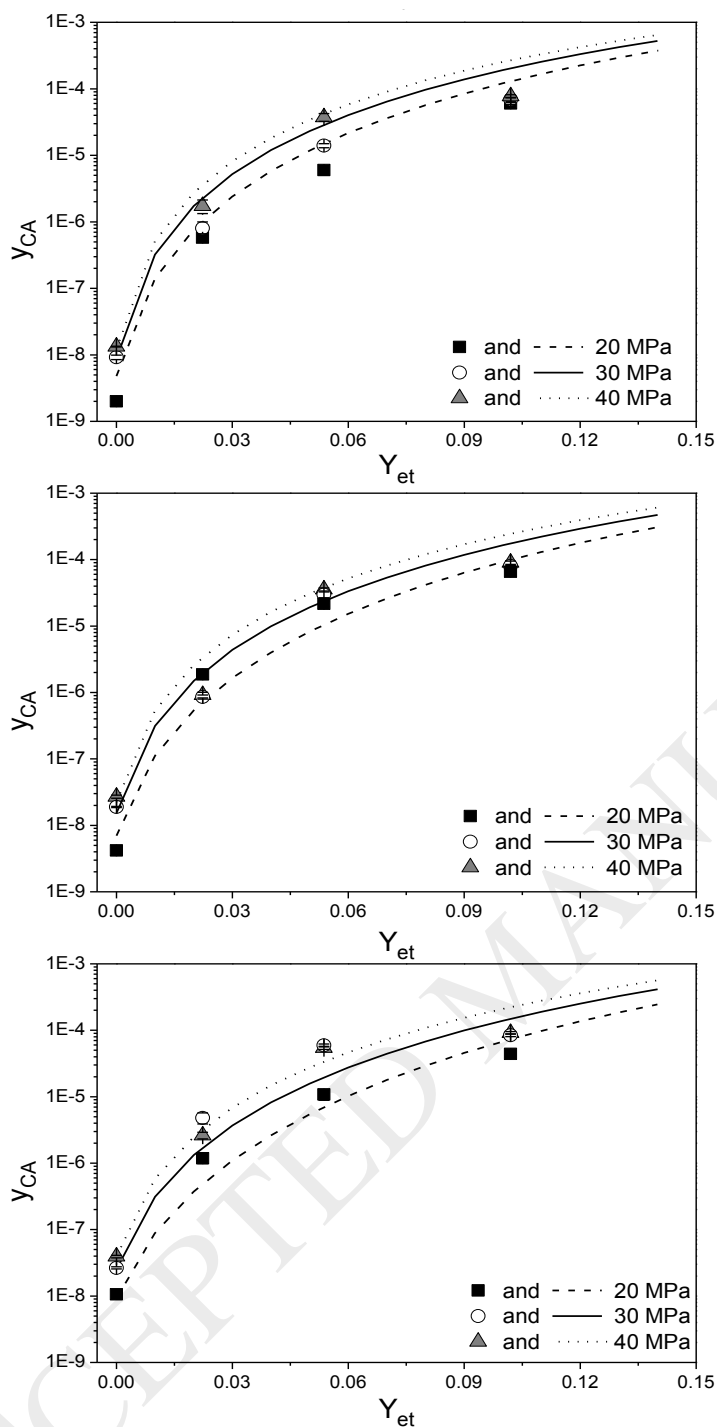
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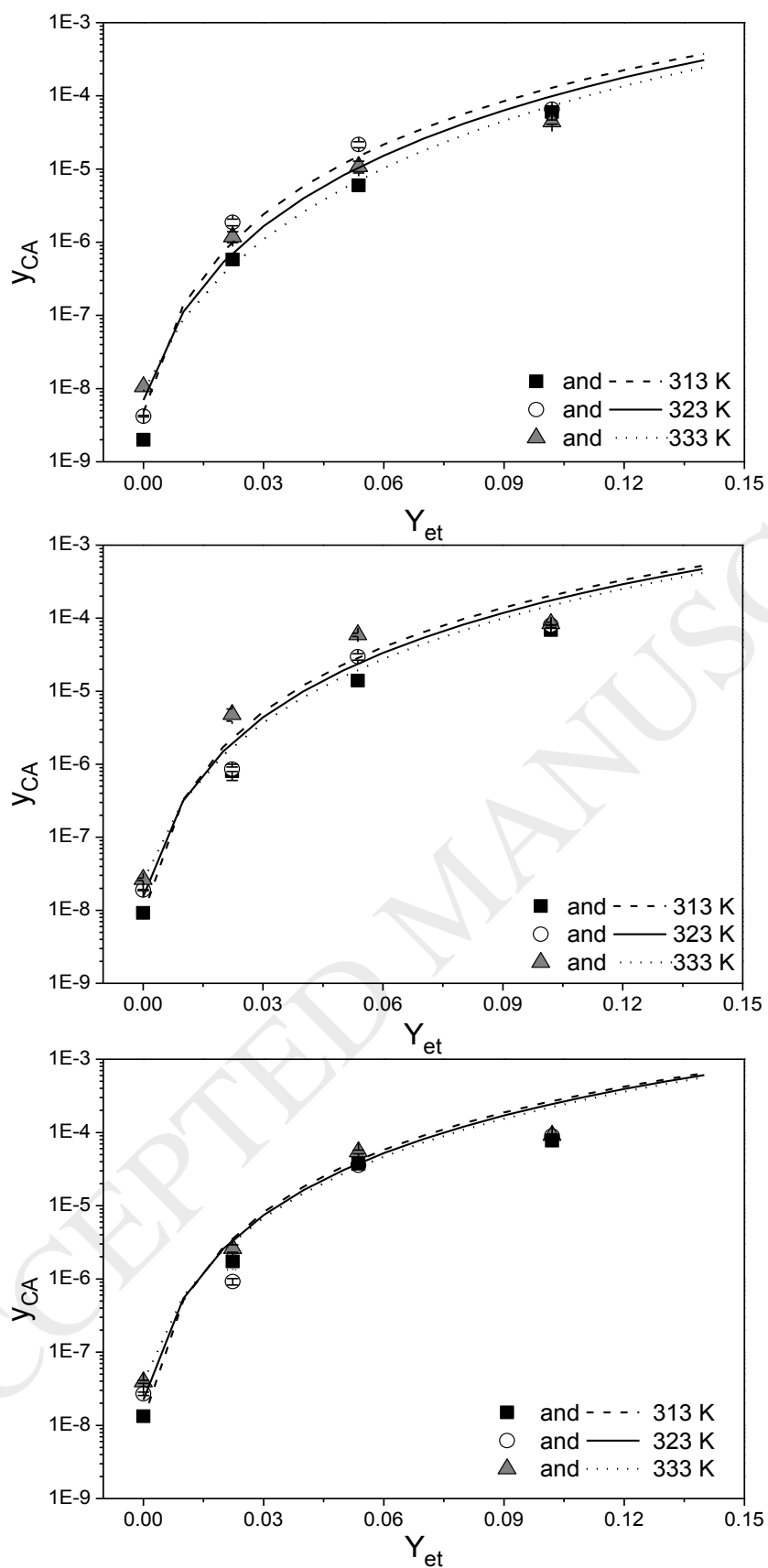
**Fig. 1.** Caffeic acid chemical structure.



**Fig. 2.** Thermodynamic modeling of the CA solubility in ethanol ( $x_{CA}$ ) at atmospheric pressure using SRK-1 and CPA-1 models

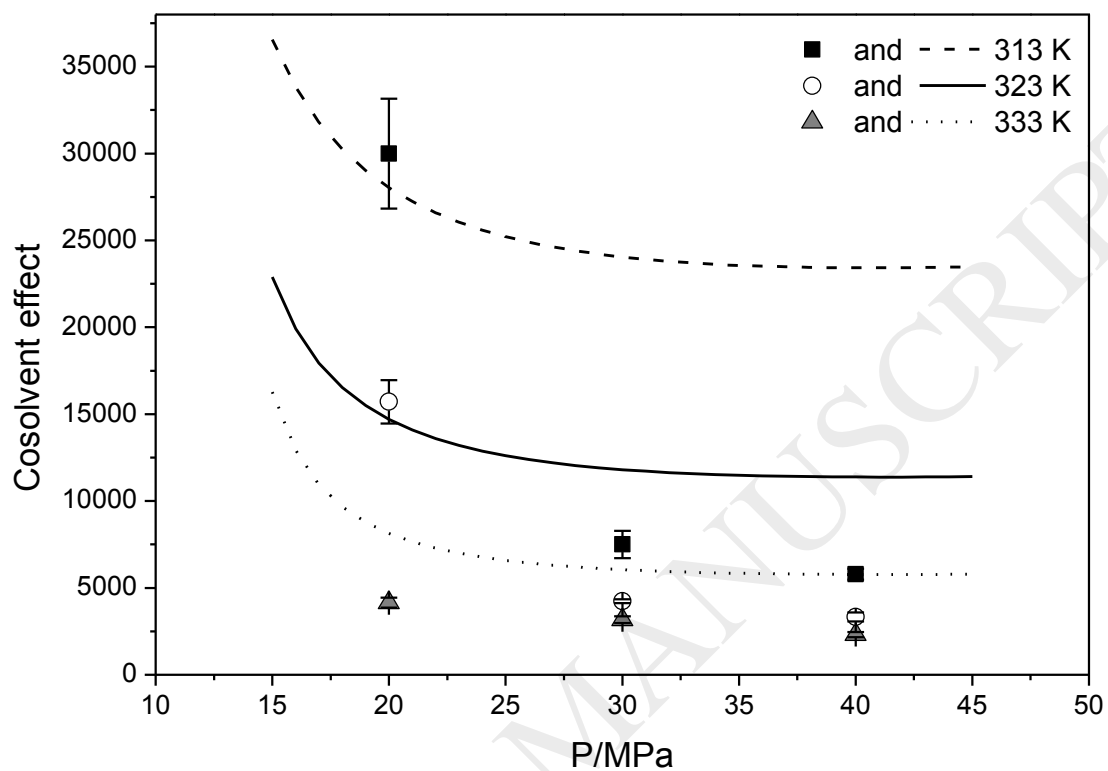


**Fig. 3.** Prediction of CA solubility in CO<sub>2</sub>/ethanol mixtures ( $y_{CA}$ ) from CPA-1: (a) 313 K; (b) 323 K; (c) 333 K. Experimental data of CA solubility in pure scCO<sub>2</sub> were obtained from Murga et al. [7].  $Y_{et}$ : ethanol mole fraction on a solute free-basis; Symbols: experimental data; Lines: predicted data.

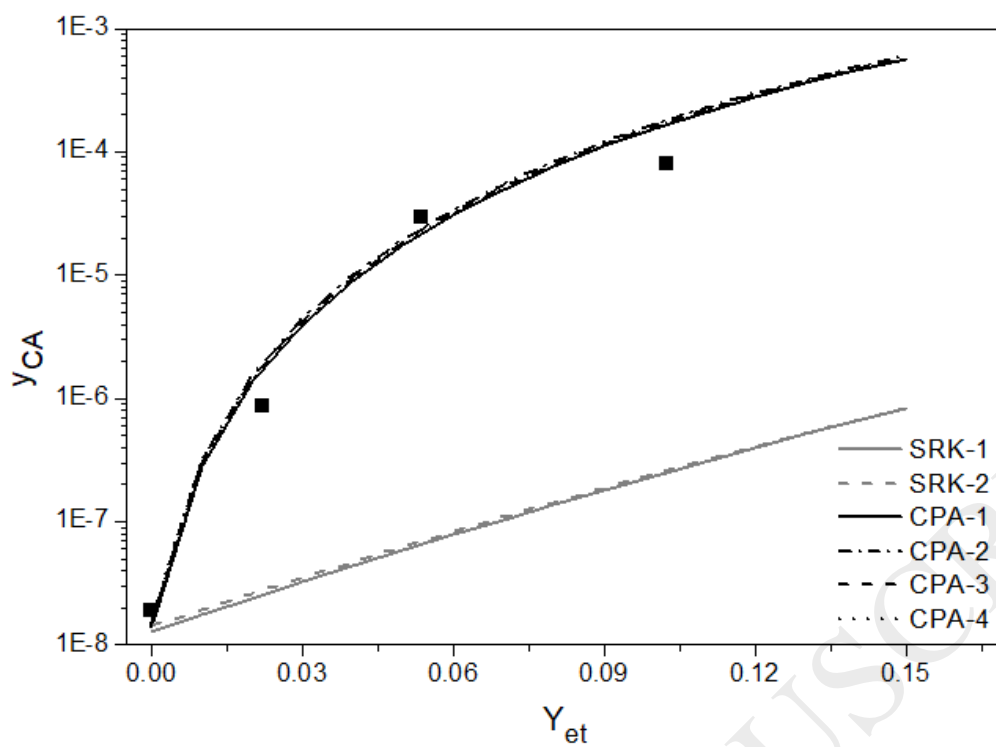


**Fig. 4.** Prediction of CA solubility in CO<sub>2</sub>/ethanol mixtures ( $y_{CA}$ ) from CPA-1: (a) 20 MPa; (b) 30 MPa; (c) 40 MPa. Experimental data of CA solubility in pure scCO<sub>2</sub> were obtained

from Murga et al. [7].  $Y_{et}$ : ethanol mole fraction on a solute free-basis; Symbols: experimental data; Lines: predicted data.



**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.



**Fig. 6.** Comparison between SRK and CPA model for prediction of ternary system caffeic acid - CO<sub>2</sub> - ethanol at 323.15 K and 30 MPa.



**Table 1**

Pure component physical properties.

Compound	$M$ (g/mol)	$T_c$ (K)	$P_c$ (MPa)	$\omega$	$T_m$ (K)	$\Delta H_f$ (J/mol)
CO <sub>2</sub>	44.01	304.13 <sup>a</sup>	7.377 <sup>a</sup>	0.223 <sup>a</sup>		
Ethanol	46.07	513.92 <sup>a</sup>	6.137 <sup>a</sup>	0.643 <sup>a</sup>		
Caffeic acid	180.16	993.05 <sup>b</sup>	5.809 <sup>b</sup>	1.056 <sup>c</sup>	469 <sup>c</sup>	13638.78 <sup>c</sup>

<sup>a</sup> Multiflash<sup>TM</sup> database [35]; <sup>b</sup> Murga et al. [7]; <sup>c</sup> 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

**Table 3**Mole fraction CA solubility in CO<sub>2</sub> and ethanol mixtures ( $y_{CA}$ ).

$Y_{et}$ (%) <sup>a</sup>	T/K <sup>b</sup>	P/MPa <sup>b</sup>	$y_{CA} \times 10^6$
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

<sup>a</sup> $Y_{et}$ : mole percentage of ethanol on a solute free-basis; <sup>b</sup>Uncertainties of temperature and pressure measurements are 0.5 K and 0.1 MPa, respectively.

**Table 4**

CPA parameters of pure components.

Compound	$a_0$ (J m <sup>3</sup> /mol )	$b \times 10^5$ (m <sup>3</sup> /mol)	$c_1$	Associative Group (AG)	Number of AG	$\epsilon$ (J/mol)	$\beta \times 10^{-3}$	AARD P (%)
CO <sub>2</sub>	0.35 <sup>a</sup>	2.72 <sup>a</sup>	0.76 <sup>a</sup>					
Ethanol	0.86716 <sup>b</sup>	4.91 <sup>b</sup>	0.7369 <sup>b</sup>	OH	1	21532 <sup>b</sup>	8.0 <sup>b</sup>	
Caffeic acid	3.8896 <sup>c</sup>	15.6 <sup>c</sup>	1.9534 <sup>c</sup>	OH and COOH	3	19090.37 <sup>d</sup>	27.88 <sup>d</sup>	7.8

<sup>a</sup> Oliveira et al [42]; <sup>b</sup> Folas et al. [43]; <sup>c</sup> Mota et al. [25]; <sup>d</sup> 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<sub>2</sub> (2) – ethanol (3) system.

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

<sup>a</sup> AARD<sub>y</sub>; <sup>b</sup> AARD<sub>P</sub>.

**Table 6**

Different model approaches evaluated, based in **Equation 1**.

Model	$\Delta C_{p,CA}$ (J/mol K)	$\Delta V_{CA}$ (m <sup>3</sup> /mol)	ALD <sup>a</sup>
SRK-1 and CPA-1	0	0	0.288 <sup>b</sup>
SRK-2 and CPA-2	50	2.549 × 10 <sup>-5</sup>	0.321 <sup>b</sup>
CPA-3	50	0	0.314 <sup>b</sup>
CPA-4	0	2.549 × 10 <sup>-5</sup>	0.297 <sup>b</sup>