Solubility of *n*-(4-Ethoxyphenyl)ethanamide in Supercritical Carbon Dioxide

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The solubility of a drug, *n*-(4-ethoxyphenyl)ethanamide (phenacetin), in supercritical carbon dioxide was determined by a saturation method at (308, 318, and 328) K from (9 to 19) MPa. The solubilities in mole fraction of *n*-(4-ethoxyphenyl)ethanamide in supercritical carbon dioxide were in the range of $1.29 \cdot 10^{-5}$ to $2.88 \cdot 10^{-5}$, $1.13 \cdot 10^{-5}$ to $3.65 \cdot 10^{-5}$, and $0.91 \cdot 10^{-5}$ to $4.28 \cdot 10^{-5}$ at (308, 318, and 328) K, respectively. The solubility data were correlated with the Peng−Robinson equation of state models and the Méndez-Santiago and Teja model.

Introduction

A fluid above its critical temperature and pressure is called a supercritical fluid (SCF) and is widely used in drug synthesis.[1,2] Carbon dioxide is commonly used as a SCF because of its moderate critical pressure, high critical density, and critical temperature close to ambient temperature.[3,4] Supercritical carbon dioxide ($SCCO_2$) based processes are important in pharmaceutical processing.[5]

n-(4-Ethoxyphenyl)ethanamide is the International Union of Pure and Applied Chemistry (IUPAC) name for phenacetin. It was widely used as a remedy for fever and pain, but it is currently banned in the U.S. because the drug causes kidney problems. However, it is still being produced in other countries as a pharmaceutical and is also used as a cutting agent to adulterate cocaine.[6] It belongs to the family of nonsteroidal anti-inflammatory drugs (NSAIDs). Although NSAIDs are among the widely used drugs in the world, their oral administration is limited because of adverse side effects such as irritation, ulceration, and nephropathy.[6,7] The solubility data of various NSAIDs are available in the recent literature.[8−14] However, the solubility of *n*-(4-ethoxyphenyl)ethanamide solubility in $SCCO_2$ has not been investigated.

The design of the SCF process requires the knowledge of the solubilities of the compounds in $SCCO_2$. Therefore, the solubilities of this drug were measured at (308, 318, and 328) K over the pressure range from (9.0 to 19.0) MPa in $SCCO_2$. The solubilities were correlated by suitable equation of state and density-based models.

Experimental Section

Materials. Carbon dioxide (CAS 124-38-9) (99 % mass fraction) was purchased from Vinayaka Gases (India). This was purified to 99.9 % (mass fraction) by passing the gas through a bed of silica gel. The purity of carbon dioxide was determined by gas chromatography/mass spectrometry (Varian Saturn GC/MS 2200 with 3800 GC with Porapak Q column). *n*-(4-Ethoxyphenyl)ethanamide (CAS 62-44-2) (97 % mass fraction; its molecular weight is 179.21 $g \cdot mol^{-1}$, and its melting point is 407 K) was procured from Alfa Aesar Inc. The chemical structure of this compound is given in Figure 1.

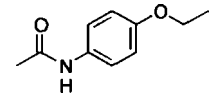

Figure 1. Chemical structure of *n*-(4-ethoxyphenyl)ethanamide.

Equipment and Procedure. The solubility measurements of *n*-(4-ethoxyphenyl)ethanamide were carried out using a flow apparatus based on the principle of saturation method, which has described in literature.[15−17] A schematic diagram of the apparatus is shown in Figure S1 (see Supporting Information). The carbon dioxide was pressurized with a pump (model: Jasco PU-1580-CO_2) and operated in a constant flow mode, and the pressure was maintained within ± 0.2 MPa with a back pressure regulator (model: Jasco BP-158081). In this method, two packed columns (300 mm × 14 mm) in series were placed in the oven, where the temperature was maintained within ± 0.1 K. Each packed column was fitted with 2 μm filters one at inlet and the other at outlet. For each measurement, about 35 g (± 0.01 mg) of pure solute was packed with glass wool. Subsequently, carbon dioxide from the gas cylinder was compressed into heated coils and then to an accumulator to make supercritical $SCCO_2$. To ensure that the exiting $SCCO_2$ stream is saturated with the solute, experiments were conducted with different flow rates (based on pump head) between $3 \cdot 10^{-6}$ and $30 \cdot 10^{-6}$ $m^3 \cdot s^{-1}$. Because no changes in solubilities were observed below $18 \cdot 10^{-6}$ $m^3 \cdot s^{-1}$, all experiments were conducted with $12 \cdot 10^{-6}$ $m^3 \cdot s^{-1}$ (0.2 $mL \cdot min^{-1}$) of $SCCO_2$. At this flow rate, the solubilities were determined after 1800 s, 3600 s, 7200 s, and so forth. After 3600 s the solubilities were invariant, and thus the experiments were conducted for 7200 s. Samples from the exiting fluid phase were collected by a quick depressurization and expansion into a small glass trap. These samples were dissolved in acetonitrile and analyzed by a UV spectrometer to determine the solubilities. On the basis of the concentration and the total flow of the SCF, the solubilities in mole fraction were determined.

A suitable wavelength for UV determination was determined by scanning the UV spectrum between (200 and 600) nm, and the observed maximum wavelength was at 248 nm for *n*-(4-ethoxyphenyl)ethanamide. The calibration was obtained by using standard samples of concentrations between (1 and 9) ppm. The calibration curve obtained (with a regression coefficient better than 99.6 %) was used to establish the concentration of *n*-(4-ethoxyphenyl)ethanamide in the glass trap. Each measurement

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Table 1. *n*-(4-Ethoxyphenyl)ethanamide Solubility in Mole Fraction ($y_2 \cdot 10^5$) in $SCCO_2$ at Temperatures of (308, 318, and 328) K and a Pressure Range of (9.0 to 19.0) MPa

	T/K		
p/MPa	308	318	328
9.0	1.29		
11.0	1.78	1.13	0.91
13.0	2.31	1.98	1.72
15.0	2.62	2.68	2.73
17.0	2.88	3.44	3.63
19.0	2.89	3.65	4.28

was carried out a minimum of three times, and the relative uncertainty (deviation) was less than ± 5 %.

Results and Discussion

The reliability of the apparatus was tested by determining the solubilities of naphthalene in supercritical carbon dioxide (see Supporting Information, Figure S1) and comparing them with the data reported earlier. Good agreement was obtained with the literature data[18] within ± 5 %.

Solubility Data. The solubility data for *n*-(4-ethoxyphenyl)-ethanamide in $SCCO_2$ at (308, 318, and 328) K at pressures between (9.0 and 19.0) MPa are shown in Table 1. Crossover points (CPs) in the Figure 1a are observed for the different isotherms at about (13.8, 14.8, and 15.8) MPa, at (308, 318, and 328) K, respectively.

Modeling. Solubilities of drugs in SCFs are modeled in several ways,[7−10] and these are broadly classified into two main approaches, namely, the equation of state (EOS) based models or density-based models. In this study, solubilities of solids in SCFs were correlated with both of these models. For modeling the Peng−Robinson EOS (PR EOS) in combination with classical van der Waals mixing rules[19] and the Valderrama modification of Kwak and Mansoori mixing rules[20−22] were used to correlate the solubilities. Previous thermodynamic studies[23] indicate that the Valderrama modification of Kwak and Mansoori mixing rules with the PR EOS was quite successful in modeling drug solubilities in $SCCO_2$. Hence these mixing rules were considered in this study. Density-based models such as models by Bartle et al.,[24] Méndez-Santiago−Teja,[25] and reformulated Chrastil[26] models were also used to correlate the experimental data.

EOS Correlation of Experimental Solubility Data. The EOS approach is often used in modeling SCF phase equilibria.[27] The molar solubility of the solid solute in the SCF, y_2, in equilibrium with a SCF is[3,27]

$$y_2 = \frac{p_2^{sub}\phi_2^{sat}}{p\hat{\phi}_2^{SCF}} \exp\left(\frac{(p - p_2^{sat})V_2^s}{RT}\right) \quad (1)$$

where V_2^s is the molar volume of the solute in $m^3 \cdot mol^{-1}$, p_2^{sat} is the vapor pressure of the solute in Pa, p is the total pressure in Pa, $\hat{\phi}_2^{sat}$ is the fugacity coefficient of the pure solid is assumed to be equal to one, and $\hat{\phi}_2^{SCF}$ is the fugacity coefficient of the solute in $SCCO_2$.

For PR EOS with van der Waals mixing rules (see Appendix A1 in Supporting Information), $\hat{\phi}_2^{SCF}$ is

$$\ln \hat{\phi}_2^{SCF} = -\ln\left(\frac{p(V-b)}{RT}\right) + \frac{\hat{b}}{b}\left(\frac{pV}{RT} - 1\right) - \frac{a}{2\sqrt{2}bRT}\left[\frac{\hat{a}}{a} - \frac{\hat{b}}{b}\right]\ln\left[\frac{V + (1+\sqrt{2})b}{V + (1-\sqrt{2})b}\right] \quad (2)$$

where $\hat{a} = (1/n)(\partial n^2 a/\partial n_i)$ and $\hat{b} = (\partial nb/\partial n_i)$.

Table 2. Estimated Critical and Thermophysical Properties of *n*-(4-Ethoxyphenyl)ethanamide

T_c/K	P_c/MPa	ω	$10^2 \cdot V_2^s/m^3 \cdot mol^{-1}$	*A*	*B*
700.3[a]	3.329[b]	0.7[c]	0.0157[d]	39[e]	14481[e]

[a] Estimated by the Fedors method.[28] [b] Estimated by the Joback and Reid modification of Lydersen's method.[28] [c] Estimated by the Lee and Kesler method.[29] [d] Estimated by the method of Immirzi and Perini.[30] [e] Adopted from the Perlovich et al.[6]

For the PR EOS consistent with the statistical−mechanical basis of the van der Waals mixing rules proposed by Kwak and Mansoori[20] (see Appendix A2 of Supporting Information), $\hat{\phi}_2^{ScF}$ is

$$\ln(\hat{\phi}_2^{SCF}) = \left(\frac{2\sum x_i b_{ij}}{b} - 1\right)(Z-1) - \ln\left(Z\left(1 - \frac{b}{V}\right)\right) - \left[\frac{\Delta}{\sqrt{2}RTb}\right]\ln\left(\frac{1 + (1+\sqrt{2})\frac{b}{V}}{1 + (1-\sqrt{2})\frac{b}{V}}\right) \quad (3)$$

where

$$\Delta = \left[\frac{G}{2} - \frac{G(\sum x_i b_{ij})}{b} + (\sum x_i a_{ij})\left(1 - \sqrt{\frac{RTc}{a}}\right) + (\sum x_i c_{ij})\left(RT - \sqrt{\frac{RTc}{a}}\right)\right]$$

$$G = a + cRT - 2\sqrt{acRT}$$

Equations 2 and 3 are used in eq 1 to determine the solubilities by the models and are compared with the experimental data. The critical temperature, critical pressure, and acentric factor of *n*-(4-ethoxyphenyl)ethanamide were estimated by the group contribution techniques,[28−30] where the properties are estimated from the molecular structure of the compound. The sublimation pressure was obtained using the formula, $\ln(p_2^{sub}/Pa) = A - (B)/(T/K)$, wherein the constants *A* and *B* were obtained from Perlovich et al.[6] Table 2 shows the estimated critical and thermophysical properties of *n*-(4-ethoxyphenyl)ethanamide.

The optimization procedure reduces the absolute averaged relative deviation percentage, AARD (%). It is defined as $(100/N_i)\sum_{i=1}^{N_i}(|y_2^{cal} - y_2^{exp}|/y_2^{exp})$ where N_i is number of data points, y_2 represents the molar solubility of the solute, and the superscripts cal and exp denote the calculated and experimental values, respectively. The correlation of the experimental solubility data requires an optimization process. The Nelder-Mead simplex algorithm, implemented in Matlab 6.1, was used to determine the interaction parameters.[23] Table 3 shows the values of interaction parameters. The model correlations based on PR EOS with classical van der Waals mixing rules are shown as dashed lines in Figure 2a, while model correlations based on PR EOS with the Valderrama modification of Kwak and Mansoori mixing rules are shown as solid lines in Figure 2a.

Density-Based Models. Three density-based models, namely, models by Bartle et al.,[24] Méndez-Santiago−Teja,[25] and the reformulated Chrastil[26] model, were also used to correlate the experimental data. The discussion related to the Bartle et al. model and the reformulated Chrastil model can be found in Appendix A3 (see Supporting Information). The correlations to the experimental data based on these models are shown in Figures S3a and S3b (see Supporting Information).

Table 3. Correlation Parameters for Solubilities of *n*-(4-Ethoxyphenyl)ethanamide in $SCCO_2$ Using Various Models

model	*T*/K	correlation parameters		ARD (%)
PR EOS with temperature-dependent mixing rules	308	$k_{ij} = -0.335$	$l_{ij} = -0.623$	5.12
	318	$k_{ij} = -0.308$	$l_{ij} = -0.576$	4.39
	328	$k_{ij} = -0.400$	$l_{ij} = -0.831$	10.68
PR EOS with temperature-independent mixing rules		$k_{ij} = -0.61$; $l_{ij} = -0.79$; $m_{ij} = 0.010$		6.28
Bartle et al. model		$M = 15.62$; $O = 0.007$; $N = -6806.7$		8.91
Mendenz-Santiago and Teja model		$A = -8581$; $B = 104\,300$; $C = 15.97$		7.87
reformulated Chrastil model		$K = 4.57$; $\alpha = -3276.89$; $\beta = -21.95$		6.81

Méndez-Santiago and Teja Model.[26] It is based on the theory of dilute solutions and relates the solubility of a solid, y_2 (in mole fraction), with the density of $SCCO_2$ (mol·mL^{-1}).

$$(T/\mathrm{K})\ln\left(\frac{y_2 p}{p_{\mathrm{ref}}}\right) = A/\mathrm{K} + (B/\mathrm{K}\cdot\mathrm{mL}\cdot\mathrm{mol}^{-1})(\rho/\mathrm{mol}\cdot\mathrm{mL}^{-1}) + C(T/\mathrm{K}) \quad (4)$$

where *A*, *B*, and *C* are temperature-independent constants. The density of supercritical carbon dioxide was determined from the Span and Wagner EOS.[31]

These constants are obtained by correlating the experimental data with eqs 4, A10, and A11 (see Supporting Information) and are shown in Table 3 along with the AARD (%). The data consistency is verified by the Méndez-Santiago and Teja model wherein experimental data at different temperatures collapse onto a single straight line. Figure 2b shows the model correlation along with experimental data, and this indicates that the experimental data is consistent.

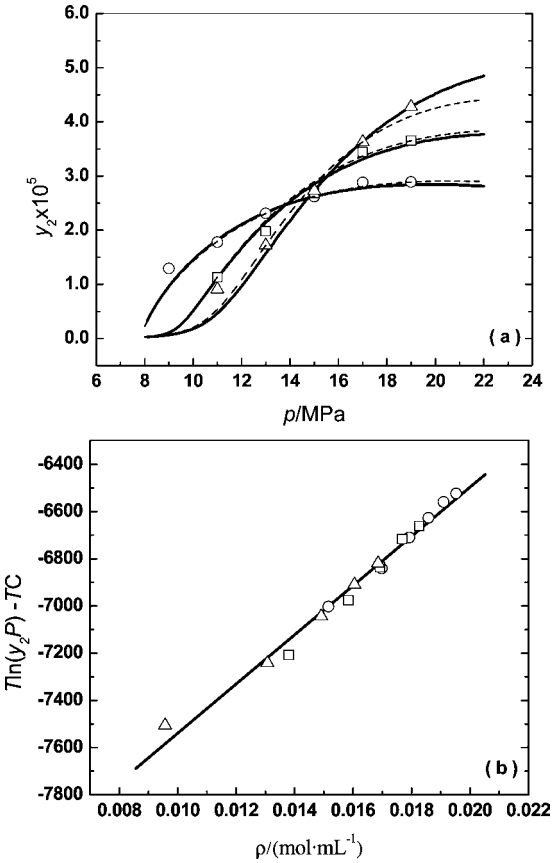

Figure 2. (a) Experimental solubility data of *n*-(4-ethoxyphenyl)ethanamide in $SCCO_2$ (y_2): ○, 308 K; □, 318 K; △, 328 K. The dashed lines are calculated by the PR EOS with temperature-dependent mixing rules; solid lines, calculation by the PR EOS with temperature-independent mixing rules. (b) Experimental solubility data of *n*-(4-ethoxyphenyl)ethanamide in $SCCO_2$ (y_2): ○, 308 K; □, 318 K; △, 328 K; solid lines, calculation based on the Méndez-Santiago and Teja model.

Conclusions

The equilibrium solubility of *n*-(4-ethoxyphenyl)ethanamide in $SCCO_2$ was measured by the saturation method in the pressure range from (9.0 to 19.0) MPa at (308, 318, and 328) K. The mole fraction of *n*-(4-ethoxyphenyl)ethanamide ranges from (0.91 to 4.28)·10^{-5}. Both EOS models and density-based models were successfully used to correlate the experimental data.

Supporting Information Available:

Additional figures and appendices. This material is available free of charge via the Internet at http://pubs.acs.org.

Literature Cited

(1) Elvassore, N.; Kikic, I. *Pharmaceutical processing with supercritical fluids*; Bertucco, A., Vetter, G., Eds.; Elsevier Science: Amsterdam, 2001; pp 612−625.
(2) Dondeti, P.; Desai, Y. *Supercritical fluid technology in pharmaceutical research*; Swarbrick, J., Boylan, J. C., Eds.; Marcel Dekker: New York, 1999; pp 219−248.
(3) Akgerman, A.; Madras, G. *Supercritical fluids: Fundamentals and Applications*; Kiran, E., Sengers, J. M. H. L., Eds.; Kluwer Academic Publishers: Netherlands, 1994; pp 669−695.
(4) McHugh, M. A.; Krukonis, V. J. *Supercritical fluid extraction*; Butterworth: Boston, 1986; pp 1−16.
(5) Subramaniam, B.; Rajewski, R. A.; Snavely, K. Pharmaceutical processing with supercritical carbon dioxide. *J. Pharm. Sci.* **1997**, *86*, 885–890.
(6) Perlovich, G. L.; Volkova, T. V.; Bauer-Brandl, A. Towards an understanding of the molecular mechanism of solvation of drug molecules: A thermodynamic approach by crystal lattice energy, sublimation, and solubility exemplified by paracetamol, acetanilide, and phenacetin. *J. Pharm. Sci.* **2006**, *95*, 2158–2169.
(7) Coimbra, P.; Fernandes, D.; Gill, M. H.; deSousa, H. C. Solubility of diflunisal in supercritical carbon dioxide. *J. Chem. Eng. Data* **2008**, *53*, 1990–1995.
(8) Duarte, A. R. C.; Coimbra, P.; de Sousa, H. C.; Duarte, C. M. M. Solubility of flurbiprofen in supercritical carbon dioxide. *J. Chem. Eng. Data* **2004**, *49*, 449–452.
(9) Stassi, A.; Bettini, R.; Gazzaniga, A.; Giordano, F.; Schiraldi, A. Assessment of solubility of ketoprofen and vanillic acid in supercritical CO_2. *J. Chem. Eng. Data* **2000**, *45*, 161–165.
(10) Macnaughton, S. J.; Kikic, I.; Foster, N. R.; Alessi, P.; Cortesi, A.; Colombo, I. Solubility of anti-inflammatory drugs in supercritical carbon dioxide. *J. Chem. Eng. Data* **1996**, *41*, 1083–1086.
(11) Ting, S. S. T.; Macnaughton, S. J.; Tomasko, D. L.; Foster, N. R. Solubility of naproxen in supercritical carbon dioxide with and without cosolvents. *Ind. Eng. Chem. Res.* **1993**, *32*, 1471–1481.
(12) Charoenchaitrakool, M.; Dehghani, F.; Foster, N. R.; Chan, H. K. Micronization by rapid expansion of supercritical solutions to enhance the dissolution rates of poorly water-soluble pharmaceuticals. *Ind. Eng. Chem. Res.* **2000**, *39*, 4794–4802.
(13) Huang, Z.; Lu, W. D.; Kawi, S.; Chiew, Y. C. Solubility of aspirin in supercritical carbon dioxide with and without acetone. *J. Chem. Eng. Data* **2004**, *49*, 1323–1327.
(14) Coimbra, P.; Fernandes, D.; Gill, M. H.; deSousa, H. C. Solubility of diflunisal in supercritical carbon dioxide. *J. Chem. Eng. Data* **2008**, *53*, 1990–1995.
(15) Aim, K.; Fermeglia, M. *The experimental determination of solubilities*; Hefter, G. T., Tomkins, R. P. T., Eds.; Wiley: New York, 2002; pp 491−553.

(16) Garlapati, C.; Madras, G. Solubilities of dodecanoic and tetradecanoic acids in supercritical CO_2 with and without entrainers. *J. Chem. Eng. Data* **2008**, *53*, 2637–2641.
(17) Garlapati, C.; Madras, G. Solubilities of hexadecanoic and octadecanoic acids in supercritical CO_2 with and without cosolvents. *J. Chem. Eng. Data* **2008**, *53*, 2913–2917.
(18) Tsekhanskaya, Y. V.; Iomtev, M. B.; Mushkina, E. V. Solubility of naphthalene in ethylene and carbon dioxide under pressure. *Russ. J. Phys. Chem.* **1964**, *38*, 1173–1176.
(19) Peng, D. Y.; Robinson, D. B. A new two-constant equation of state. *Ind. Eng. Chem. Fundam.* **1976**, *15*, 59–64.
(20) Kwak, T. Y.; Mansoori, G. A. van der Waals mixing rules for cubic equations of state - applications for supercritical fluid extraction modelling. *Chem. Eng. Sci.* **1985**, *41*, 1303–1309.
(21) Valderrama, J. O. The state of the cubic equations of state. *Ind. Eng. Chem. Res.* **2003**, *42*, 1603–1618.
(22) Valderrama, J. O.; Alvarez, A. H. Temperature independent mixing rules to correlate the solubility of solids in supercritical carbon dioxide. *J. Supercrit. Fluids* **2004**, *32*, 37–46.
(23) Garlapati, C.; Madras, G. Temperature independent mixing rules to correlate the solubilities of antibiotics and anti-inflammatory drugs in $SCCO_2$. *Thermochim. Acta* **2009**, DOI: 10.1016/j.tca.2009.06.022.
(24) Bartle, K. D.; Clifford, A. A.; Jafar, S. A.; Shilstone, G. F. Solubilities of solids and liquids of low volatility in supercritical carbon dioxide. *J. Phys. Chem. Ref. Data* **1991**, *20*, 713–756.
(25) Garlapati, C.; Madras, G. Solubilities of solids in supercritical fluids using dimensionally consistent modified solvate complex models. *Fluid Phase Equilib.* **2009**, *283*, 97–101.
(26) Mendez-Santiago, J.; Teja, A. S. The solubility of solids in supercritical fluid. *Fluid Phase Equilib.* **1999**, *158*, 501–510.
(27) Brennecke, J. F.; Eckert, C. E. Phase equilibria for supercritical fluid process design. *AIChE J.* **1989**, *35*, 1409–1427.
(28) Joback, K. G.; Reid, R. C. Estimation of pure-component properties from group-contributions. *Chem. Eng. Commun.* **1987**, *57*, 233–243.
(29) Reid, R. C.; Prausnitz, J. M.; Poling, B. E. *The properties of gases and liquids*; McGraw-Hill: New York, 1988; pp 14−15.
(30) Lyman, W. J.; Reehl, W. F.; Rosenblatt, D. H. *Handbook of chemical property estimation methods*; McGraw-Hill: New York, 1982; pp 16−20.
(31) Span, R.; Wagner, W. A new equation of state for carbon dioxide covering the fluid region from the triple-point temperature to 1100 K at pressures up to 800 MPa. *J. Phys. Chem. Ref. Data* **1996**, *25*, 1509–1596.

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