THERMODYNAMIC MODELING OF PHASE EQUILIBRIUM BEHAVIOR OF CURCUMIN - CO_2 - ETHANOL

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Abstract. Turmeric (*Curcuma longa* L) is one of the most used sources of natural color in the food industry. The extract obtained from rhizomes of Curcuma possesses many biological activities: antibacterial, antioxidant, anti-inflammatory, anticancer, antimutagenic, among other. Knowledge of SC-CO_2 solubility of the substances of interest which are present in the vegetable matrix is of great importance to the success of procedures that employ supercritical technology; it influences directly the choice operating conditions of the process. The knowledge of the equilibrium phases in supercritical conditions involving bioactive compounds can be based on experimental determinations and robust models that can correlate the available experimental information and thus predict (extrapolate) values under different conditions from those available. The availability of data from phase equilibrium along with a thermodynamic modeling are important insights that help optimize processes for extraction and fractionation of compounds derived from natural sources, as well as microencapsulation process using supercritical fluid. For this reasons, the objective of this study was to use the Peng-Robinson equation of state with the van der Waals mixing rules with two interaction parameters to predict the phase equilibrium system curcumim-CO_2-ethanol. The solubility of curcumin in SC-CO_2 and in SC-CO_2-ethanol was obtained experimentally by the dynamic method at the temperature of 313 K and pressures of 200 and 300 bar. The solubility of curcumin in ethanol also was measured at atmospheric pressure at temperatures of 25 to 60 °C. The thermodynamic model with Peng-Robinson equation satisfactorily represented the experimental data of ternary system using binary system data.

Keywords: Thermodynamic modeling, Phase equilibrium behavior, Peng-Robinson equation of state, *Curcuma longa* L.

1. Introduction

The growing interest in natural medicines is becoming increasingly important to the growth and development of diseases such as pancreatic cancer, malignant melanoma and other cancers that are aggressive and highly resistant to chemotherapeutic agents. Due to the low efficiency of agents currently used, it is essential develop new agents that do not trigger the chemoresistance [1]. Among these new agents can highlight natural curcumin. This substance is obtained from the rhizome of Curcuma longa L. what is a herbaceous perennial plant of the family Zingiberácea. This plants mainly produced in India, China and other tropical countries. The dried rhizomes of *Curcuma longa* L. have between 2 – 5% essential oil and 0.02– 2% of curcumin [2]. Curcumin (Fig. 1) has a main unsaturated aliphatic group and an aryl group [3] which is responsible for the color, together with the dimethoxy curcumin and bis-dimethoxy curcumin.

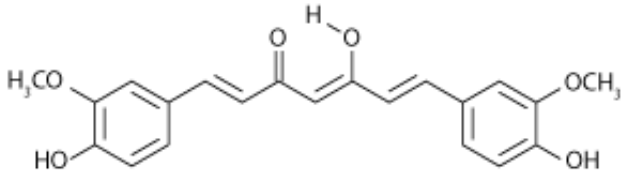

Figure 1. Curcumin (E,E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione

There are an increasing interest in process which minimizes or prevents any damage to the environment or human health, especially when it comes to food and pharmaceutical industries. Research has shown that curcumin has therapeutic effect on various diseases like Alzheimer's, AIDS and cancer. However, the clinical application of curcumin is limited due to low solubility in aqueous solution. An alternative for producing nanoparticles of curcumin is the use of supercritical technology rather than traditional techniques that use organic solvents [4]. Carbon dioxide is the most widely used solvent in supercritical extraction processes (SC-CO_2) in order that CO_2 is inert and nontoxic, generating pure extracts without waste.

To be able to optimize and improve the extractive processes, it is necessary to develop models that can predict the behavior of thermodynamic systems and is used in those cases the thermodynamic modeling. In the thermodynamic treatment, two different methods are commonly employed to calculate the phase equilibria: 1) Method γ - ϕ making a different treatment between the liquid phase and vapor phase. Employs models for calculation of the activity coefficient (γ_i) in the liquid phase and calculate the fugacity coefficient (ϕ_i) in the vapor phase. It is typically applied to systems that are around atmospheric pressure.. 2) Method ϕ - ϕ that calculates fugacity coefficients of the components of a mixture by a single equation of state that may represent the PVT properties of any fluid phase (liquid, gas and supercritical fluids). It is often used to high pressure, in which method γ - ϕ is not suitable. The modeling need of the binary interaction parameters between the pairs of components that compose the system in equilibrium, which being obtained from the fit the experimental data to the thermodynamic modeling and these are used in the multicomponent mixture.

Curcumin has a strong polarity, two phenyl groups and two carbonyl groups present in its structure. Knowledge of the phase equilibrium of the system solvent+solute offers an important role to determine the best operating conditions to conduct processes of extraction, fractionation and microencapsulation. However, most studies that use supercritical technology deal with supercritical extraction and a few approach the topic of phase equilibrium.

In this context, the objective of this study was to thermodynamic modeling of phase equilibrium system Curcumin - (ethanol + CO_2), employing the method ϕ - ϕ and using the equation of state of Peng-Robinson with classical mixing rule for the binary interaction parameters CO_2 - ethanol, CO_2 - curcumin and curcumin - ethanol, and testing the model using the binary interaction parameters in ternary systems consisting of mixtures of CO_2, ethanol and curcumin and from solubility data from the literature, for the system ethanol - SC-CO_2 and experimentally for binary systems curcumin - ethanol and curcumin - SC-CO_2.

2. Material e Methods

2.1. Experimental methodology: dynamic method

The unit basically consists of a CO_2 cylinder (1), thermostat bath, manometers Bourdon-type (5 and 6), heat exchanger (2), high pressure pump (3), tank (4), extractor (7) peristaltic pump (8), the extract collection bottle (9), the flow meter (11) that provides beyond the gas flow, temperature and absolute pressure, volume totalizer (12). The injection system of co-solvent comprises the flask co-solvent (14) and a co solvent pump (13) that takes the co-solvent in to extractor and valves (Figure 2).

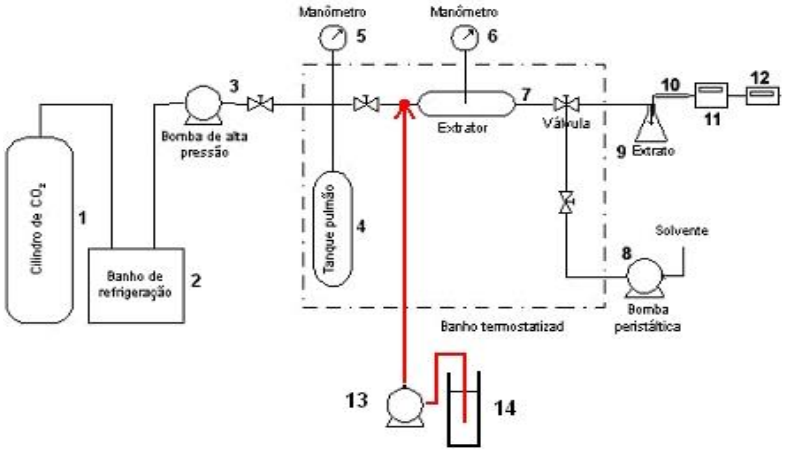

Figure 2. Schematic diagram of the system.

2.2. Collect samples to analysis of the binary systemCO_2–curcumin

The extractor 7 (Figure 2) was packed manually with a certain amount of Curcumin, which was mixed with purified sand and glass beads. Supercritical carbon dioxide has been drained through the bed under set conditions of temperature and pressure. There were four different conditions for sample collection and all in quadruplicate. In the first collection were used 300 bar pressure and bath temperature of 50 °C. In the second collection were used 300 bar pressure and bath temperature of 60° C. In the third collection were used 400 bar pressure and bath temperature of 50 °C. In the fourth collection was used 400bar pressure and bath temperature of 60° C. The extraction was started flowing supercritical CO_2 through the bed and collect up the collector extract. The CO_2 flow rate was kept constant and below a maximum value of 0.8 L/mim.

2.3. Collect samples to analysis of the binary system ethanol-curcumin at atmospheric pressure

The experiments were carried out in three jacketed glass vessels (triplicate) connected to a bath. It was performed on five different temperature conditions, 65° C, 55° C, 45° C, 35° C and 25° C, when the thermostatic bath reached the desired temperature and the solution was stirred for one hour. The stirring was turned off and was expected 30 min to stabilize the system. After the system stabilization, was collected a small portion of each sample and diluted for reading in the spectrophotometer at wavelength of 424 nm.

2.4. Estimation of thermodynamic properties of curcumin

From the molecular structure (Figure 1) were estimated critical properties, acentric factor and the vapor pressure of curcumin. The normal boiling temperature (Tb) of curcumin was obtained using the group contribution method proposed by TSIBANOGIANNIS [5] for compounds of medium and high molecular weight. The critical properties and vapor pressure was determined by the method of effective carbon number (ECN) proposed by Willman and Teja [6] and the acentric factor was obtained by the relation of Edmister.

2.5. Binary interaction parameters Ka_{ij} Kb_{ij}

The binary interaction parameters Ka_{13} and Kb_{13} for the system CO_2 (1) – curcumin (3), Ka_{12} and K_{b12} for the system CO_2 (1) - ethanol (2) and Ka_{23} for the system ethanol (2) - curcumin (3) were obtained by adjusting the thermodynamic modeling that uses the Peng-Robinson equation of state with classical mixture rules to the equilibrium solid-fluid to the systems curcumin-CO_2 and curcumin-ethanol and vapor and liquid equilibrium of the system CO_2-ethanol.

2.6. Prediction of solubility of curcumin in the mixture CO_2/ethanol

The solubility of curcumin in the mixture CO_2/ethanol was calculated by the thermodynamic modeling employing the Peng-Robinson equation of state with quadratic mixing rule and binary interaction parameters Ka_{12}, Ka_{13} and Ka_{23} obtained in experimental method of binary systems.

3. Results and Discussion

3.1. Estimation of thermodynamic properties of Curcumin

Based on the molecular structure (Figure 1) were estimated the critical properties. The vapor pressure of curcumin was determined by the method of effective carbon number (ECN) proposed by Willman and Teja (1985) [6] and the factor acentric were obtained by relation of Edmister. The calculated values are shown in the Table 1.

Table 1. Curcumin properties.

Critical temperature (T_c)	856.1849K
Critical pressure (P_c)	9.4536bar
Acentric factor	1.0212
Vapor pressure at 40 ºC	$4.393x10^{-12}$ bar
Vapor pressure at 50 ºC	$3.261x10^{-11}$ bar
Vapor pressure at 60 ºC	$2.040z10^{-10}$ bar

3.2. Solubility values (binary and ternary systems)

Binary system of CO_2 (1) – curcumin (3) and ethanol (2) – curcumin (3)

For the binary system of curcumin- CO_2 the solubility was calculated as the quotient between the mass of curcumin collected and the total mass of carbon dioxide used. The results are shown in Table 2. For the binary system curcumin– ethanol the solubility was calculated as the quotient between the mass of curcumin read in the spectrophotometer at wavelength of 424nm and the total mass of ethanol used. The results are shown in Table 3.

Table 2. Solubilities of the binary system curcumin-CO_2

Temperature (ºC) / Pressure (bar)	**Solubility (mg curcumin/g CO_2)**
50 / 300	$1.85x10^{-4}$
50 / 400	$9.0x10^{-4}$
60 / 300	$48.0x10^{-4}$
60 / 400	$33.0x10^{-4}$

Table 3. Experimental values of solubility of curcumin in ethanol at atmospheric pressure.

Temperature (ºC)	**Solubility (g curcumin/kg ethanol)**
25	12.5 ± 1.4
35	15.7 ± 0.8
45	16.09 ± 0.03
55	23.1 ± 1.1
65	30.8 ± 4.6

Binary system of CO_2 (1) - ethanol (2)

For the binary system CO_2-ethanol were considered the values reported in the literature by Borges et. al. (2007) [7]

Ternary system of CO_2 (1) -ethanol (2) – curcumin (3)

For the ternary system CO_2-ethanol-curcumin was calculated from the molar fractions (Y) obtained in the experiments.

Table 4. Experimental molar fractions (Y) for the ternary system.

40ºC/300 bar			40ºC/200 bar			50ºC/350 bar		
Y (1)	**Y (2)**	**Y (3)**	**Y (1)**	**Y (2)**	**Y (3)**	**Y (1)**	**Y (2)**	**Y (3)**
0.9176	0.0824	$(5.7\pm0.9).10^{-6}$	0.9176	0.0824	$(3.8\pm0.3).10^{-6}$	0.9261	0.0739	$(5.8\pm0.6).10^{-6}$

3.3 Solubility values (binary and ternary systems)

Adjustment of binary interaction parameters

- **Binary system CO_2 (1)-curcumin (3)**

The binary interaction parameters were adjusted to experimental solubility data, obtaining Ka_{13} = 0.8277 and Kb_{13} = 0.09627.

Table 5 shows the experimental values and its comparison to the calculated values with the parameters Ka and Kb adjusted to these same experimental data. The results show that the adjustment is satisfactory, with values calculated in the same order of magnitude of the experimental values.

Table 5. Experimental values and calculated by modeling the solubility of curcumin in supercritical CO_2.

Temperature (ºC)	Pressure (bar)	Solubility (mg/g)	Molar solubility	Calculated solubility
50	300	$1.85x10^{-4}$	$2.21x10^{-8}$	$2.74x10^{-8}$
	400	$48.0x10^{-4}$	$57.34x10^{-8}$	$18.5x10^{-8}$
60	300	$9.0x10^{-4}$	$10.75x10^{-8}$	$7.05x10^{-8}$
	400	$33.0x10^{-4}$	$39.42x10^{-8}$	$47.12x10^{-8}$

- **Binary system CO_2(1)-ethanol (2)**

The binary interaction parameters were taken from the literature Borges et al. (2007) [7]: Ka_{12}= 0.0703 and Kb_{12}= -0.0262.

- **Binary system ethanol (2)-curcumin (3)**

The interaction parameters Ka were adjusted for each experimental value for all temperatures and shown in Table 6.

Table 6. Values of interaction parameters for the binary system versus temperature.

Temperature (ºC)	Solubility(g/kg)	Molar Solubility	$Ka_{23}$with Kb_{23}=0
25	12.5 ± 1.4	$1.58 . 10^{-3}$	-0.1825
35	15.7 ± 0.8	$1.99 . 10^{-3}$	
45	16.09 ± 0.03	$2.041 . 10^{-3}$	-0.1587
55	23.1 ± 1.1	$2.948 . 10^{-3}$	-0.148
65	30.8 ± 4.6	$3.987 . 10^{-3}$	-0.148

The parameters were correlated with temperature (in K) by the equation:

$$Ka_{23}=-0.5281+0.00116.T \quad (1)$$

Using the binary interaction parameters correlated by Equation (1), obtained values calculatec thermodynamic modeling of solubility of curcumin in ethanol. The Figure 3 compares the calculated values experimental, showing a good fit of the model to experimental data.

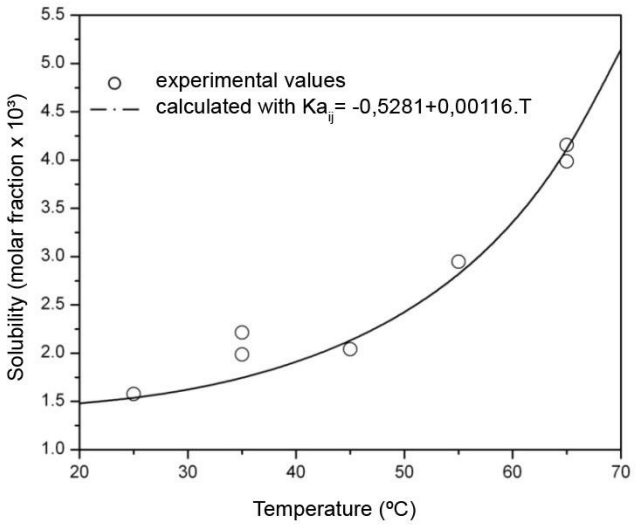

Figure 3. Experimental values of solubility of curcumin in ethanol compared to values calculated by thermodynamic modeling

3.4 Prediction of ternary system CO_2 (1)-ethanol (2)-curcumin (3) solubility values (binary and ternary systems)

To verify the modeling was effective in predicting the multicomponent equilibrium mixture, experimental values of solubility in the mixture of curcumin/ethanol/CO_2 were experimentally measured and calculated using thermodynamic modeling binary parameters, under the same experimental conditions of temperature, pressure and the ratio of the CO_2/ethanol. In the Table 7, 8 and 9 was compared the experimental values with the calculated values.

Table 7. Experimental values calculated for the condition 40° C and 300 bar.

Experimental			Calculated		
Y (1)	**Y (2)**	**Y (3)**	**Y (1)**	**Y (2)**	**Y (3)**
0.9176	0.0824	$(5.7\pm0,9).10^{-6}$	0.9176	0.0824	49.10^{-6}
0.9261	0.0739	$(4.5\pm0,6).10^{-6}$	0.9261	0.0739	22.10^{-6}

Table 8. Experimental values calculated or the condition 40° C and 200 bar.

Experimental			Calculated		
Y (1)	**Y (2)**	**Y (3)**	**Y (1)**	**Y (2)**	**Y (3)**
0.176	0.0824	$(3.8\pm0,3).10^{-6}$	0.9176	0.0824	$6.0.10^{-6}$

Table 9. Experimental values calculated for the condition 50° C and 350 bar.

Experimental			Calculated		
Y (1)	**Y (2)**	**Y (3)**	**Y (1)**	**Y (2)**	**Y (3)**
0.9261	0.0739	$(5.8\pm0,6).10^{-6}$	0.9261	0.0739	83.10^{-6}

The results showed that in general the average values calculated was an order of magnitude larger than experimental. The condition that best results were provided at 40 ºC and 200 bar with the experimental value of solubility of $3.8x10^{-6}$ molar against the calculated value of $6.0x10^{-6}$ molar. In thermodynamic modeling, it was necessary to make various estimates of properties for curcumin, and the critical properties (critical temperature and critical pressure), vapor pressure, acentric factor, molar volume. Possible estimation errors may have caused a lower quality of modeling.

4. Conclusion

The solubility values of curcumin in CO_2, mixtureCO_2/ethanol and ethanol were of the order of magnitude of 10^{-8}, 10^{-6} and 10^{-3} showing the increased solubility with increasing polarity of the solvent. Although the modeling calculate values of solubility in the mixture of curcumin/CO_2/ethanol, an order of magnitude higher than the experimental values showed similar behavior, increases the solubility with temperature and pressure.

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