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Measurement and modeling of solubilities of capsaicin in high-pressure CO_2

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Abstract

Measurements on solid–fluid equilibrium were performed for capsaicin in sub- and supercritical carbon dioxide (CO_2) at several temperatures (298, 308, 313 and 318 K) and over a pressure range from 6 to 40 MPa, to verify the operation of a new static–analytic set-up. This set-up consisted of a high-pressure static equilibrium cell coupled to a high-performance liquid chromatograph (HPLC). The new equilibrium data have been critically compared with available literature data; some differences were observed, especially at the two highest assayed temperatures. Experimental solubility values were correlated by using three different models, a density-based model, a cubic equation of state with quadratic mixing rules, and a group contribution equation of state. The density correlation results showed good agreement with the experimental data, in contrast to the results of both equations of state.
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Keywords: Capsaicin; Carbon dioxide; Density correlation; Equation of state; Group contribution; Solubility

1. Introduction

The production of plant extracts is currently limited by safety and regulatory constraints to the concentration of toxic residues of conventional organic solvents [1]. Carbon dioxide (CO_2) is an excellent alternative as a solvent due to its inertness, non-toxicity, non-flammability, and low cost [2]. When CO_2 (T_c = 304.2 K) is applied in supercritical fluid (SCF) extraction (SCFE) processes, near-environmental temperatures are employed, thus minimizing heat requirement and thermal damage to bioactive compounds [2].

Thermodynamic constraints to solute solubility and extraction selectivity have to be established to replace organic solvents with supercritical CO_2 (SC-CO_2), and to optimize the design and operational conditions of an SCFE process. At present, available thermodynamic models have difficulties in predicting the actual phase equilibrium (i.e., phase concentrations, temperature, and pressure), even for simple mixtures. However, models can be used for interpolation purposes, to estimate solubility values based on the limited experimental database currently available [3]. Some models exploit the relationship between solute solubility and SCF density. More fundamental models are based on cubic and group-contribution equations of state to represent PVT behavior of single- and multi-component fluid mixtures. At any rate, progress in SCFE processes for natural substrates will be positively affected by availability of experimental data for mixtures solute + SC-CO_2 for relevant bioactive components.

Experimental devices typically employed to measure high-pressure phase equilibrium are expensive in that means may be required to recycle the loaded SCF phase, assess attainment of equilibrium conditions, direct sampling of one or more phases without disturbance of equilibrium, and on-line compositional analysis. Simpler and less costly experimental devices are generally looked after. In this work, an experimental system was devised to illustrate inexpensive means to accelerate equilibration, to allow sampling, and to establish the attainment of equilibrium conditions. This cor-

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responds to a static–analytic set-up, which was coupled to a high-performance liquid chromatography (HPLC) device for on-line analysis of the loaded SCF phase. The performance of this experimental devise was evaluated with mixtures of capsaicin and CO_2 because of two main reasons: (i) there exist literature reports on the solubility of capsaicin in high-pressure CO_2 under various conditions from several sources [4–6] and (ii) capsaicin is a bioactive component from plant material that is of importance in foods and pharmaceuticals, which can be extracted from hot peppers using SC-CO_2.

Capsaicin (8-methyl-*N*-vanillyl-6-noneamid) is the most pungent of a group of compounds called capsaicinoids that can be isolated from hot peppers (*Capsicum annuum* L.). Capsaicin is of interest in foods because of its hot flavor [7]. It is also of interest in pharmaceuticals, because of its direct action on pain receptors; when topically applied capsaicin is useful in alleviating the pain associated with diabetic neuropathy, osteoarthritis, and psoriasis [8,9]. del Valle et al. [10] reviewed antecedents on the extraction of capsicum species using SC-CO_2 both for analytical and process design purposes. The authors have reported the use of SC-CO_2 for the extraction of oleoresins and capsaicin from pre-pelletized Jalapeño peppers at 308–338 K and 12–50 MPa [10,11].

The objective of this work was to verify the operation of a new low-cost equilibration device by measuring the solubility of solid capsaicin in sub- and supercritical CO_2 at various temperature and pressure conditions.

2. Experimental

2.1. Materials

Capsaicin with a minimum purity of 95.0% was supplied by Sigma (St. Louis, MO). CO_2 (99.99% pure) was purchased from AGA S.A. (Santiago, Chile). For HPLC analysis, HPLC quality water (Caledon Laboratories Ltd., Georgetown, Ontario) and acetonitrile for HPLC analysis (Fisher Scientific, New Jersey, NJ) were employed.

2.2. Methods

A schematic diagram of the low-cost experimental apparatus used to measure the solubility of solid capsaicin in high-pressure CO_2 is presented in Fig. 1. The static–analytic set-up consisted of a high-pressure 30 mL capacity equilibrium cell (home-made) with two windows for observation of the phases presents, i.e., fluid, liquid or solid, coupled to an HPLC chromatograph for direct measurement of the composition of the CO_2-rich phase at equilibrium. The chromatographic system consisted of a Hitachi L-7100 pump, L-7350 oven, and L-7455 photodiode array detector (Hitachi LaChrom, Japan). The samples of the fluid phase were withdrawn from the cell using a six-port high-pressure valve (Rheodyne 7010, Rohnert Park, CA) fitted with a 20-μL loop. The equilibrium pressure was measured with a pressure transducer (Heise, Shelton, CT) with a precision of 0.1% and accuracy of 0.1%. Temperatures inside the cell and the air-bath around the cell were measured and adjusted to within 0.1 K of the set values with a PID controller (Digi-Sense, Vernon Hills, IL) that was connected to four electrical resistances on the cell (1000 W), and a PI controller (Cole-Parmer, Vernon Hills, IL) that was connected to an electrical resistance (1800 W) + fan combination, respectively. CO_2 was loaded to the cell with a manual pressure generator (HIP 62-6-10, Erie, PA). The mixture solute + CO_2 in the cell was stirred with a magnetic bar activated by a magnet. The apparatus can be operated up to 343 K and 40 MPa. This system was built with a budget of about 10,000 USD plus taxes. This cost can be broken down in 20% for the equilibrium cell, 15% for the manual compressor and vac-

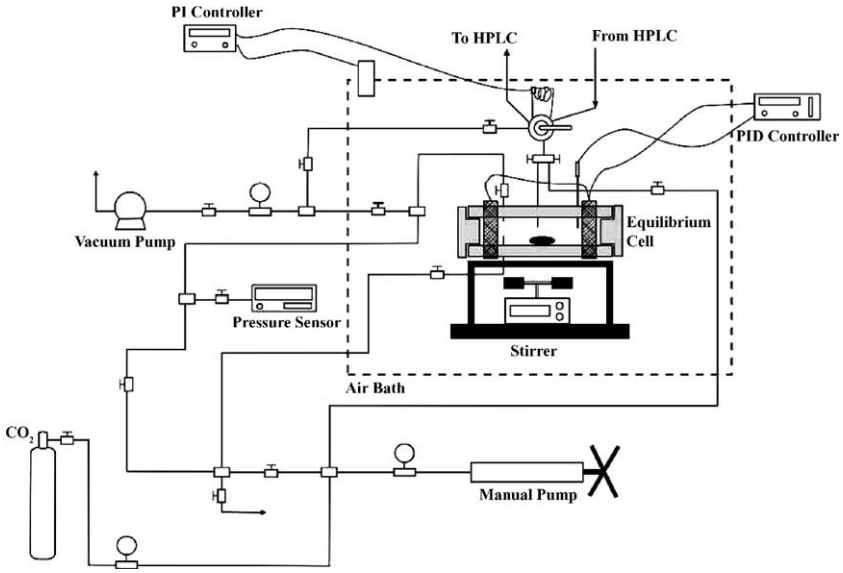

Fig. 1. Schematic diagram of the low-cost experimental apparatus used to effect equilibration and sampling of loaded supercritical fluid phase.

uum pump, 40% for instrumentation and control, and 25% for valves, fittings, and tubing.

In order to determine the solubility of capsaicin (2) in high-pressure CO_2 (1), approximately 0.3 g (weighed accurately) of solid capsaicin were charged into the equilibrium cell for each solubility isotherm, prior to displacing residual air with low-pressure CO_2. After the system reached the desired temperature, the pressure was increased to the desired value using the manual compressor. For a typical experimental run, a 12-h equilibration period was allowed to ensure equilibrium conditions. The CO_2-rich equilibrated phase was then loaded to the loop of the six-port high-pressure valve and sent to the HPLC chromatograph for analyses. The mole fraction of capsaicin in the CO_2-rich phase (y_2) was estimated according to [12]:

$$y_2 = \left(\frac{A_{FP}}{A_S}\right)\left(\frac{V_{CL}}{V_{FP}}\right)\left(\frac{M_1}{\rho_1}\right)C_S \quad (1)$$

where A_{FP} and A_S are the chromatographic peak areas for fluid phase and standard injection, respectively, V_{CL} the volume of HPLC sample loop injector (20 μL), V_{FP} the volume of sample of equilibrated fluid phase, M_1 the molecular weight of CO_2 (44 g/mol), ρ_1 the density of CO_2 at the test temperature and pressure conditions of the cell, which was calculated with NIST Standard Database v5.0 [13], and C_S the concentration of capsaicin in an standard solution employed for calibration of the HPLC.

Solubility isotherms were measured at 298, 308, 313, and 318 K over pressures ranging from 6 to 40 MPa. Typically, five HPLC injections were made for each solubility data point. The variation in the pressure observed while sampling was ≤0.2 MPa. The estimated uncertainties in the temperature and pressure were 0.5 K and 0.2 MPa, respectively. The reproducibility of the solubility data was ≥20% and it decreased as the temperature increased.

2.3. Analytical

Quantification of capsaicin content in the loaded SCF phase was determined on-line by HPLC analysis employing the method proposed by Hansen and Bruno [12]. Separation was done in a C_{18} LiChroCART 150833 column (Merck, Darmstadt, Germany) which was protected by a LiChrospher 150957 precolumn (Merck, Darmstadt, Germany). The mobile phase was a 70:30 (v/v) acetonitrile/water mixture at 298 K (1 mL/min). UV detection was done at 280 nm. In order to avoid the formation of CO_2 bubbles in the HPLC detector, a back-pressure regulator was included at the end of it to maintain the pressure close to 10 MPa.

3. Results and discussion

3.1. Experimental results

Fig. 2 shows the solubility results for solid capsaicin in sub- and supercritical CO_2 at 298–318 K and 6–40 MPa.

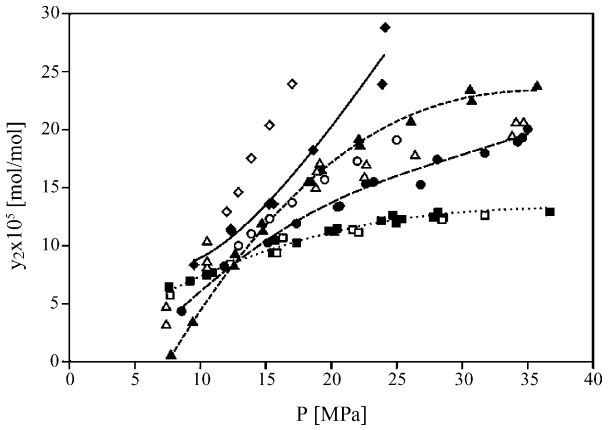

Fig. 2. Solubility isotherms of capsaicin (2) in sub- and supercritical CO_2 for: (1) 298 K (· · · trend line, ■ this work, □ Škerget et al. [4]); 308 K (– – – trend line, ● this work, ◯ Hansen et al. [6]); 313 K (- - - trend line, ▲ this work, △ Škerget et al. [4]); and 318 K (—trend line, ♦ this work, ◊ Hansen et al. [6]). Lines represent trends and symbols experimental data points.

Within this experimental region, the mole fraction of capsaicin in the fluid phase was $\leq 2.88 \times 10^{-6}$. This low value is due to the poor solvent power of CO_2 for polar solutes such as capsaicin. A crossover point was observed at around of 13 MPa for the tree lower isotherms (298–313 K). The effect of an increase in temperature on the solubility of capsaicin shifts from negative at low pressures (≤13 MPa) to positive at higher pressures. On the other hand, at constant temperature the solubility increases with the pressure, and this effect is the greatest for the highest temperature (the positive effect of pressure on solubility is 2.5 times larger at 318 K than at 298 K). The solubility data points for the higher isotherm (318 K) corresponding to pressures above 24.1 MPa are not included due to their poor reproducibility. The reason for this could be the large amount of solute sampled, which cannot be quantified accurately by the HPLC methodology that was employed (the moles of capsaicin sampled increased by a factor of approximately 5 within the experimental region in Fig. 2). Indeed poor reproducibility is a common occurrence in system employing on-line analysis by HPLC when the solubility is high [14]. In addition, it could be possible that at 318 K capsaicin were more susceptible to thermal degradation than at lower temperatures.

Fig. 2 also includes solubility data found in the literature for capsaicin in dense CO_2. Data of Škerget et al. [4] were obtained utilizing a static equilibrium cell without windows and gravimetric determination of capsaicin content in the fluid phase at 298 and 313 K. Hansen et al. [6] reported solubility values obtained using a semi-continuous equipment with direct HPLC analysis of the fluid phase at 308 and 318 K. Data informed by Škerget et al. [4] show good agreement with experimental values obtained in this work. The differences between both data sets were higher at high pressure, but were ≤15% at 313 K. Škerget and Knez [5] claimed that data from Škerget et al. [4] were affected by the presence of melted capsaicin at 313 K and ≥10 MPa, without any experimental

evidence (observation). However, direct observation in this study indicated that capsaicin remained as a solid for all temperatures and pressures in Fig. 2. Discrepancies between data of Hansen et al. [6] and in this work reached levels as high as 50%, and were especially high at high pressure for both 308 and 318 K. The differences have no direct explanation and it could be attributed to a systematical error which was not account for.

3.2. Modeling with a density-based correlation

In order to correlate low solubilities of solids in SCF as a function of absolute temperature and solvent density, Harvey [15] has proposed a semi-empirical equation with two adjustable parameters, which requires as data, the sublimation pressure of solid. This sublimation pressure is not generally available for natural compounds. The equation of Harvey [15] was modified by Méndez-Santiago and Teja [16], who included a Clausius–Clapeyron-type expression to account for the sublimation pressure of the solute:

$$T \ln(y_2 P) = A' + B'\rho_1 + C'T \tag{2}$$

This correlation incorporates three adjustable parameters, A', B', and C', which are independent of temperature and pressure. Eq. (2) considers that y_2 is low enough to ignore the effect of the dissolved solute on the density of the mixture (ρ_m), so that ρ_1 can be used instead of ρ_m. This is generally valid for densities ranging from half to twice the critical density of CO_2 ($\rho_c = 467.6\,kg/m^3$). Eq. (2) not only has shown to be appropriate for correlating the solubility values of large numbers of organics in SC-CO_2, but it has been claimed that could be used both to extrapolate data, and to identify questionable data [16].

Eq. (2) was fitted to solubility data obtained in this work. The best-fit parameters were $A' = -9297$ K, $B' = 2.308\,m^3$ K/kg, $C' = 18.07$, and the average absolute deviation (AAD) between experimental and calculated values of solubility was 11.4%. Fig. 3 shows the best-fit line, our data, and data from literature. Since all isotherms collapse to a single trend line in Fig. 3, it can be surmised that the parameters of Eq. (2) are temperature- and pressure-independent. In addition, the low value of AAD suggests that the experimental data points are self-consistent. Experimental data points by Škerget et al. [4] agree also with the best-fit line. This was not the case for the 318 K isotherm reported by Hansen et al. [6].

3.3. Modeling with a cubic equation of state

The application of an equation of state (EOS) for the prediction and correlation of solubilities of biomolecules in SC-CO_2 has been described in the literature [17]. If the solid phase does not dissolve the SC-CO_2, the solubility of the solute in the CO_2-rich fluid phase at equilibrium can be

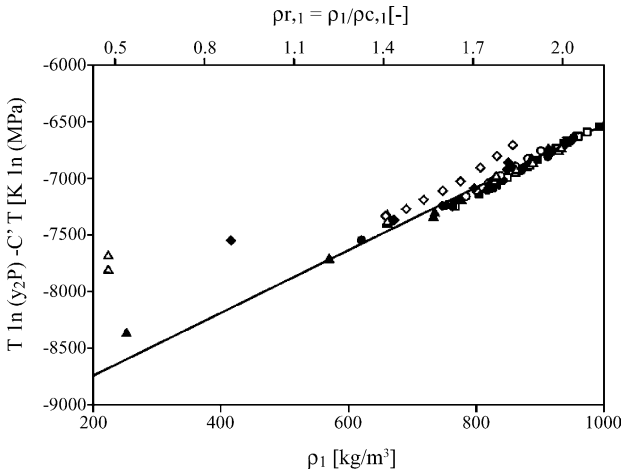

Fig. 3. Modeling of solubility of capsaicin (2) in CO_2 (1) using a density-based correlation for: 298 K (■ this work, □ Škerget et al. [4]); 308 K (● this work, ○ Hansen et al. [6]); 313 K (▲ this work, △ Škerget et al. [4]); and 318 K (♦ this work, ◊ Hansen et al. [6]). The lines represent model predictions and symbols experimental data points.

calculated using the isofugacity criteria [18]:

$$y_2 = \frac{P_2^{Subl}}{\phi_2^{FP} P} \exp\left[\frac{v_2(P - P_2^{Subl})}{RT}\right] \tag{3}$$

where P_2^{Subl} is the sublimation pressure of the solute, ϕ_2^{FP} the fugacity coefficient of the solute in the fluid phase, v_2 the saturated molar volume of solid solute at the equilibrium temperature, and R the gas constant (8.314 J/(mol/K)). The Peng–Robinson [19] EOS (PE-EOS) has been selected to calculate ϕ_2^{FP}, because it has proved to combine the simplicity and accuracy which are required to model the solubility of some solids in SCFs [20]:

$$P = \frac{RT}{v - b_m} - \frac{a_m}{v(v + b_m) + b_m(v - b_m)} \tag{4}$$

where v is the molar volume of the mixture, and a_m and b_m the mixing rule parameters, which are related to the energetic and volumetric interaction between solute and SCF, respectively. In order to calculate both parameters, classical quadratic mixing rules were selected in this work, among others that have been proposed in the literature [21]:

$$a_m = \sum_i \sum_j a_{ij} y_i y_j \tag{5a}$$

$$b_m = \sum_i \sum_j b_{ij} y_i y_j \tag{5b}$$

where

$$a_{ij} = \sqrt{a_i a_j}(1 - k_{ij}) \tag{5c}$$

$$b_{ij} = \frac{b_i + b_j}{2}(1 - l_{ij}) \tag{5d}$$

The pure component a_i and b_i values depend on the critical temperature (T_c), critical pressure (P_c), and acentric factor

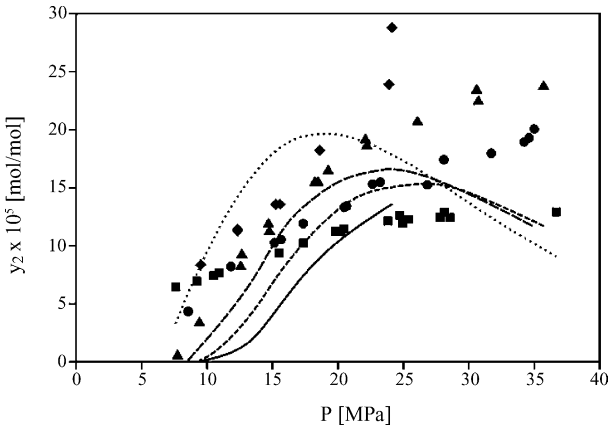

Fig. 4. Modeling of solubility isotherms of capsaicin (2) in CO_2 (1) using the PR-EOS for: 298 K (· · · ■), 308 K (– – –, ●), 313 K (- - -, ▲), and 318 K (—, ♦). Lines represent predictions of PR-EOS model and symbols experimental data points.

(ω). In addition, interaction parameters k_{ij} and l_{ij} are estimated so as to minimize the differences between predicted and experimental values of solute solubility. The physical properties of pure capsaicin cannot be measured since it degrades at low temperature. Thus, group contribution methods are utilized to estimate these properties. In this study, the solid capsaicin properties used were: $T_c = 1106.21$ K, $P_c = 17.125$ MPa, $\omega = 1.1851$, $P_2^{Subl} = 1.4 \times 10^{-13}$ Pa (298 K) [5], $P_2^{Subl} = 1.4 \times 10^{-12}$ Pa (308 K) [5], $P_2^{Subl} = 4.0 \times 10^{-12}$ Pa (313 K) [5], $P_2^{Subl} = 1.1 \times 10^{-11}$ Pa (318 K) [5], and $v_2 = 2.898 \times 10^{-4}$ m^3/kg (298 K) [22]. Fitting of all experimental solubility values obtained in this study to the PR-EOS provided best-fit values of the interaction coefficients $k_{12} = -0.0831$ and $l_{12} = -0.2482$. The value of AAD was 42.2% for the whole data set. A more negative value of l_{12} than k_{12} is frequently reported in the literature for asymmetric systems consisting of small solvent molecules and large solute molecules (the molar weight of CO_2 and capsaicin are 44 and 305, respectively). The agreement between best-fit PR-EOS lines and experimental values in Fig. 4 was poor; the model cannot follow the trend of the measured values. A temperature–solubility crossover point can be verified at around of 28 MPa. For pressures above 28 MPa, there are not differences among the tree lower estimated isotherms, and at 313 K the model shows the largest deviations from the experimental behavior with values up to 100%. Differences between experimental and predicted values were larger for pressures >28 MPa. A decrease in solubility was predicted as pressure increased, which contradicts the experimental evidence. The results shown in Fig. 4 could be improved by applying a methodology that considers the sublimation pressure of solid capsaicin as an adjustable parameter in the optimization algorithm [23].

3.4. Modeling with a group contribution equation of state

The group contribution equation of state (GC-EOS) proposed by Skjold-Jørgensen [24] is based on the generalized van der Waal's partition function and a group contribution principle. The repulsive term is a Carnahan–Starling-type expression, which is characterized by the critical hard-sphere diameter. It is a function of the molecular size of the pure component. The attractive term is calculated using the NRTL model with density-dependent mixing rules. The attractive energy between like groups is calculated from pure group parameters. Binary parameters account for interactions between unlike groups. A detailed description of GC-EOS is given in the original work of Skjold-Jørgensen [24]. The GC-EOS correlated the phase equilibrium of non-polar mixtures with large molecular size differences accurately [25]. In order to utilize the GC-EOS, it is necessary to define the different groups present in the mixture. The capsaicin molecule was considered as a single group as a first attempt in this work. Table 1 reports the parameters for the attractive term used to model the solubility. These parameters were adjusted for capsaicin and were taken from the literature for CO_2 [26]. The AAD between experimental and calculated solubility values is 50.5%. The reference temperature T^* is assumed to be equal to the critical temperature. The surface parameter q is estimated with the UNIFAC model from vapor pressure data of pure components. The energy group parameters g^*, g', and g'' are estimated by fitting vapor pressure data. The interaction parameters k_{12}^*, k_{12}', and α_{ij} are estimated by simultaneously fitting vapor pressure and phase equilibrium data for the binary mixture. The critical hard-sphere diameter for capsaicin ($d_c = 7.726$) was estimated from group contribution estimates of T_c and P_c, whereas a value $d_c = 3.129$ was adopted for CO_2 [26].

Fig. 5 compares measured solubility values with those estimated using GC-EOS; large discrepancies between both

Table 1
Pure group and binary interaction parameters for GC-EOS

Group	T^* (K)	q	g^*	g'	g''
Pure group parameters					
CO_2	304.2	1.261	531890	−0.15780	0.00000
Capsaicin	1062.1	9.739	476900	−0.84101	−0.70106
Group		k_{12}^*	k_{12}'	α_{12}	α_{21}
Binary interaction parameters					
CO_2 (1)–capsaicin (2)		1.0481	0.0289	−2.000	−2.000

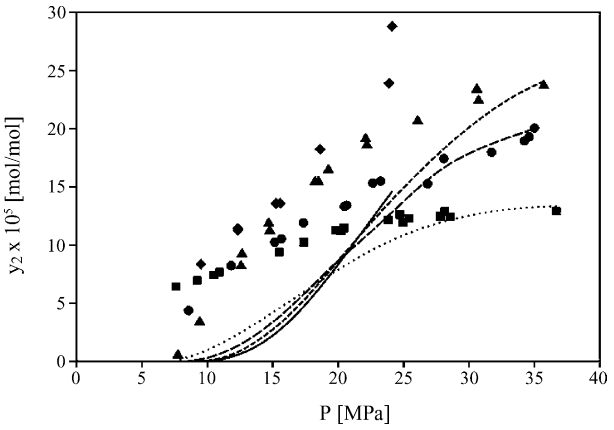

Fig. 5. Modeling of solubility isotherms of capsaicin (2) in CO_2 (1) using the GC-EOS for: 298 K (· · · ■), 308 K (– – –, ●), 313 K (- - -, ▲), and 318 K (—, ♦). Lines represent predictions of GC-EOS model and symbols experimental data points.

data sets can be observed. A crossover point was verified at a pressure around 19 MPa. There was not an important effect of temperature on predicted solubility values for pressures <19 MPa. The largest discrepancies between the model and experimental data occurred at 318 K particularly for low pressures. According to Bottini et al. [27], the quality of phase equilibrium predictions for large solutes using GC-EOS strongly depends on good estimates of d_c values. Therefore, an alternative procedure should be employed to determine d_c for capsaicin, possibly based on data of infinite dilution activity coefficients [27].

4. Conclusions

A high-pressure static equilibrium cell was built by the authors, at a considerably less expense than the selling price of many commercial systems built by specialized companies for an equivalent purpose. This low-cost apparatus was coupled to an HPLC and used to measure the solubility of solid capsaicin in high-pressure CO_2 at 298, 308, 313 and 318 K, for pressure ranging from 6 to 40 MPa. The new equilibrium solubility data agree with data reported in literature; for the three lower isotherms, the differences were $\leq$25%, for the highest isotherm discrepancies reached 50% especially at higher pressures. Three models were used in order to correlate the experimental solubility values reported in this contribution. A density-based model [16] fitted the experimental data appropriately, indicating self-consistence for the data. The PR-EOS with quadratic mixing rules and two interaction parameters ($k_{12} = -0.0831$ and $l_{12} = -0.2482$) showed poor agreement with the experimental data. The same was observed when using the GC-EOS to fit the solubilities of capsaicin (considered as a single group), case where there were large discrepancies between model predictions and experimental data, especially at low pressures.

Acknowledgements

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