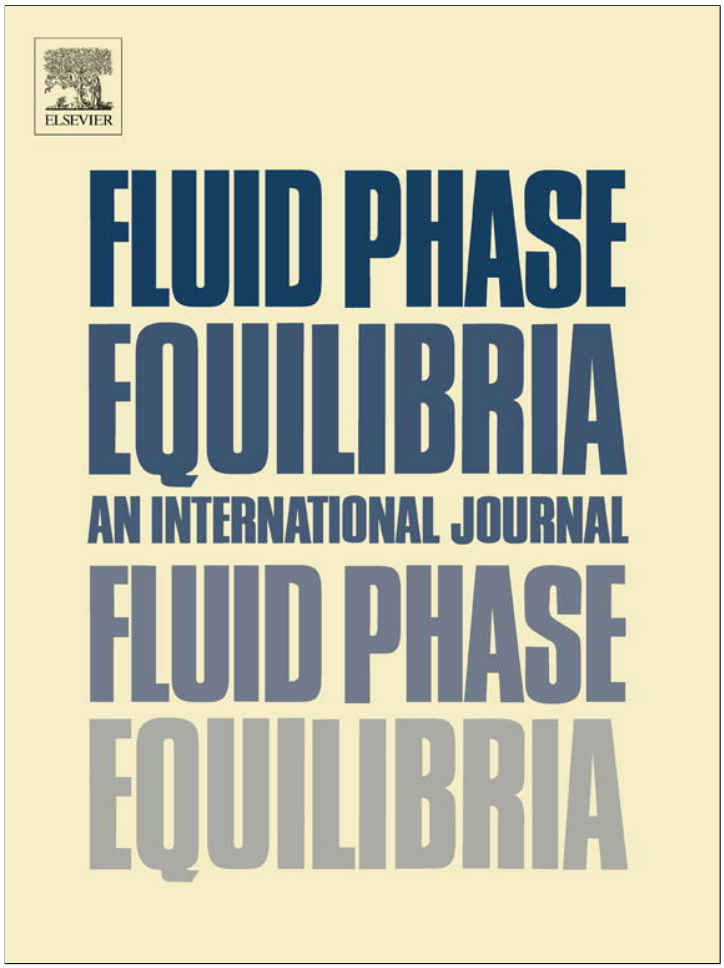

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Measurement and modeling of epicatechin solubility in supercritical carbon dioxide fluid

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ABSTRACT

The experimental equilibrium solubility of epicatechin in supercritical carbon dioxide was measured at several temperatures (313.15, 323.15, 333.15 and 343.15 K) and pressure in the range of 12–26 MPa. The solubilities of epicatechin in supercritical CO_2 increased with pressure and temperature. The effect of increasing temperature on the solubility is more significant at high pressure than low pressure. The experimental data were fitted very well by three density-based models of Chrastil, del Valle and Aguilera and the model of Méndez-Santiago and Teja. Reasonable fitting parameters of the models were obtained.

1. Introduction

Epicatechin ((−)-*cis*-3,3′,4′,5,7-pentahydroxyflavane (2*R*,3*R*)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-1(2*H*)-benzopyran-3,5,7-triol) is a flavonol belonging to the group of flavonoids and widely present in fruits and vegetables. High quantities of epicatechin can be found in cocoa [1], tea [2–4] and grapes [5–7]. Epicatechin is also found in staple plant such as sago (*Metroxylon sago*) [8]. Epicatechin exerts beneficial health-related effects since it acts as free radical scavengers and inhibitors of eicosainoid biosynthesis [9,10]. Epicatechin also reduces low-density lipoprotein in oxidation, risk of stroke, heart failure, cancer and diabetes [1,9,11,12].

The initial step in the recovery and purification of flavonoids from plant materials is extraction. Soxhlet extractions using organic–aqueous solvents are commonly used; however this method is time consuming and uses a lot of organic solvents. Recently, microwave-assisted extraction [13], accelerated solvent extraction [14,15] and supercritical fluid extraction were employed to obtain better recoveries and to reduce extraction time [16,17]. Among these extraction methods, supercritical fluid extraction (SFE) offers an environmental friendly choice in terms of using less amount of organic solvent. SFE works in the absence of light and air that cause degradation of flavonoids. Among many supercritical fluids, carbon dioxide is extremely attractive because of it has relatively low critical temperature (304.15 K), is less possible to cause degradation of thermally labile compounds and is easily separable from the extracted solutes. Other benefits in using supercritical carbon dioxide (SC CO_2) are it is nontoxic, nonflammables and inexpensive.

Process design based on SFE and the determination of optimum operating conditions require knowledge of phase equilibria and compound solubility in a supercritical fluid. In the last two decades, many attempts have been reported on the solubility of flavonoid compounds. Song et al. [18] determined the solubility of epigallocatechin gallate in SC CO_2 with ethanol cosolvent (0.044 and 0.084 mole fraction) at a temperature ranging from 313 to 333 K and pressure from 15 to 35 MPa. Their solubility data were correlated using a thermodynamic model, a modified Chrastil model and the Méndez-Santiago and Teja [19] model. Cháfer et al. [20] reported experimental measurements and thermodynamic modeling of the solubility of quercetin with ethanol as the cosolvent (5–30%) at 313.15 K and pressure ranging from 8 to 12 MPa. The same operating conditions were used by Berna et al. [21] for catechin and Cháfer et al. [22] for epicatechin and the data were modeled using equations of state (EOS): Peng–Robinson and Soave–Redlich–Kwong models. Other solubility data of hydroxycinnamic acids in SC CO_2 were reported for 4-hydroxycinnamic acid (*p*-coumaric acid), 3,4-dihydroxycinnamic acid (caffeic acid), 4-hydroxy-3-methoxycinnamic acid (ferulic acid) [23–25].

The existing solubility data for epicatechin in SC CO_2 + ethanol [22] was limited at one fixed temperature (313 K) and a narrow pressure range of 8–12 MPa. Wider ranges of temperature and pressure are essential in order to determine optimum operating

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conditions for separation of epicatechin from plant materials using SC CO_2. Epicatechin is almost insoluble in SC CO_2 due to its strong polarity; therefore ethanol is the best choice as cosolvent especially for food and pharmaceutical applications. In their report, Cháfer et al. [22] used ethanol as cosolvent in the range of 5–30%. The presence of high amount of ethanol in their system may have changed the supercritical condition of CO_2 into subcritical [26–29]. Joung et al. [29] found that the maximum concentration of ethanol in the system should be 6.49 mol% at 8.15 MPa and 313.15 K in order to obtain supercritical condition. Under subcritical condition, most epicatechin dissolved in ethanol rather than in SC CO_2. Further separation of epicatechin from ethanol is needed in order to obtain pure epicatechin.

Considering the importance of solubility data of solids in supercritical fluids for the developing of the extraction process and the dependency of solubility on density, temperature and pressure of supercritical fluids; extensive amounts of data are needed. Moreover, the present of cosolvent in SC CO_2 extraction produces impure extract with the cosolvent as an impurity. Therefore, in order to obtain pure extract, separation of extract and cosolvent is needed. The objective of this paper is to measure the solubilities of epicatechin in SC CO_2 without cosolvent at different temperatures (313.15, 323.15, 333.15, and 343.15 K) and pressures (12–26 MPa). The experimental data were then correlated using density-based models (Chrastil [30], del Valle and Aguilera [31] and Méndez-Santiago and Teja [19] models). To the best of knowledge, there is no literature available on the solubility of epicatechin in SC CO_2 in the range of pressures and temperatures studied in this work.

2. Experimental

2.1. Materials

HPLC grade (−)-epicatechin with a purity of 98 wt.% was obtained from Sigma–Aldrich (Singapore) and was used without any further purification. Analytical grade ethanol was supplied by Merck (Darmstadt, Germany) and was used as a solvent to collect extract for further analysis. Food grade carbon dioxide (99% purity) was used as the supercritical solvent and supplied as liquid CO_2 by Aneka Gas Pty Ltd (Indonesia) with a purity of 99.9%.

2.2. Experimental procedure

The experiments of epicatechin solubility in supercritical CO_2 were carried out in a static system consists of a 50 ml long equilibration column (Swagelok, USA), a high pressure pump (Eldex AA-100-S-2-CE, USA) and a pressure transducer (Druck PTX 611, USA) with a digital process indicator (Druck DPI 280, USA) which gives a pressure measurement uncertainty of ±0.01 MPa. The system temperature was controlled by a heating chamber (Oven Memmert, Germany). The uncertainty of temperature measurement in the heating chamber is ±1 K. All fitting and tubing used in this system were made of stainless steel 316 (Swagelok, USA). The maximum working pressure and temperature of the supercritical extraction system were 40 MPa and 373.15 K, respectively.

Epicatechin solubility data were obtained by adding 100 mg of (−)-epicatechin in a sample holder in the equilibration column. The system was heated to a desired temperature (313.15, 323.15, 333.15, or 343.15 K). Subsequently, liquid CO_2 was pumped into the system using the high-pressure pump until a desired pressure was reached (12–26 MPa). After equilibrium condition was achieved in 4 h (insignificant increase of epicatechin concentration in CO_2 was observed after 3 h), the output valve was released, and the sample flowed into a collector containing a known amount of ethanol to separate epicatechin and CO_2. At least three replications of trials were carried out for every set of temperature and pressure, and the equilibrium composition was represented by average of the three replications. The uncertainty of each measurement was within ±2%. The determination of epicatechin concentration in ethanol was based on the method of Zuo et al. [32] by using a HPLC (Jasco HPLC PU-2089 plus) with a UV–vis detector (UV-2077 plus).

3. Results and discussion

The experimental equilibrium solubility data of epicatechin and the result of calculated densities of supercritical SC CO_2 at various pressures and temperatures using the Stryjek and Vera [33] modification of the Peng–Robinson equation of state are reported in Table 1. The solubility of epicatechin in SC CO_2 increases with increasing pressure and temperature. At constant temperature, increasing pressure raises SC CO_2 density and increases its ability to dissolve solute. At constant pressure, increasing temperature raises solute vapor pressure as well as the diffusivities of both solvent and solute.

The correlation of experimental solubility data was investigated using several semi-empirical models. Chrastil [30] proposed the first model for density-based correlation. It is based on the hypothesis that one molecule of a solute A associates with k molecules of a solvent B to form one molecule of solvato-complex AB_k in equilibrium with the system. The definition of the equilibrium constant through thermodynamic consideration resulted in the following model for the solubility:

$$c_1 = \rho^k exp\left(\frac{a}{T} + b\right) \quad (1)$$

where c_1 is the concentration of the solute in the gas ($g\,l^{-1}$), ρ is the density of the gas ($g\,l^{-1}$), k is an association number, a is a function of the enthalpy of solvation and enthalpy of vaporization (K^{-1}), and b is a function of association number and molecular weights of the solute and supercritical fluids.

Various modifications on Chrastil model were proposed such as modified Chrastil by Garlapati and Madras [34,35], modified Chrastil by Wang [36], and modified Chrastil by del Valle and Aguilera [31]. Among these modified Chrastil models, del Valle and Aguilera [31] claimed that their model fitted well for temperatures from 293 to 353 K and pressure between 15 and 88 MPa and adequately predicted solubility under 100 $g\,l^{-1}$ within the region suggested for commercial supercritical fluid extraction of food components (Eq. (2)).

$$c_1 = \rho^{k'} \exp\left(b' + \frac{a'}{T} + \frac{d}{r^2}\right) \quad (2)$$

The physical meaning of the parameters k', b', and a' are similar to Chrastil model. The parameter d' is introduced to compensate the variation of enthalpy of vaporization (ΔH_{vap}) with temperature.

Multivariable non-linear regression analysis of all experimental data was performed to estimate the constants in Chrastil model and modified Christil model by del Valle and Aguilera. The quality of all data correlations is quantified by the sum of squared errors (SSE), defined as follows:

$$SSE = \left(\frac{\left(\sum c_{1(exp)} - c_{1(cal)}\right)^2}{N}\right)^{1/2} \quad (3)$$

where $c_{1(exp)}$ is the actual solubility of epicatechin in SC CO_2, $c_{1(cal)}$ is the calculated solubility, and N is the number of experimental data. Multivariable non-linear regression technique employed an iterative curve fitting procedure. An initial estimation for each parameter was provided, and then calculation of a point-by-point sum of squares (Eq. (3)) for each iteration was conducted until convergence criteria were fulfilled.

Table 1
Solubility of epicatechin in SC CO_2 and the SC CO_2 density.

P (MPa)	T = 313.15 K			T = 323.15 K			T = 333.15 K			T = 343.15 K		
	ρ (g l^{-3})	$10^3\,c_1$ (g l^{-3})	$10^6\,y^a$	ρ (g l^{-3})	$10^3\,c_1$ (g l^{-3})	$10^6\,y^a$	ρ (g l^{-3})	$10^3\,c_1$ (g l^{-3})	$10^6\,y^a$	ρ (g l^{-3})	$10^3\,c_1$ (g l^{-3})	$10^6\,y^a$
12	669	2.90 ± 0.06	0.66 ± 0.014	537	3.28 ± 0.077	0.93 ± 0.022	417	2.95 ± 0.088	1.09 ± 0.032	342	3.25 ± 0.053	1.49 ± 0.024
13	701	3.56 ± 0.10	0.77 ± 0.022	588	4.51 ± 0.136	1.16 ± 0.035	474	5.07 ± 0.136	1.65 ± 0.044	390	5.64 ± 0.152	2.27 ± 0.059
14	727	3.97 ± 0.02	0.83 ± 0.004	627	6.48 ± 0.162	1.57 ± 0.039	523	7.64 ± 0.222	2.27 ± 0.064	436	9.07 ± 0.165	3.26 ± 0.057
15	750	4.40 ± 0.12	0.89 ± 0.024	659	7.83 ± 0.196	1.80 ± 0.045	563	9.85 ± 0.207	2.88 ± 0.056	478	13.90 ± 0.160	4.38 ± 0.051
16	769	5.15 ± 0.12	1.02 ± 0.024	685	9.19 ± 0.259	2.03 ± 0.057	598	14.25 ± 0.322	3.50 ± 0.082	515	19.91 ± 0.358	5.56 ± 0.011
17	787	5.65 ± 0.10	1.09 ± 0.019	709	10.70 ± 0.195	2.290 ± 0.042	627	17.89 ± 0.292	4.09 ± 0.071	549	24.20 ± 0.544	6.85 ± 0.015
18	803	6.02 ± 0.18	1.14 ± 0.034	729	11.50 ± 0.129	2.39 ± 0.027	653	20.10 ± 0.308	4.67 ± 0.071	578	30.01 ± 0.430	8.10 ± 0.011
19	818	6.53 ± 0.02	1.21 ± 0.004	748	13.36 ± 0.338	2.72 ± 0.068	675	22.50 ± 0.215	5.19 ± 0.048	604	36.21 ± 0.927	9.34 ± 0.023
20	831	6.97 ± 0.03	1.27 ± 0.006	765	14.10 ± 0.229	2.79 ± 0.045	696	25.70 ± 0.402	5.73 ± 0.088	628	44.78 ± 0.961	10.57 ± 0.023
21	844	7.49 ± 0.06	1.34 ± 0.011	780	15.60 ± 0.409	3.03 ± 0.079	714	29.51 ± 0.507	6.22 ± 0.108	649	51.38 ± 0.904	11.77 ± 0.021
22	856	8.01 ± 0.03	1.42 ± 0.005	794	17.08 ± 0.482	3.26 ± 0.092	732	32.01 ± 0.465	6.73 ± 0.096	669	57.96 ± 0.569	12.98 ± 0.13
23	867	8.32 ± 0.22	1.46 ± 0.038	808	18.10 ± 0.275	3.40 ± 0.052	747	36.01 ± 0.343	7.18 ± 0.070	687	62.06 ± 0.673	14.14 ± 0.015
24	877	8.87 ± 0.09	1.53 ± 0.016	820	19.50 ± 0.316	3.60 ± 0.058	762	38.05 ± 0.474	7.66 ± 0.094	704	70.15 ± 0.635	15.31 ± 0.014
25	887	9.20 ± 0.12	1.57 ± 0.021	832	20.73 ± 0.273	3.77 ± 0.050	775	41.14 ± 0.328	8.10 ± 0.064	719	77.72 ± 0.694	16.38 ± 0.015
26	896	9.68 ± 0.08	1.64 ± 0.014	843	21.82 ± 0.203	3.92 ± 0.036	788	44.92 ± 0.263	8.54 ± 0.051	734	85.86 ± 0.673	17.53 ± 0.014

[a] y is mole fraction. The standard uncertainty is estimated using standard deviation of the mean:

$$u(x_i) = \left(\frac{1}{n(n-1)}\sum_{k=1}^{n}(X_{i,k} - \bar{X}_i)^2\right)^{1/2}$$

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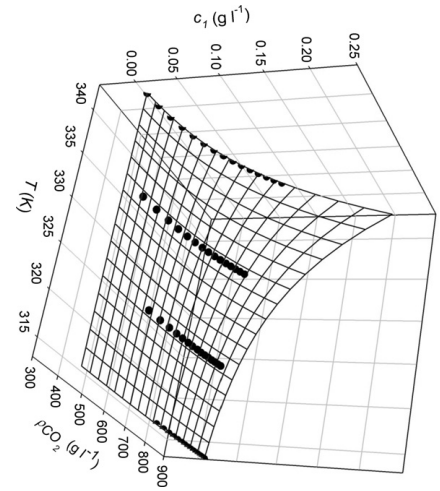

Fig. 1. Chrastil model fittings (wire mesh) and experimental solubility data (●).

Fig. 1 shows the fitting of solubility data of epicatechin in SC CO_2 using Chrastil model. Chrastil model fits well to the experimental solubility data. The parameters of Chrastil model, k, a, and b resulted from multivariable non-linear regression are 4.2311, −10,788, and 1.067, respectively, with a SSE of 0.04%. The fitting of solubility data of epicatechin in SC CO_2 using del Valle and Aguilera model is shown in Fig. 2. This modified Chrastil model also fits very well the experimental data and the values of k', b', a', and d are 4.2313, 2.279, −11,596 and 134,374, respectively, with a SSE of 0.06%.

The parameter k is an association number, and its values from both models are similar. This indicates that one molecule of epicatechin (A) is associated with four molecules of gas CO_2 (B) to form one molecule of a solvato complex AB_4. The parameter b in Chrastil model and in del Valle and Aguilera is a function of association number and molecular weight of solute and supercritical fluid. Therefore, the value should be similar. However, since there is an extra parameter d in the modified Chrastil model by del Valle and Aguilera as shown in Eq. (2), the parameter b in Eq. (1) is not the same as that in Eq. (2). The effect of enthalpy of solvation

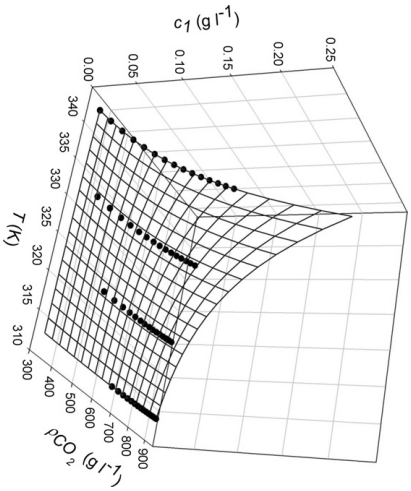

Fig. 2. del Valle and Aguilera model fittings (wire mesh) and experimental solubility data (●).

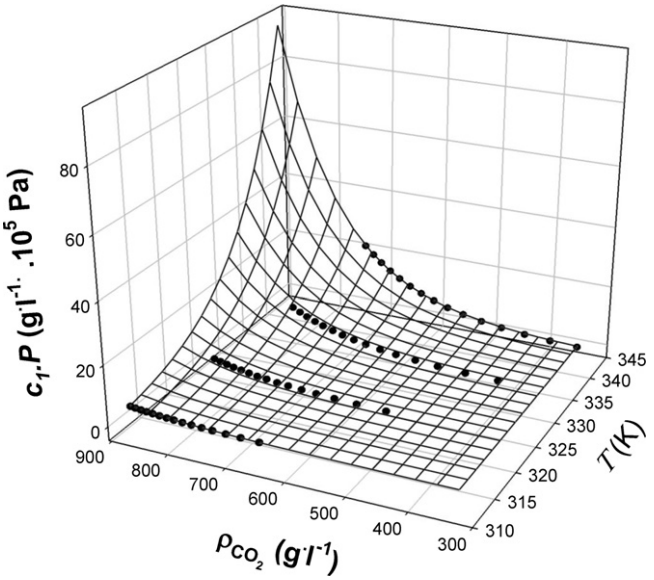

Fig. 3. Méndez-Santiago and Teja model fittings (wire mesh) and experimental solubility data (●).

and enthalpy of vaporization in Chrastil model is presented in the parameter a ($a = \Delta H/R$). However, del Valle and Aguilera [31] modified this parameter to compensate the variation of enthalpy of vaporization with temperature ($\Delta H(T) = R(a' + 2d/T)$). The heat of solution (ΔH) for epicatechin and CO_2 using Chrastil model is 89.7 kJ/mol, while using del Valle and Aguilera the heat of solution falls in a range of 87.3–89.9 kJ/mol. From the analyses of all parameters for both models, we conclude that the solubility of epicatechin in SC CO_2 can be well fitted by both models.

Another semi-empirical density based model was proposed by Méndez-Santiago and Teja [19] based on the theory of dilute solutions. This model took into account Henry's law, infinite dilution partition coefficients near the critical point of the solvent and Clausius–Clapeyron-type expression for the sublimation pressure. The equation has three adjustable parameters (A', B' and C'), defined as follow:

$$T \ln(c_1 P) = A' + B'\rho + C'T \quad (4)$$

Fig. 3 shows that the Méndez-Santiago and Teja model can represent the experimental solubility data of epicatechin in SC CO_2 well. Values of A', B' and C' are −15,230, 3.008 and 4.108, respectively, and the SSE is 1.18%. The three constants (A', B' and C') are the result of multivariable non-linear regression analysis, which is independent of temperature and pressure without any significant physical meaning, therefore, can be used to extrapolate solubility data to other temperature [19].

4. Conclusion

Solubility data of epicatechin in SC CO_2, in wider ranges of temperature and pressure, were obtained in this study. The experimental data was fitted by using density-based models (Chrastil, del Valle and Aguilera and Méndez-Santiago and Teja). The models fitted very well to the experimental data and resulted in reasonable values of the fitting parameters.

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