Solubility of Aspirin in Supercritical Carbon Dioxide with and without Acetone

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The equilibrium solubility of aspirin in supercritical CO_2 has been determined using a dynamic method. Measurements were performed at pressures ranging from (10 to 25) MPa and temperatures from (308.15 to 328.15) K. The effect of a polar cosolvent, acetone, on the solubility of aspirin in supercritical carbon dioxide was also studied. The results show that the addition of acetone produces up to a 5-fold increase in the aspirin solubility. The solubility of aspirin in CO_2 is well described by the Peng−Robinson equation of state and density based correlations over the pressure and temperature ranges studied.

Introduction

Supercritical fluid (SCF) extraction is a practical separation technology that has received a great deal of attention and can potentially be used for purification and crystallization of thermally labile, nonvolatile pharmaceuticals and foods. Since the solvent strength increases with the density of solvent, solubilities of dissolved solutes change markedly in the near critical region with small changes in temperature and pressure. Knowledge of solute solubility is essential for efficiently designing supercritical fluid processes such as micronization of drug particles to improve the dissolution properties and enhance bioactivity. Among the factors responsible for the limited acceptance of SCF extraction processes and other SCF technologies, the insufficiency of supercritical solubility data has been frequently cited.[1−4]

Because carbon dioxide is environmentally benign, nonflammable, nontoxic, and inexpensive and has a relatively low critical pressure and critical temperature, it is one of the most commonly used solvents for supercritical fluid extraction. Carbon dioxide, however, has the limitation that it is not a particularly good solvent for polar organic compounds, owing to its lack of polarity and lack of capacity for specific solvent−solute interactions. It is known that the addition of a small amount of polar cosolvent to supercritical CO_2 can dramatically increase its power to dissolve polar organic compounds. To date, there are a number of studies on the solubility of polar organic solids in supercritical carbon dioxide in the presence of a polar cosolvent.[5−8] These studies show that a small amount of cosolvent leads to significant solubility enhancement in supercritical carbon dioxide.

In this study, we investigate the solubility of aspirin in supercritical carbon dioxide in the presence of a cosolvent, acetone, in different temperature and pressure ranges. Aspirin is a very common pain-killer drug, and its chemical structure is shown in Figure 1. It has two polar groups (−COOH and CH_3COO−) ortho-binding on the benzene skeleton, thus resulting in a dipole moment of 4.36 D.[9] Acetone is a hydrogen bond acceptor with a dipole moment of 2.76 D.[9] Hence, aspirin is expected to interact strongly with acetone, leading to enhanced solubility. To the best of our knowledge, besides the work of Tavana and Randolph,[10] who measured the solubility of aspirin in supercritical carbon dioxide at 318.15 K, aspirin solubility in CO_2 has not been reported in the literature. This investigation will re-examine the published solubility data and also supplement existing data by providing aspirin solubility data at (308.15 and 328.15) K in pure supercritical CO_2 and at (318.15 and 328.15) K in CO_2 + acetone. The measured solubilities are correlated using empirical density based correlations and the Peng−Robinson equation of state.

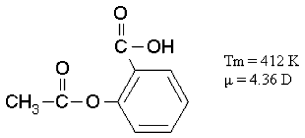

Figure 1. Chemical structure of aspirin (dipole moment is taken from ref 9).

Experimental Section

Materials. The compounds used in this study were purchased from commercial suppliers: aspirin (Sigma Chemicals, USA, USP grade, >99.5%), carbon dioxide (Soxal, Singapore, >99.8%), and acetone (Tedia Company Inc., USA, HPLC/Spectro grade, 99.97%). They were used as received without further purification.

Experimental Procedure. (1) Binary Systems (Carbon dioxide/Aspirin). The solubility of aspirin in supercritical carbon dioxide was measured using a continuous flow technique. A schematic of the apparatus used is shown in Figure 2. Briefly, it consists of a CO_2 cylinder, a cosolvent reservoir, two HPLC pumps, an extraction vessel, an oven, a back-pressure-regulator, a solute collector, a wet gas meter, and tubings, valves, and fittings of various types.

High purity carbon dioxide (Soxal, 99.8%), liquefied through a chiller (Polyscience model 911), was fed into an HPLC pump (Jasco, PU-980). Carbon dioxide was pumped, via a 5 m long stainless steel tubing coil (which serves as a preheater to allow the CO_2 to reach the desired super-

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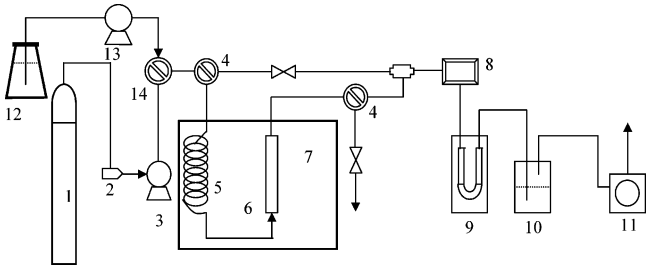

Figure 2. Schematic of the experimental apparatus used in measuring the solubility in the supercritical fluid: (1) CO_2 cylinder; (2) circulating freezer; (3) HPLC pump; (4) switching valve; (5) premixing coil; (6) equilibrium vessel; (7) oven; (8) back-pressure-regulator; (9) collection U-tube; (10) saturator; (11) wet gas meter; (12) cosolvent flask; (13) HPLC pump; (14) switching valve.

critical conditions and to ensure that complete mixing of carbon dioxide and cosolvent is achieved), into a 10 mL extraction vessel (Jasco EV-2). Both the preheating coil and the vessel were placed inside an oven (GL Science, model GC390B, ±0.01 K). The extraction vessel was loaded with alternate layers of aspirin powder (~5 g) and (1.0 to 1.5) mm diameter glass beads. The extraction temperature and pressure were set by the oven (±0.01 K) and the back-pressure-regulator (BPR) (Jasco model 880-01, ±1 bar), respectively. Downstream to the extraction vessel, the saturated CO_2 + aspirin solution was depressurized to ambient conditions through the BPR and aspirin was precipitated in a glass U-tube collector immersed in an ice bath. The gas released was led through a saturator for further pressure reduction, followed by a wet gas meter (Sinagawa, model W-NK-1, ±0.01 L) for volume measurement. To completely recover the solute, precipitated solid upstream to the BPR was flushed out by carbon dioxide at a flow rate of 1 mL/min for at least 30 min. We found that this procedure ensures complete recovery of all precipitated solids between the extractor and the BPR. The collected aspirin (~50 mg per run) was weighed using a balance (Mettler AE200, ±0.01 mg). By means of the measured solute mass and solvent volume, the solubility value was readily obtained.

(2) Ternary Systems (Carbon Dioxide/Aspirin/Acetone). For ternary systems, liquid acetone was directly delivered into the system by a second HPLC pump that was calibrated to accurately introduce the liquid cosolvent by volume (±0.1 μL). Carbon dioxide and the cosolvent were mixed completely before they entered the extraction vessel to dissolve the solute. The solid was collected in the U-tube after the ternary supercritical mixture was depressurized. Acetone, instead of CO_2, was used to rinse the precipitation line in order to recover all dissolved solute. After evaporation, the mass of the solid was obtained gravimetrically. Similar to the case of the binary system, the solubility (in terms of mole fraction) was determined from the total mass of the solute collected and the corresponding volume of carbon dioxide.

Results and Discussion

Binary Solubility. The dynamic flow method used in this study is a well-developed technique that has been shown to produce reliable solubility measurements in supercritical fluids.[6−8,11,12] Measurements were carried out at carbon dioxide (liquid based) flow rates ranging from 0.4 mL/min to 1.0 mL/min. Variation of the flow rate within this range was found to have no effect on the observed solubilities, thereby confirming that equilibrium between the solid phase and the fluid phase was achieved at these flow rates. Hence, the supercritical carbon dioxide solvent leaving the extraction vessel was saturated with the solute and equilibrium between the solid and supercritical phase was achieved.

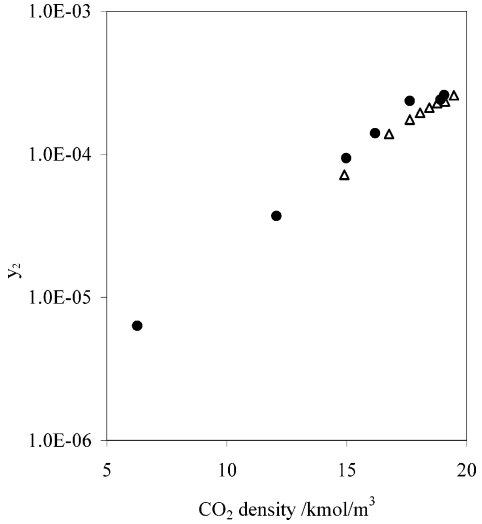

Figure 3. Comparison of aspirin mole fraction solubility between Tavana and Randolph's work (ref 10) and this work at 318.15 K: △, this study; ●, ref 10.

Table 1. Aspirin Mole Fraction Solubility y_2 in Pure Supercritical CO_2

	$10^4\ y_2$		
P/MPa	T/K = 308.15	T/K = 318.15	T/K = 328.15
12.0	0.89	0.72	0.63
15.0	1.12	1.39	1.37
17.2	1.22	1.75	1.82
18.5	1.29	1.95	2.34
20.0	1.33	2.12	2.77
21.5	1.42	2.28	2.86
23.0	1.45	2.34	3.03
25.0	1.51	2.58	3.47

The solubility isotherms of aspirin in pure supercritical CO_2 at 308.15, 318.15, and 328.15 K were measured at pressures ranging from (12 to 25) MPa. Aspirin solubility data at 318.15 K were previously reported by Tavana and Randolph where a similar but relatively rough method was employed.[10] As shown in Figure 3, we observe qualitative agreement between our data and those of Tavana and Randolph; their data, however, are slightly higher than ours. In their study, details of the experimental measurements and accuracy, and the purity of aspirin, were not provided. Hence, it is difficult to make a rigorous comparison of our data with those reported in their work.[10] Our measurements were repeated at least twice with an error within 5%, indicative of the reliability of the method used and the expected accuracy of experimental results obtained. Furthermore, we wish to note that the *o*-hydroxybenzoic acid solubility data obtained by these authors[10] are also systematically higher than those reported by Gurdial and Foster.[13]

The solubility results obtained are presented in Table 1 and shown graphically in Figure 4. The aspirin solubility in supercritical CO_2, as expected, increases with pressure. Temperature affects the solubility in a different way, as evidenced by the presence of a crossover pressure at around 12.5 MPa, as seen in Figure 4. Temperature has an effect via two competing factors: the solvent density and the solute vapor pressure. At pressures lower than the crossover pressure, the density effect is dominant; the solute is

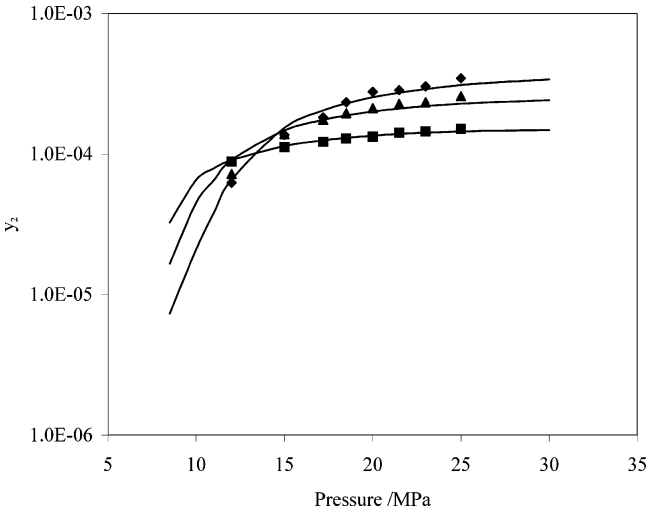

Figure 4. Mole fraction solubility of aspirin in pure supercritical CO_2 correlated with the Peng−Robinson equation of state: ■, 308.15 K; ▲, 318.15 K; ◆, 328.15 K. Solid lines represent calculations from the Peng−Robinson equation of state.

Table 2. Aspirin Mole Fraction Solubility y_2 in Supercritical CO_2 + Acetone[a]

	T = 318.15 K		T = 328.15 K	
P/MPa	$10^3\,y_2$	cosolvent effect	$10^3\,y_2$	cosolvent effect
10.0	0.218		0.113	
12.0	0.337	4.67	0.321	5.13
15.0	0.428	3.08	0.498	3.64
17.2	0.525	3.00	0.612	3.36
20.0	0.615	2.90	0.757	2.73

[a] 3.0 mol % cosolvent composition (solute free basis).

more soluble at low temperature. On the other hand, the volatility effect becomes dominant at pressures higher than 12.5 MPa and the density of the solvent is not as sensitive to the pressure as it is in the low-pressure region; hence, the solubility increases with rising temperature.

Ternary Solubility. In the case of CO_2 + aspirin + acetone, the operating pressures and temperatures were chosen so that the mixture lies in the supercritical fluid region.[8] The solubility of aspirin in supercritical CO_2 with 3.0 mol % acetone was measured at 318.15 K and 328.15 K and is presented in Table 2. The introduction of a cosolvent results in a dramatic increase in the solubility of aspirin in supercritical CO_2. For example, at 15 MPa and 318.15 K, the aspirin mole fraction solubility is 1.39 $\times$ 10^{-4} in pure supercritical CO_2 but increases to 4.28 $\times$ 10^{-4} in supercritical CO_2 + acetone.

To clearly illustrate the solubility enhancement as the result of the introduction of cosolvent, we consider the *cosolvent effect*, which is defined as the ratio of the solute solubility measured in the presence of a cosolvent to that obtained without a cosolvent; that is, *cosolvent effect* = $y_{2,\text{ternary}}/y_{2,\text{binary}}$. The *cosolvent effect* is also included in Table 2. As shown in Table 2, there is a 5-fold increase in aspirin solubility with the addition of 3.0 mol % acetone. There are two possible contributions to the pronounced cosolvent effect. First, after the polar cosolvent acetone is introduced into the system, the bulk density of the fluid mixture generally increases, and this contributes to the solubility enhancement. This density effect is expected to be very limited, leading to a small solubility enhancement approximately proportional to the amount of cosolvent added. Second, the polarity of acetone plays an important role in the cosolvent effect because both aspirin and acetone are polar molecules, as reflected in their dipole moments. Strong attractive polar interactions and hydrogen bonding between them result in enhanced solubility.[14]

The cosolvent effect is observed to decrease with increasing pressure, consistent with other investigations.[4,14−16] This variation of cosolvent effect with pressure is related to the effect of solvent compressibility on the local composition of cosolvent molecules around solute molecules. Yonkers and Smith[15] reported that the local composition of cosolvent around solute molecules decreases with increasing pressure or density. This observation was corroborated by computer simulations,[17] which predict the local composition of organic cosolvent decreases as density (pressure) increases and approaches that of the limit of the bulk composition as pressure increases. Note that the absolute composition of the cosolvent around solute molecules increases, since the bulk density increases.

Modeling Results

Binary Solubility. The solubility of solids in supercritical fluids can be correlated with pressures using the Peng−Robinson equation of state (PR EOS). The physical properties of CO_2 and aspirin, required by the PR EOS, were shown in Table 3. None of the required properties of aspirin, such as critical pressure, critical temperature, vapor pressure, molar volume, and acentric factor, are available in the open literature, and thus, they were estimated through group contribution methods and correlations presented by Lyman et al.[18] The aspirin molar volume is 129.64 cm^3/mol, estimated using Immirzi and Perini's method.[19]

To model solubility data, we use the one-parameter mixing rules which involve the temperature-dependent binary interaction parameter k_{ij} between CO_2 and aspirin. For each isotherm, we obtain the value of k_{ij} by minimizing the percent average absolute relative deviation (% AARD) between the calculated and measured solubilities. The modeling results for aspirin solubility in pure supercritical CO_2 are shown in Table 4. Very good agreement between model calculations and experimentally measured solubility is observed, with an average % AARD not exceeding 6%.

In addition to using the PR EOS, the solubility data can be correlated to the density of the supercritical solvent.[20] By assuming chemical association equilibrium between the solute and the compressed gas, Chrastil derived the following equation relating solute solubility y_2 and solvent density ρ[21]

$$\ln y_2 = a_0 + a_1 \ln \rho + a_2/T \qquad (1)$$

where the parameters a_0, a_1, and a_2 are determined through data regression. Another density model proposed by Kumar and Johnston has also been used in the litera-

Table 3. Physical Properties of Substances Used in This Study

					P^{sat}/Pa[18]		
compound	M_W	T_c/K	P_c/MPa	ω	T = 308.15 K	T = 318.15 K	T = 328.15 K
CO_2	44.02	304.2	7.38	0.225[25]			
aspirin	180.16	762.9[18]	3.28[18]	0.817[18]	0.09021	0.2803	0.8011
acetone	58.08	508.1	4.70	0.309[25]			

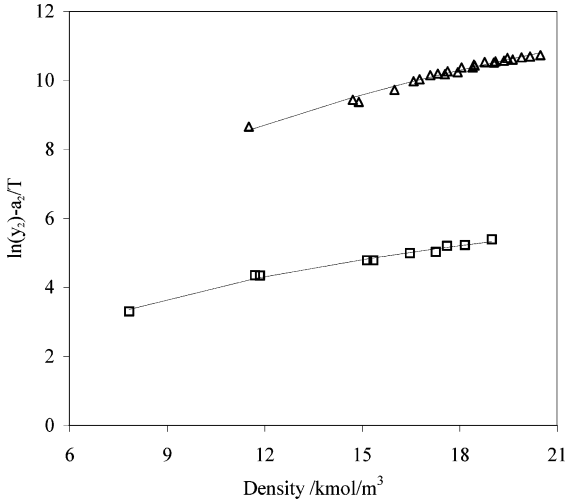

Figure 5. Aspirin solubility in binary and ternary systems correlated with the Kumar and Johnston model: △, binary CO_2 + aspirin system; □, CO_2 + aspirin + acetone system. Solid lines represent correlations using the Kumar and Johnston model.

Table 4. Modeling Results for Aspirin Solubility Obtained Using the Peng−Robinson EOS

	CO_2 (1) + aspirin(2)		CO_2 (1) + aspirin (2) + acetone (3)		
T/K	k_{12}	% AARD	k_{13}	k_{23}	% AARD
308.15	0.2088	2.24			
318.15	0.2056	8.19	0.0037	−0.3209	3.12
328.15	0.2062	7.45	0.0037	−0.3849	8.48
average		5.96			5.81

ture.[22] In this model, we have

$$\ln y_2 = c_0 + c_1\rho + c_2/T \qquad (2)$$

Again, the parameters c_0, c_1, and c_2 are obtained by fitting the correlation to experimental data.

The correlated parameters and %AARD of aspirin solubility with these two density based models are tabulated in Table 5. Both models perform very well with an % AARD of 5.0 for the Chrastil model and 5.6 for the Kumar and Johnston model. It must be noted that the units of solubility and density are mole fraction and moles per cubic meter, respectively. Correlations obtained using the Kumar and Johnston model are plotted as $\ln y_2 - a_2/T$ versus ρ. This treatment cancels the temperature effect and results in a straight line, as shown in Figure 5. A comparison of Table 4 and Table 5 shows that the results correlated with empirical density models (Chrastil model and Kumar and Johnston model) are comparable to those obtained with the PR EOS.

Ternary Solubility. The ternary solubility data are depicted in Figure 6, along with calculations from the Peng−Robinson equation of state. As seen from the figure, the effect of pressure or temperature on the ternary aspirin solubility is similar to that observed in binary systems. To correlate the ternary solubility with the PR EOS model, three interaction parameters, that is, k_{12}, k_{13}, and k_{23}, are required. The parameter k_{12} was available and had been

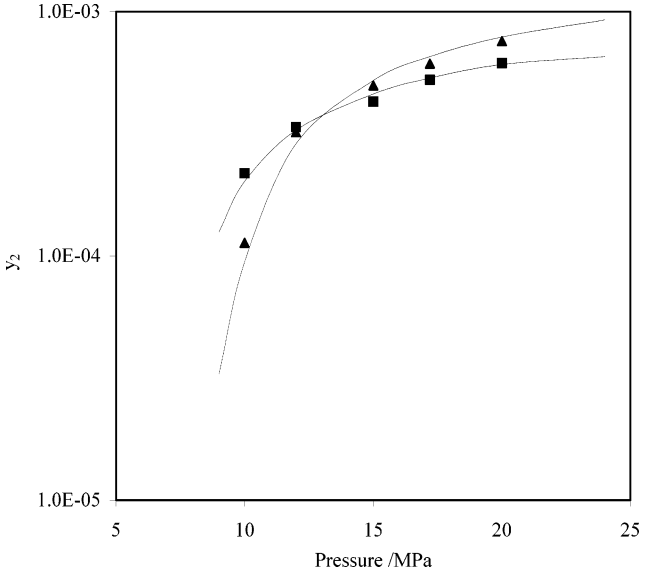

Figure 6. PR EOS correlation of aspirin mole fraction solubility in supercritical CO_2 with acetone as a cosolvent: ■, 318.15 K; ▲, 328.15 K. Solid lines represent correlations of the Peng−Robinson equation of state.

previously obtained from the CO_2 (1) + aspirin (2) binary system. The parameter k_{13} was independently obtained from the correlation of the CO_2 (1) + acetone (3) vapor−liquid equilibrium data[23] to the PR EOS. The interaction parameters k_{23} between aspirin (2) and methanol (3) at different temperatures are obtained by regressing the PR EOS predictions against experimental data. As shown in Table 5, the regressed values of k_{23} for the ternary systems were unusually negative, indicating that strong associating interactions occur between aspirin and acetone, consistent with greatly enhanced aspirin solubility.

Additionally, the density based correlations, that is, eqs 1 and 2, are extended to model the cosolvent enhanced aspirin solubility. For the sake of simplicity, we estimate the solvent mixture density with the simple additive rule, that is, 97% of the pure CO_2 density[20] and 3.0% of the liquid acetone density.[24] The correlated results are also included in Table 4. The %AARD values obtained are 5.4 and 7.8 for the Chrastil model and the Kumar and Johnston model, respectively. The Kumar and Johnston correlation of aspirin ternary solubility is plotted in Figure 5, and a linear relationship between $\ln y_2 - a_2/T$ and ρ is obtained.

Conclusion

The solubility behavior of aspirin in pure supercritical CO_2 and acetone + supercritical CO_2 mixtures was investigated at pressures ranging from (10 to 25) MPa and at temperatures ranging from (308.15 to 328.15) K. It was found that, consistent with the cases of other studies, acetone greatly enhanced the solubility of aspirin in supercritical CO_2. The solubility data were well correlated with the one-parameter Peng−Robinson equation of state and empirical density based models.

Table 5. Calculated Regression Parameters and Deviations for Two Density Based Models[a]

	Chrastil model: $\ln y_2 = a_0 + a_1 \ln \rho + a_2/T$					Kumar and Johnston model: $\ln y_2 = c_0 + c_1\rho + c_2/T$				
system	a_0	a_1	a_2/K	% AARD	% rms	c_0	$10^4\,c_1$	c_2/K	% AARD	% rms
aspirin + CO_2	−27.859	3.894	−6017.54	5.02	6.55	6.714	2.49	−6310.23	5.78	6.88
aspirin + CO_2 + acetone	−16.587	2.225	−4066.88	5.42	6.12	2.189	1.71	−4072.89	7.72	10.63

[a] %rms is defined as the percentage root-mean-square deviation.

Acknowledgment

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Literature Cited

(1) McHugh, M. A.; Krukonis, V. J. *Supercritical Fluid Extraction: Principals and Practice*; Butterworth: Boston, 1994.
(2) McNally, M. E. P. Environmental SFE. *Anal. Chem*. **1995**, *67*, A308−315.
(3) Yamini, Y.; Bahramifar, N. Solubility of polycyclic aromatic hydrocarbons in supercritical carbon dioxide. *J. Chem. Eng. Data* **2000**, *45*, 53−56.
(4) Eckert, C. A.; Knutson, B. L.; Debenedetti, P. G. Supercritical fluids as solvents for chemical and materials processing. *Nature* **1996**, *383*, 313−318.
(5) Guan, B.; Liu, Z. M.; Han, B. X.; Yan, H. K. Solubility of Behenic Acid in Supercritical Carbon Dioxide with Ethanol. *J. Supercrit. Fluids* **1999**, *14*, 213−218.
(6) Sovova, H. Solubility of Ferulic Acid in Supercritical Carbon Dioxide with Ethanol as Cosolvent. *J. Chem. Eng. Data* **2001**, *46*, 1255−1257.
(7) Sahle-Demessie, E.; Pillai, U. R.; Junsophonsri, S.; Levien, K. L. Solubility of Organic Biocides in Supercritical CO_2 and CO_2 + Cosolvent Mixtures. *J. Chem. Eng. Data* **2003**, *48*, 541−547.
(8) Huang, Z.; Kawi, S.; Chiew, Y. C. Solubility of Cholesterol and its Esters in Supercritical Carbon Dioxide with and without Cosolvents. *J. Supercrit. Fluids* **2004**, *30*, 25−39.
(9) McClellan, A. L. *Tables of Experimental Dipole Moments*, v. 2; W. H. Freeman: San Francisco, CA, 1974.
(10) Tavana, A.; Randolph, A. D. Isobaric−Isothermal Fractional Crystallization of Organic Solids from Supercritical Fluid Mixtures. *AIChE Symp. Ser., No. 284* **1991**, *87*, 5−15.
(11) Shinoda, T.; Tamura, K. Solubilities of C. I. Disperse Orange 25 and C. I. Disperse Blue 354 in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2003**, *48*, 869−873.
(12) Xing, H. B.; Yang, Y. W.; Su, B. G.; Huang, M.; Ren, Q. L. Solubility of Artemisinin in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2003**, *48*, 330−332.
(13) Gurdial, G. S.; Macnaughton, S. J.; Tomasko, D. L.; Foster, N. R. Influence of Chemical Modifiers on the Solubility of o- and m-Hydroxybenzoic Acid in Supercritical CO_2. *Ind. Eng. Chem. Res.* **1993**, *32*, 1488−1497.
(14) 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.
(15) Yonker, C. R.; Smith, R. D. Solvatochromic behaviour of binary supercritical fluids: the carbon dioixed/2-propanol system. *J. Phys. Chem*. **1988**, *92*, 2374−2378.
(16) Ekart, M. P.; Bennett, K. L.; Ekart, S. M.; Gurdial, G. S.; Liotta, C. L.; Eckert, C. A. Cosolvent interactions in supercritical fluid solutions. *AIChE J*. **1993**, *39*, 235−248.
(17) Lee, K. H.; Sandler, S. I.; Patel, N. C. The generalized van der Waals partition function. III. Local composition models for a mixture of equal size square-well molecules. *Fluid Phase Equilib.* **1986**, *25*, 31−49.
(18) Lyman, W. J.; Reehl, W. F.; Rosenblatt, D. H. *Handbook of Chemical Property Estimation Methods*; McGraw-Hill: New York, 1982.
(19) Immirzi, A.; Perini, B. Prediction of Density in Organic Crystals. *Acta Crystallogr*. **1977**, *A33*, 216−218.
(20) Angus, S.; Armstrong, B.; de Reuck, K. M. *IUPAC International Thermodynamic Tables of the Fluid State (v. 3)-Carbon Dioxide*; Pergamon Press: New York, 1976.
(21) Chrastil, J. Solubility of Solids and Liquids in Supercritical Gases. *J. Phys. Chem*. **1982**, *86*, 3016−3021.
(22) Kumar, S. K.; Johnston, K. P. Modeling the Solubility of Solids in Supercritical Fluids with Density as the Independent Variable. *J. Supercrit. Fluids* **1988**, *1*, 15−22.
(23) Day, C. Y.; Chang, C. J.; Chen, C. Y. Phase Equilibrium of Ethanol + CO_2 and Acetone + CO_2 at Elevated Pressures. *J. Chem. Eng. Data* **1996**, *41*, 839−843.
(24) Gallant, R. W.; Railey, J. M. *Physical Properties of Hydrocarbons*; Gulf Pub. Co.: Houston, TX, 1984.
(25) Rowley, R. J. *Statistical Mechanics for Thermophysical Property Calculations*; Prentice-Hall PTR: Upper Saddle River, NJ, 1994.

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