Solubility of Flurbiprofen in CO_2 and CO_2 + Methanol

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The solubility of (*R*,*S*)-2-(2-fluorobiphenyl-4-yl)propanoic acid (flurbiprofen) in supercritical carbon dioxide and in a mixed solvent consisting of carbon dioxide and methanol at (303.15 and 313.15) K between the pressures of (10.0 and 20.0) MPa is reported. The solubilities were measured using a direct visualization technique. The experimental data is described using the Peng−Robinson equation of state (PR EoS) together with a one-parameter van der Waals mixing rule.

Introduction

Fluids that exist at a pressure and temperature above their respective critical values are termed as supercritical fluids. These fluids have properties that can be tuned to suit desired process requirements and hence have received special attention in the chemical process industry. Supercritical carbon dioxide has received particular attention as it is inexpensive, inert, nonflammable, and benign. It has been used to replace significant amount of organic solvents in processes such as extraction,[1,2] chromatography,[3,4] particle formation,[5] reactions,[6] and so forth.

An important physical property that is crucial for the design of these processes is the solubility of the solute in the supercritical solvent. In several processes, such as in chromatography, owing to the polar nature of the solutes, it is customary to add cosolvents such as alcohols to the nonpolar carbon dioxide. This provides the motivation to measure solubilities not only in pure CO_2 but also in mixed solvents. Our interest in measuring solubilities stems from the need to design preparative supercritical fluid chromatography processes. Preparative chromatography is often performed out at high solute concentrations. The knowledge of the solubility is important to determine the concentration of the solute in the sample that is injected or to determine the feed concentration in continuous processes such as the supercritical fluid simulated moving bed chromatography.[7−9]

In this work, the solubility of (*R*,*S*)-2-(2-fluorobiphenyl-4-yl)propanoic acid (flurbiprofen), a nonsteroidal anti-inflammatory drug (NSAID), in pure CO_2 and in a mixed phase containing CO_2 + methanol is reported. While both enantiomers of flurbiprofen have been shown to possess anti-inflammatory properties, the *R*, compared to the *S* enantiomer, has minor side effects and is hence the desired product.[10] Recently, the isotherm data required for the design and scale-up of a supercritical fluid chromatographic enantioseparation route has been reported.[11] Among three cosolvents screened, namely, methanol, ethanol, and iso-propanol, methanol yielded the best separation and hence was considered for solubility measurements. The solubility was measured using a high pressure view cell apparatus with suitable modifications. The experimental procedure is validated by comparing the measured solubility data with those reported in the literature, and based on this confidence, the measurements for the case of CO_2 + methanol were performed. Finally, the Peng−Robinson equation of state (PR EoS) along with a one-parameter van der Waals mixing rule is used to model the solubility data.

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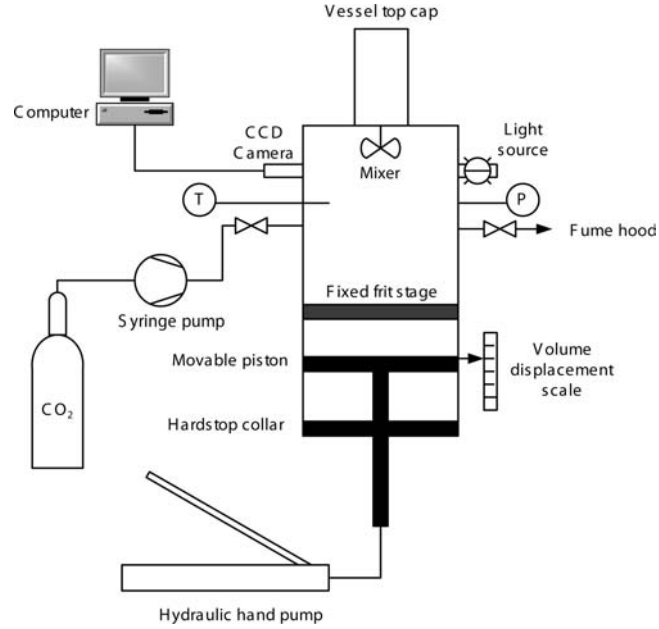

Figure 1. Schematic diagram of experimental setup using the phase monitor.

Experimental Section

Materials. Racemic flurbiprofen, (CAS No. 5104-49-4) with a purity of $w = 0.99$, where w is the weight fraction of flurbiprofen, was purchased from Sigma-Aldrich, Singapore. HPLC grade methanol, (CAS No. 67-56-1) was obtained from Aik Moh Paints and Chemicals, Singapore, and carbon dioxide ($w = 0.998$) was obtained from Singapore Oxygen Air Liquide, Singapore.

Experimental Setup. The experimental setup used for the solubility measurement is shown in Figure 1. The heart of the system is the phase monitor (Thar Technologies, Pittsburgh, PA). The phase monitor consists of a high pressure view cell that can be operated up to a pressure of 20.0 MPa and 423 K. The volume of the cell can be varied using the piston whose position

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can be adjusted by a hydraulic hand pump. The volume displaced by the piston can be read from a scale attached to the unit. The contents of the cell are mixed using a electrical mixer located at the top of the unit. A sapphire window positioned on the wall of view cell allows for the direct visualization of the contents. In this case, a charge-coupled device (CCD) camera was used to observe the state of the cell. A video interface allows the recording of the visuals on a computer. The temperature of the cell was controlled, within ± 1 K, using an electrical thermostat. The temperature and pressure of the fluid phase are measured in situ using a thermocouple and a pressure transducer, respectively. Ports with isolation valves are provided to fill and empty the cell. A syringe pump, ISCO 260D (Teledyne Technologies Company, Lincoln, NE), was used to pump the CO_2 to a desired pressure. The CO_2 in the syringe pump was maintained as a liquid by cooling it to 277 K. Adequate instrumentation is provided to measure pressure and the volume of the syringe pump.

Before the experiments were performed, a calibration was performed to obtain the volume of the vessel at different positions of the piston. The vessel was filled with CO_2, and the initial pressure and temperature were measured. Later, using the hydraulic pump, the volume of the vessel was changed in increments of 1 mL, and the corresponding reading on the system pressure and temperature were noted. From the measured pressure, P, and temperature, T, readings, the density of the fluid, ρ, in the container was calculated using the Span−Wagner equation of state.[12] Since the vessel was a closed system, the change in density was inversely proportional to the volume of the cell. From the known displacements and the measured density the volume of the vessel at full expansion can be calculated. The calibration experiments were repeated thrice, and the volume of the vessel at full expansion was calculated as 19.79 mL ± 2.2 %, which compared nicely with value reported by the manufacturer which was 20 mL. The uncertainty in the volume will hence result in a 2.8 % uncertainty in the measured value of the solubility.

Experimental Procedure. Solubility in Pure CO_2. The top cap was removed to introduce the solid sample in the cell. A certain amount of flurbiprofen was then measured using an analytical balance (accuracy of 0.1 mg) and placed in the cell. The top cap was closed, and CO_2 was introduced through the inlet port while the piston was at the fully expanded state. Simultaneously, the stirrer was started to ensure good mixing in the system. Once the pressure and temperature reached a steady state, the visuals from the CCD camera were inspected. If particulate matter was observed, the piston was raised using the hydraulic pump to increase pressure and was then locked in position by the hard-stop collar. After stirring for about 15 min, values of temperature and corresponding pressure were recorded. The stirrer was then stopped to check if flurbiprofen was completely dissolved. If solid particles could still be observed, the piston was raised again to further increase the pressure. These steps were repeated until all solute was dissolved. The position of the piston was changed gradually around this state, and the pressure interval over which the solubilization was achieved was noted down. For all of the experiments this interval was of the order of 0.5 MPa. At the end of each experiment, the hard-stop collar was released, and the piston was fully expanded. Finally, the mixture was released through the outlet valve into the fume hood; the vessel was cleaned manually, and the procedure was repeated. It is worth noting that this method depends on the manual observation of a vanishing point and hence should be used with caution for materials that are sparingly soluble ($y_2 < 10^{-7}$).

Table 1. Experimentally Measured Solubilities of Flurbiprofen, y_2 and S, in Pure CO_2 at Temperatures T, Pressures P, and Density ρ

T / K	P / MPa	ρ / g·L^{-1}	$10^5\ y_2$	S / g·L^{-1}
303.15	11.80	805.67	3.42	0.15
	16.33	860.29	4.39	0.21
	17.14	867.61	6.02	0.29
	22.12	905.02	6.24	0.31
313.15	10.76	672.89	2.42	0.09
	12.07	719.84	3.95	0.16
	14.06	764.33	6.08	0.26
	15.75	791.35	8.01	0.35
	18.11	820.73	10.24	0.47
	21.14	850.01	14.18	0.67
323.15	11.84	573.84	3.35	0.11
	13.31	648.36	5.26	0.19
	15.54	712.37	7.64	0.30
	16.26	727.26	10.27	0.42
	16.59	733.51	10.67	0.44
	17.53	749.77	12.55	0.53
	19.96	783.77	15.84	0.69

Solubility in CO_2 + Methanol. Unlike the pure CO_2 case, the measurement of solubility in a mixed phase, requires the knowledge of the amount of CO_2 transferred into the phase monitor. Hence, a minor modification in the procedures is required. Initially, a known amount of flurbiprofen and methanol is added to the view cell. The system is then boxed up, and CO_2 is introduced using the syringe pump. Initial and final values of pressure and the volume of the syringe pump were measured from which the amount of CO_2 transferred to the view cell can be determined. Care was taken to account for the CO_2 trapped in the transfer lines. Following this, the determination of the pressure at which flurbiprofen solubilizes is similar to the case of pure CO_2.

Experimental Results

The solubility of flurbiprofen in pure CO_2, y_2 (mole fraction of flurbiprofen in the system) and S (mass of flurbiprofen in a volume of the fluid phase), measured at three temperatures, namely, (303.15, 313.15, and 323.15) K, are reported in Table 1. The measured solubility is plotted in Figure 2 along with the data reported in the literature which was measured using a static method where the mixture at equilibrium is sampled and analyzed externally.[13] As observed in the figure, experimental results collected showed the expected trend, that is, at a particular temperature, solubility increased with increasing density of CO_2. Further, at a given fluid phase density, the solubility increases with increasing temperature. Also from Figure 2b, it can be seen that a crossover point, around 12.0 MPa, is observed when the solubility of flurbiprofen, y_2, is plotted as a function of pressure. This compares well with the observations in the literature.[13] The crossover point is a well-known phenomena in the study of solubility. The solubility of a solute is dependent on the density of the fluid phase and the vapor pressure of the solute. At pressures lower than 12 MPa, the solubility of the solid solute decreases with an increase in temperature. In this region the effect of density on the solubility is predominant, while at pressures above 12 MPa, the effect of vapor pressure is dominant. It can be seen that the data from the present study correlates well with those from the literature at all temperatures. This confirmation provided an important validation of the experimental technique. It is worth noting that the points corresponding to pressures of (16.26 and 16.59) MPa

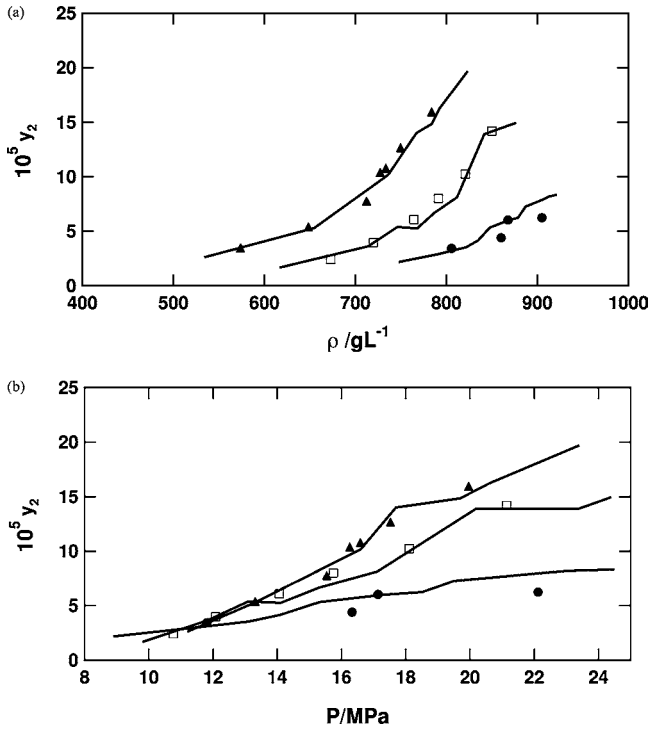

Figure 2. Solubility of flurbiprofen in pure CO_2 as a function of (a) fluid density and (b) pressure. Symbols and lines represent the data measured in this study and those reported in the literature,[13] respectively. Symbols: ●, $T = 303.15$ K; □, $T = 313.15$ K; ▲, $T = 323.15$ K.

at a temperature of 323.15 K were attempts to check the reproducibility. These experiments were conducted after a gap of several days, and they indicate that the experiments are indeed reproducible.

As a next step, it was important to validate the measurement protocol for the solubility in CO_2 + cosolvent. The solubility of flurbiprofen in mixture of CO_2 + ethanol with $y_3 = 0.05$, at 313.15 K and 18.0 MPa, has been reported to be $y_2 = 78.519 \cdot 10^{-5}$.[13] To replicate this experiment, a mixture containing CO_2 + ethanol with $y_3 = 0.0535$ and $y_2 = 81.137 \cdot 10^{-5}$ at 313.15 K was prepared. The solubility of flurbiprofen in this solvent mixture achieved at 18.1 MPa compared well with that reported in the literature and thus provided the necessary validation for the experimental protocol.

The solubility measurements in CO_2 + methanol was performed at (303.15 and 313.15) K for three different nominal compositions of the cosolvent, $y_3 = 0.067$, 0.122, and 0.167. The experimental data are listed in Table 2 and plotted in Figure 3. It can be clearly seen that the trends observed for the case of a solvent containing pure CO_2 are also applicable for the case where a cosolvent was added; that is, at a given density and modifier composition, the solubility increases with increasing temperature. Further, at a fixed density and temperature, the solubility increased with increasing cosolvent composition. The enhancement factor, E, defined as:

$$E = \frac{y_2|_{\text{with cosolvent}}}{y_2|_{\text{without cosolvent}}} \tag{1}$$

is often used to quantify the effect of cosolvent addition. In the present case, the enhancement factor is plotted as a function of cosolvent composition in Figure 4. As can be seen, the enhancement factor increases exponentially with modifier composition.

Table 2. Experimentally Measured Solubilities of Flurbiprofen, y_2 and S, in CO_2 + Methanol at Temperatures T, Pressures P, Modifier Mole Fraction y_3, and Density ρ

T	y_3		P	ρ		S
K	nominal	actual	MPa	g·L^{-1}	$10^5\ y_2$	g·L^{-1}
303.15	0.0670	0.0656	10.03	842.5	22.3	1.06
		0.0637	12.55	870.5	26.3	1.30
		0.0669	16.81	912.2	38.7	2.00
		0.0656	22.55	951.9	43.6	2.35
		0.0707	24.07	962.6	50.3	2.74
	0.1220	0.1208	11.87	904.9	66.9	3.48
		0.1198	13.65	916.8	79.2	4.17
		0.1243	17.13	939.4	93.1	5.03
		0.1224	18.70	947.4	98.5	5.37
		0.1238	19.86	953.7	107.9	5.92
	0.1670	0.1689	11.07	925.3	851.2	46.25
		0.1697	13.18	936.8	908.7	50.03
		0.1646	14.02	940.1	945.0	52.15
		0.1684	15.34	947.8	1031.8	57.52
		0.1627	20.33	968.6	1064.6	60.58
313.15	0.0670	0.0656	9.19	740.1	22.3	0.93
		0.0637	11.66	785.5	26.3	1.17
		0.0669	15.16	837.2	38.7	1.83
		0.0656	16.83	854.3	43.6	2.11
		0.0707	18.97	878.3	50.3	2.50
	0.1220	0.1208	10.82	838.5	66.9	3.22
		0.1198	11.57	845.3	79.2	3.84
		0.1243	13.43	865.4	93.1	4.63
		0.1224	14.91	876.1	98.5	4.96
		0.1238	16.29	887.2	107.9	5.51
	0.1670	0.1689	10.62	874.5	851.2	43.71
		0.1697	12.05	885.0	908.7	47.26
		0.1646	12.87	888.5	945.0	49.29
		0.1684	14.24	899.1	1031.8	54.57
		0.1627	17.33	915.0	1064.6	57.22

Modeling

There are several models suggested for describing the solubility of solids in supercritical fluids.[13,14] In this work, we use the PR EoS, with a one-parameter van der Waals mixing rule. In this formalism, the solubility, expressed in the mole fraction of the solute, y_2, at a particular pressure and temperature is given by:

$$y_{2,\text{calc}} = \frac{p_v(T)}{P} \frac{\Phi_2^{\text{solid}} \exp\left[\frac{V_m}{RT}(P - p_v(T))\right]}{\Phi_2^{\text{SCF}}} \tag{2}$$

where V_m is the molar volume of the pure solid, R is the universal gas constant, and Φ_2^{solid} is the fugacity of the solid at its vapor pressure, $p_v(T)$. The fugacity coefficient of the solid in the supercritical fluid phase, Φ_2^{SCF} can be obtained using:

$$\ln \Phi_2^{\text{SCF}} = \ln\left(\frac{RT}{P(V-b)}\right) + \frac{b_2}{b}\left(\frac{PV}{RT} - 1\right) - \frac{a}{2\sqrt{2}RTb} \cdot \left(\frac{2\sum_j y_j a_{ij}}{a} - \frac{b_i}{b}\right) \ln\left(\frac{V + (1+\sqrt{2})b}{V + (1-\sqrt{2})b}\right) \tag{3}$$

where a and b are the parameters in the PR EoS and V is the molar volume of the fluid. The other equations describing the PR EoS and the mixing rules are given in Table 3.

The critical properties, acentric factors, and molar volume of CO_2, flurbiprofen, and methanol are given in Table 4. For the one-parameter van der Waals mixing rule, the three temperature dependent binary interaction parameters, namely, k_{12}, k_{13}, and k_{23}, are treated as adjustable variables. The interaction parameter, k_{13}, that characterizes the interaction between CO_2 (1) and methanol (3), was obtained from litera-

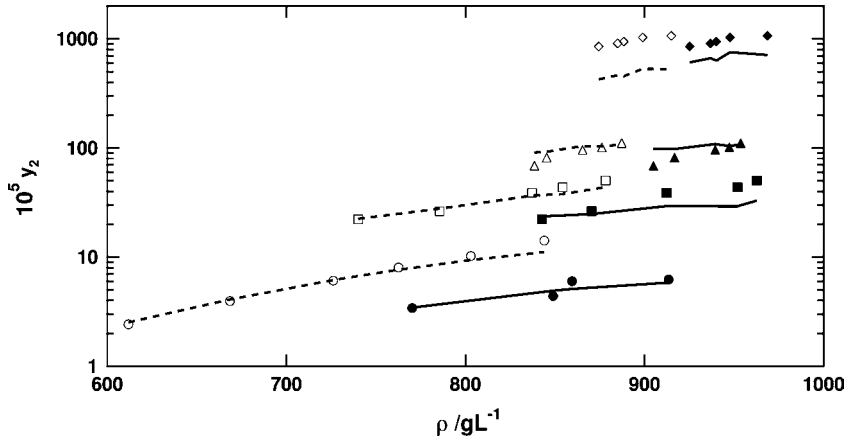

Figure 3. Solubility of flurbiprofen in pure CO_2 + methanol. Closed and open symbols represent the data measured at (303.15 and 313.15) K, respectively. The solid and dashed lines correspond to the calculated solubilities using the PR EoS at (303.15 and 313.15) K, respectively. Symbols: ○, $y_3 = 0.0$; □, $y_3 = 0.067$; △, $y_3 = 0.122$; ▽, $y_3 = 0.167$.

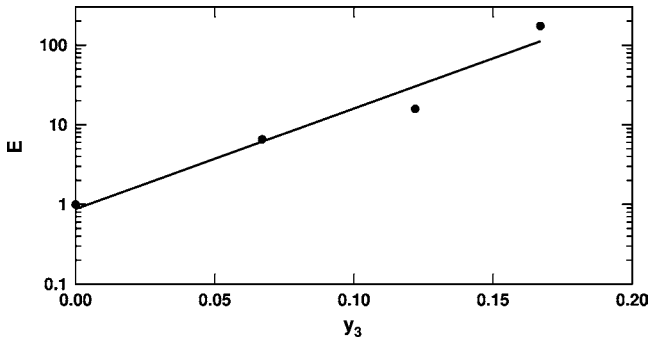

Figure 4. Enhancement factor as a function of cosolvent composition at 303.15 K and 18.0 MPa. At conditions where no experimental data was available, the values were obtained by linear interpolation. The line represents the best fit of an exponential function.

Table 3. Equations Describing the PR EoS and the One-Parameter van der Waals Mixing Rule

PR EoS

$$P = \frac{RT}{V - b} - \frac{a(T)}{V(V + b) + b(V - b)}$$

$$a_i = \frac{0.4572R^2T_{c,i}^2}{P_{c,i}}\left[1 + K_i\left(1 - \sqrt{\frac{T}{T_{c,i}}}\right)\right]^2$$

$$K_i = 0.37464 + 1.5422\omega_i - 0.26992\omega_i^2$$

$$b_i = \frac{0.07780RT_{c,i}}{P_{c,i}}$$

van der Waals mixing rule

$$a = \sum_i \sum_j y_i y_j a_{ij};\ a_{ij} = \sqrt{a_i a_j}(1 - k_{ij})$$

$$b = \sum_i \sum_j y_i y_j b_{ij};\ b_{ij} = (b_i + b_j)/2$$

ture.[15] The value of k_{12}, characterizing the interaction between CO_2 (1) and flurbiprofen (2), was fitted to the experimental data

Table 4. Critical Pressure, $P_{c,i}$, Temperature, $T_{c,i}$, and Acentric Factors, ω_i, for the Substances Used in the Experiments

component	$P_{c,i}$/MPa	$T_{c,i}$/K	ω_i
carbon dioxide (1)	7.380	304.15	0.225
flurbiprofen (2)	2.401	830.40	0.967
methanol (3)	8.091	512.60	0.556

Table 5. Values of the Temperature Dependent Binary Interaction Parameters, k_{ij}

T/K	k_{13}	k_{12}	AARD for k_{12}/%	k_{23}	AARD for k_{23}/%
303.15	0.05506	0.1530	8.79	−0.0528	19.04
313.15	0.06800	0.1417	4.55	0.0093	18.52
323.15		0.1304	8.99		

reported in Table 1 by minimizing the average absolute relative deviation (AARD) which is defined as:

$$\text{AARD} = \frac{100}{N_{exp}} \sum_{i=1}^{N_{exp}} \frac{|y_{2,calc} - y_{2,exp}|}{y_{2,exp}} \quad (4)$$

where $y_{2,exp}$ and $y_{2,calc}$ denote the experimental and calculated values of solubility, respectively, and N_{exp} represents the number of experiments considered. For the parameter estimation, an in-built Matlab optimization algorithm *fmincon* was used. The values of k_{12} obtained in this fashion are listed in Table 5 and compared well with those reported in the literature.[16] Finally, the value of k_{23}, that denotes the interaction between flurbiprofen (2) and methanol (3), was obtained by minimizing the AARD for experiments listed in Table 2. For these calculations, the values of k_{12} and k_{13} as listed in Table 5 were retained. The regressed values given in Table 5 show that, at 313.15 K, k_{23} shows a negative value indicating strong interaction between the two species. The comparison of the measured and calculated values of solubilities is shown in Figure 3. It can be seen that while the match is very good at lower cosolvent compositions, the match at highest modifier composition is rather modest. However, it is worth noting that a simple model such as the PR EoS along with a one-parameter van der Waals mixing rule can be used to estimate solubilities over a wide range of modifier composition. For higher values of modifier composition, more sophisticated equations of state may be necessary.[17]

Conclusions

The solubility of a NSAID drug, flurbiprofen, in both pure CO_2 and CO_2 + methanol was measured at conditions that have practical significance. The measurement technique based on direct visualization was validated using independent measure-

ments reported in the literature. The PR EoS together with a single-parameter van der Waals mixing rule was used to describe the solubilities.

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