The Solubility of Benzocaine, Lidocaine, and Procaine in Liquid and Supercritical Carbon Dioxide

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The solubility of three local anesthetics (benzocaine, lidocaine, and procaine) was measured in liquid and supercritical carbon dioxide at (298, 308, and 318) K and at pressures between (70 and 280) bar. The solubilites were experimentally measured by observing the cloud point using a variable-volume stirred vessel with visual access. Interestingly, although the three anesthetics were structurally very similar, the solubilites of lidocaine and benzocaine were strong functions of only density while that of procaine was a function of both density and temperature. The Peng−Robinson equation of state did not adequately predict the solubilites, while a simple enhancement factor correlation did predict them. The hydrochlorides of lidocaine and procaine did not have any measurable solubility in carbon dioxide over the conditions tested.

Introduction

Compressed carbon dioxide is environmentally benign, nonflammable, inexpensive, and basically inert, making it an ideal solvent for a variety of applications. Carbon dioxide also has a low critical temperature (304 K) and pressure (74 bar) allowing for easy access to the supercritical region. Because of these favorable properties combined with its low viscosity, high diffusivity, and liquidlike densities, carbon dioxide has found many uses in the food[1] and pharmaceutical[2] fields where its nontoxic nature is essential. For example, carbon dioxide has been used for the extraction and separation of natural materials,[1,3−6] for the recrystallization and particle formation of drugs,[2,7] for the formation of sustained drug delivery devices,[7−9] and as an environmentally friendly solvent replacement for pharmaceutical synthesis[10] and enzymatic catalysis.[11] Although a seemingly ideal solvent, the fact that many compounds often have low and unpredictable solubilities in carbon dioxide makes the experimental investigation of solubilities extremely important.

The basis for this solubility study is the future use of liquid and supercritical carbon dioxide to dissolve local anesthetics and then transport them into biodegradable polymeric sutures. Carbon dioxide has already been shown to be an excellent swelling agent for many polymers.[12] Local anesthetics can be divided into two broad categories referred to as ester types and amide types. The type refers to the functional group that connects a benzene ring to a tertiary amine structure. The two most common ester types, benzocaine and procaine, and the most common amide type, lidocaine, are investigated in the free base and hydrochloride salt form. Hydrochloride salts are routinely used to enhance water solubility. Figure 1 shows the free-base structures.

Before creation and optimization of the drug delivery process can take place, the solubilities of the solid anesthetics as a function of the temperature and pressure of carbon dioxide must be known. The solubilities of solids in carbon dioxide generally increase as the pressure increases. However, the degree of increase and the magnitude of the dissolving power of carbon dioxide varies significantly from component to component and is not often predictable. Furthermore, the effect of temperature (at fixed pressure) is not always the same for each compound, and solubility increases with increasing temperature for some compounds and decreases with increasing temperature for others.

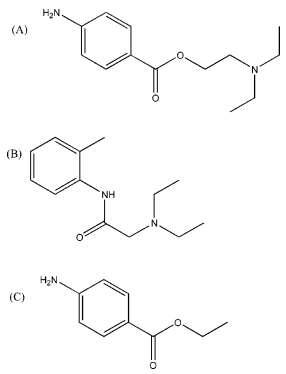

Figure 1. The structures of: A, procaine ($C_{13}H_{20}N_2O_2$); B, lidocaine ($C_{14}H_{22}N_2O$); and C, benzocaine ($C_9H_{11}NO_2$).

Many attempts have been made to model the solubilities of solids such as pharmaceutical compounds in carbon dioxide. Most popular are the use of empirical correlations, which are usually a function of the system density,[13−17] and the use of an equation of state for the binary mixture. The equation of state used most frequently for the prediction the solubilities of low volatile compounds in high-pressure carbon dioxide is the Peng−Robinson equation of state.[18,19] It is difficult to predict which models work well for specific compounds and usually a vast amount of experimental data is required to verify the accuracy of selected models. It is also important to note that some solubility data is usually required to fit model parameters and pure drug properties such as the critical temperature, critical pressure, ascentric factor, and sublimation pressure are also required. Usually these properties are not known. Attempts have been made

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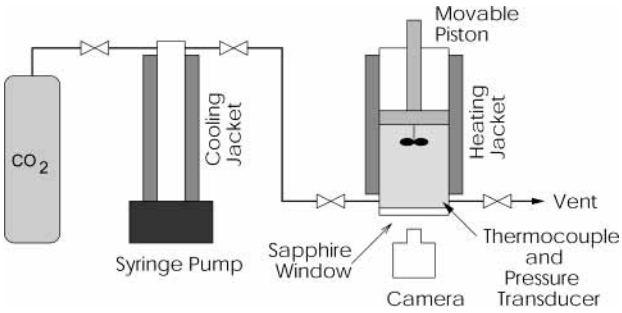

Figure 2. Schematic of phase equilibrium apparatus.

to use group contribution theory[20,21] as well as fusion properties[22] to obtain the desired values. It is often believed that errors in these estimated properties do not allow for adequate modeling of the solubility. Therefore, until better predictive methods are developed, it is best to obtain experimental data of the solubilites of compounds of interest as a function of temperature and pressure and use the experimental data to verify models.

Experimental Section

Materials. Research-grade-5 carbon dioxide with a purity of 99.999% was supplied by BOC Gases. Lidocaine (>98% purity), benzocaine (>99% purity), lidocaine hydrochloride (>99% purity), and procaine hydrochloride (>99% purity) were supplied by Sigma−Aldrich. Procaine (>99% purity) was supplied by ICN Biomedicals. All chemicals were used as received.

Experimental Procedures. Several research groups have investigated the solubilities of a variety of pharmaceutical products in compressed carbon dioxide using various experimental systems. The most common experimental system involves the dynamic flow of carbon dioxide over a packed bed of the drug, depressurizing an effluent stream and analyzing for the drug offline using UV−vis spectroscopy,[3−5,23−27] liquid chromatography,[28] or a gas-flow meter and cold-trap apparatus followed by the weighing of collected drug.[15,29] In this study, a view window inside a variable volume vessel is used to allow for the solubility of the drugs in the carbon dioxide to be visually determined.

A dynamic system manufactured by Thar Design Technologies (PEA-30ML phase equilibrium analyzer shown in Figure 2) was used to observe the cloud points of the anesthetics in carbon dioxide. A computer-controlled carbon dioxide syringe pump (240 mL) was cooled to 5 °C and was connected to the PEA vessel. The PEA vessel was equipped with a computer-controlled movable piston that allowed the system volume (5.5−30) mL to be modified during operation. This piston also housed a stirrer to agitate the contents of the vessel. An external circulating bath pumped ethylene glycol through a cooling/heating jacket around the PEA vessel to provide temperature control. Located on the bottom of the vessel was a sapphire window, which provided visual access into the entire contents of the 1.9-cm (inside diameter) vessel via a camera attached to a television monitor. Temperature (accurate to ±0.2 K) was monitored by a type-K thermocouple, and pressure was measured by a Honeywell pressure transducer (accurate to ±0.1%).

For an experimental solubility measurement, a small amount of solid was weighed with an analytical balance accurate to within ±0.00005 g. Typical samples used were in the range of (0.0015−0.5000) g. The sample would be placed in the bottom of the vessel and sealed. Low-pressure carbon dioxide would be purged through the system while it was preheating to the desired temperature. In a typical experiment at fixed temperature (held to within 0.3 K of the desired temperature), the volume of the vessel would be held constant while the pressure was increased by adding a known amount of carbon dioxide using the syringe pump. Once the desired pressure was obtained, the pressure was held constant with the syringe pump (within 0.5 bar) while the vessel volume was increased by raising the piston slowly. Once all the solid particles were observed to dissolve, the syringe pump was then isolated from the vessel via a valve and the volume of the vessel was increased slowly until the cloud point was observed (the point at which material dropped out of solution). At this point, the system volume, the known amount of carbon dioxide added to the system, and the pressure and temperature were recorded. The cloud point occurred at a pressure very close to the pressure at which all the material was observed to dissolve. With the known amount of drug added initially, the mole fraction at the solubility point could be calculated. The vessel was then vented, cleaned with ethanol, and dried prior to the next measurement.

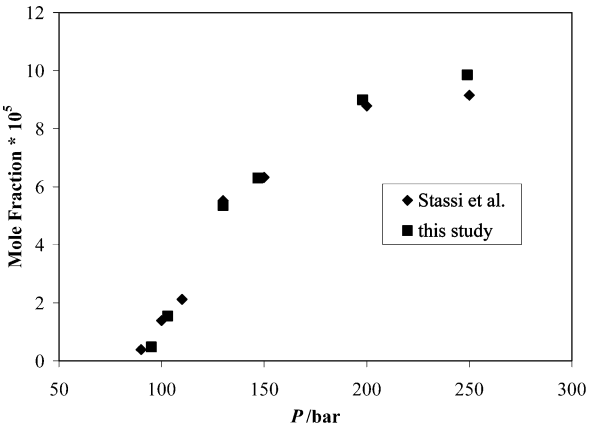

Figure 3. The comparison of the solubility of ketoprofen in carbon dioxide at 313 K to that measured by Stassi et al.[20]

Table 1. Solubility Mole Fraction (y) of Ketoprofen in Supercritical Carbon Dioxide at 313 K

P/bar	$y \times 10^5$ [a]	P/bar	$y \times 10^5$
90	0.39	95	0.48
100	1.39	103	1.55
110	2.12	130	5.35
130	5.52	147	6.30
150	6.32	198	8.99
200	8.78	249	9.85
250	9.15		

[a] Stasis et al.

Results and Discussion

To check the accuracy of the experimental procedure, the solubility of ketoprofen at 313 K was measured and compared to the results obtained by Stassi et al.,[20] who had also matched some of their data to others.[15,30,31] The data presented in Figure 3 and Table 1 verifies that our experimental procedure is able to duplicate the solubility measurements of a flow system found in the literature.

After verifying that our procedures were able to accurately measure solubilities, we proceeded with measuring the solubilities of procaine, lidocaine, and benzocaine in carbon dioxide. We found the solubility of procaine in carbon dioxide (Table 2 and Figure 4) to have mole fractions on the order of 10^{-4}−10^{-5}. As expected, the solubility increased with increasing pressure. It also increased with

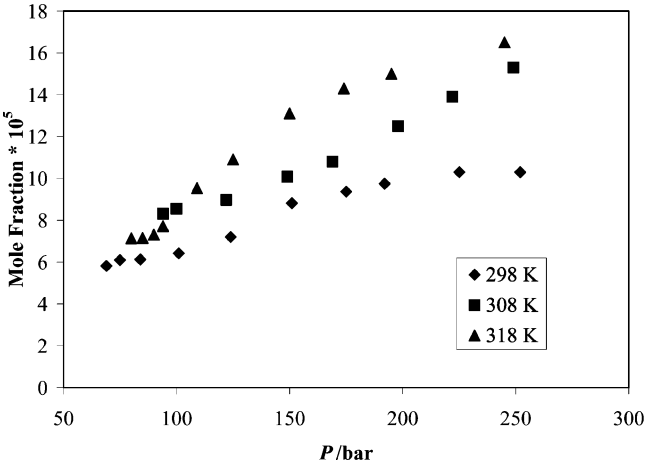

Figure 4. The solubility of procaine in liquid and supercritical carbon dioxide.

Table 2. Solubility of Procaine in Liquid and Supercritical Carbon Dioxide

$T = 298$ K			$T = 308$ K			$T = 318$ K		
P	ρ	y	P	ρ	y	P	ρ	y
bar	g·cm^{-3}	(10^5)	bar	g·cm^{-3}	(10^5)	bar	g·cm^{-3}	(10^5)
69	0.54	5.82	94	0.71	8.31	80	0.25	7.14
75	0.75	6.10	100	0.72	8.55	85	0.29	7.15
84	0.78	6.13	122	0.75	8.97	90	0.35	7.31
101	0.82	6.42	149	0.81	10.08	94	0.39	7.72
124	0.84	7.20	169	0.83	10.80	109	0.51	9.54
151	0.88	8.82	198	0.86	12.50	125	0.58	10.90
175	0.89	9.37	222	0.88	13.90	150	0.74	13.10
192	0.91	9.75	249	0.90	15.30	174	0.77	14.30
225	0.93	10.30				195	0.80	15.00
252	0.94	10.30				245	0.85	16.50

Table 3. Solubility of Lidocaine in Liquid and Supercritical Carbon Dioxide

$T = 298$ K			$T = 308$ K			$T = 318$ K		
P	ρ	y	P	ρ	y	P	ρ	y
bar	g·cm^{-3}	(10^5)	bar	g·cm^{-3}	(10^5)	bar	g·cm^{-3}	(10^5)
70	0.81	7.44	78	0.60	1.55	75	0.23	3.33
74	0.81	7.59	85	0.63	2.57	85	0.35	2.91
89	0.82	8.3	89	0.66	3.11	100	0.5	3.14
100	0.83	7.9	99	0.72	3.2	122	0.69	3.92
114	0.85	8.74	123	0.78	3.53	148	0.75	4.09
124	0.87	10.8	146	0.81	3.88	176	0.79	6.88
143	0.89	13.2	166	0.83	5.59	197	0.82	9.78
156	0.90	15.4	175	0.85	6.67	221	0.84	13.8
177	0.92	18.7	197	0.86	9.07	234	0.85	16.2
195	0.93	22.2	212	0.87	10.8	252	0.87	19.7
248	0.95	27.5	234	0.89	13.2			
			248	0.91	16.3			

increasing temperature. One would expect an increase in temperature to increase the sublimation pressure of the drug, thus increasing its solubility.[27] However, in carbon dioxide, an increase of temperature also causes a significant decrease in density and hence the potential solvating power of the solvent. With procaine, the decrease in solvent density is compensated for by the increase in sublimation pressure and hence the solubility increased with increasing temperature.

The solubility of lidocaine (Table 3 and Figure 5) also increased as the pressure increased; however, it had solubilities 2 orders of magnitude greater (mole fractions on the order of 10^{-2}–10^{-3}) than procaine. An interesting trend observed with lidocaine solubility was that the liquid carbon dioxide (298 K) produced a greater solubility than those in supercritical carbon dioxide (308 and 318 K). With

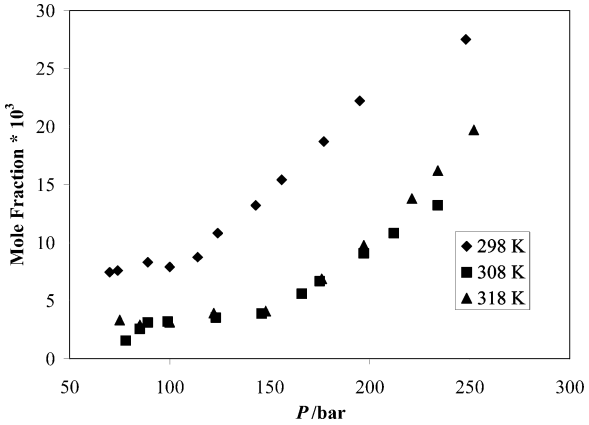

Figure 5. The solubility of lidocaine in liquid and supercritical carbon dioxide.

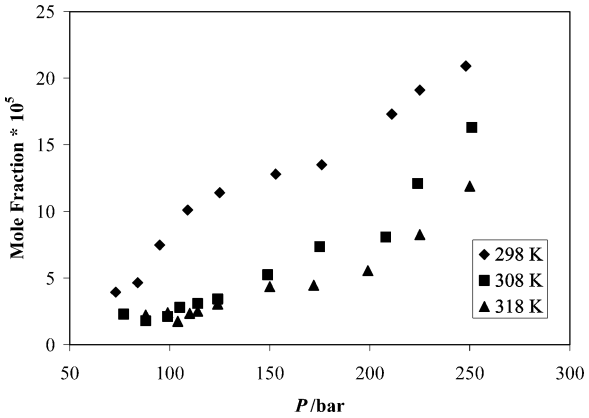

Figure 6. The solubility of benzocaine in liquid and supercritical carbon dioxide.

Table 4. Solubility of Benzocaine in Liquid and Supercritical Carbon Dioxide

$T = 298$ K			$T = 308$ K			$T = 318$ K		
P	ρ	y	P	ρ	y	P	ρ	y
bar	g·cm^{-3}	(10^5)	bar	g·cm^{-3}	(10^5)	bar	g·cm^{-3}	(10^5)
84	0.83	4.65	88	0.67	1.79	99	0.50	2.40
95	0.84	7.47	99	0.72	2.12	104	0.65	1.75
109	0.87	10.1	105	0.73	2.80	110	0.63	2.35
125	0.88	11.4	114	0.77	3.09	114	0.65	2.52
153	0.91	12.8	124	0.78	3.43	124	0.69	3.05
176	0.92	13.5	149	0.81	5.25	150	0.76	4.36
211	0.94	17.3	175	0.86	7.36	172	0.79	4.46
225	0.95	19.1	208	0.88	8.07	199	0.80	5.55
248	0.96	20.9	224	0.89	12.10	225	0.86	8.26
			251	0.90	16.30	250	0.86	11.90

lidocaine, the expected positive effect of the temperature increase on solubility is diminished by the decreasing density of the solvent, and hence the solubility of lidocaine decreases with increasing temperature. It was also observed that, for the runs performed at 308 K and 318 K, the solubilities are almost undistinguishable until approximately 200 bar, where the higher temperature produces the larger solubility.

Finally, the solubility of benzocaine (Table 4 and Figure 6) was found to be similar in scale with procaine, having solubility mole fractions on the order of magnitude of 10^{-4}–10^{-5}. Although the benzocaine solubilities were on the same scale as those of procaine, the trends of solubility with temperature followed those of lidocaine.

The addition of an another tertiary amine to benzocaine to produce procaine (see Figure 1) had a minimal effect on

the solubility of the compounds, even though others[32] have observed that the addition of tertiary amine groups increases the solubility of compounds as long as the K_b remains smaller than 10^{-9}. Esterification has generally been shown to increase solubility in carbon dioxide,[32] and one would expect the removal of an ester linkage from procaine to produce lidocaine (see Figure 1) would decrease the solubility. The opposite was observed and has been attributed to the additional removal of a primary amine (which tend to hinder solubility) and the addition of an amide linkage. *N*-Alkyl substitution on amides has been shown to increase solubility.[32] Therefore, as a first pass at finding anethestics that have high solubilities in carbon dioxide, one should look for amide linkages and minimize the use of primary amines. The effect of temperature on the solubility is difficult to predict and should be explored experimentally while high pressures should be used to maximize solubility.

Modeling and Data Analysis

It is of customary practice to model the solubility of solids in supercritical fluids with an equation of state such as the Peng−Robinson equation of state.[33,34] The fugacity of the pure solid is set equal to the fugacity of the drug dissolved in carbon dioxide

$$P^{\text{sub}} \exp\left(\frac{1}{RT}\int_{P^{\text{sub}}}^{P}\frac{dP}{\rho^{s}}\right) = y_1 P \hat{\phi}_1 \qquad (1)$$

where P^{sub} is the sublimation pressure of the pure solid at temperature T, ρ^s is the density of the pure solid, R is the universal gas constant, y_1 is the solubility mole fraction of the drug in the carbon dioxide phase, P is the system pressure, and $\hat{\phi}_1$ is the fugacity coefficient of the drug in the carbon dioxide phase. Equation 1 requires the sublimation pressure to be low as is the case for our compounds and generally holds the density of the solid constant in the integration.

To use the Peng−Robinson equation of state to calculate the fugacity coefficient of the drug, the critical properties and acentric factor need to be known or approximated for carbon dioxide and the pharmaceutical compound. The critical properties and acentric factor were not available for our anethestics so they were estimated by the Joback group contribution method,[21,35,36] and a second set was also obtained from the Marrero and Pardillo estimation method.[21,37] The sublimation pressure required for the solid fugacity calculation was estimated using a modified Clausius−Clapeyron equation[20,21] since it too was not available for any of our compounds. The critical properties and acentric factor of carbon dioxide were readily available.[21] Because traditional mixing rules for the Peng−Robinson equation of state did not adequately predict the experimental data (as in most cases), we attempted to use a binary-interaction parameter.[33] This parameter was fit from a linear leas-squares regression of the data and the fugacity expression (eq 1) where the Peng−Robinson equation of state was used to calculate the fugacity coefficient. Even with the binary-interaction parameter, the Peng−Robinson equation of state did not adequately fit the experimental solubility data. The model was, however, able to capture general trends. It tended to do better over the (100 to 200) bar range being within a factor of 3 to 4, while at lower pressures, it could be off an order of magnitude or more. It consistently underpredicted the solubility.

Since the equation of state did not model the data in this study very well, other prediction methods were explored.

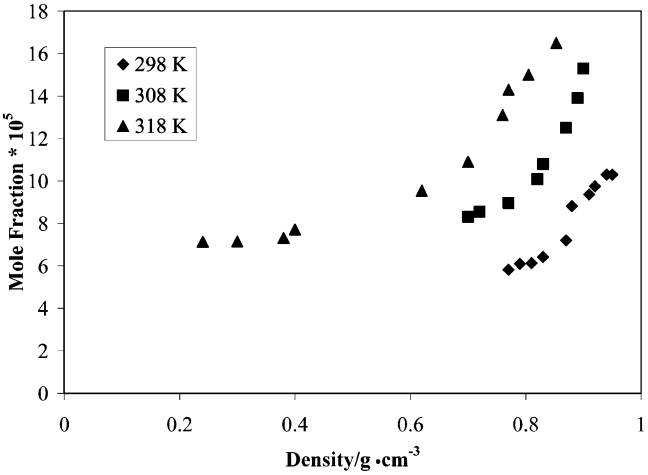

Figure 7. The solubility of procaine as a function of density in liquid and supercritical carbon dioxide.

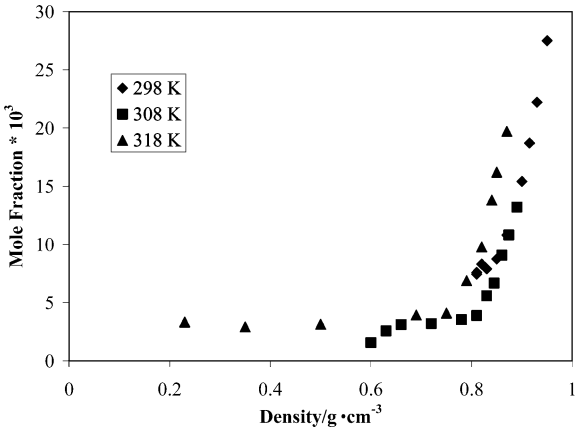

Figure 8. The solubility of lidocaine as a function of density in liquid and supercritical carbon dioxide.

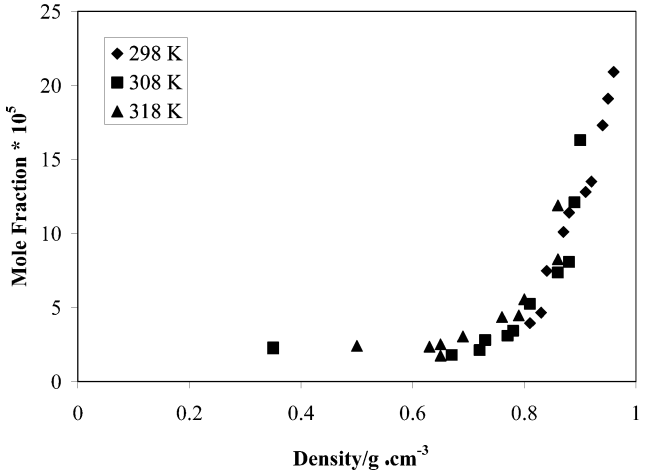

Figure 9. The solubility of benzocaine as a function of density in liquid and supercritical carbon dioxide.

We wanted to avoid other equations of state that would also require the use of properties that would need to be estimated and could possibly lead to large modeling errors. Examination of the solubility vs density instead of vs pressure (see Figures 7−9) revealed some interesting trends in the data. Lidocaine's and benzocaine's solubilities each collapsed onto one line independent of temperature, demonstrating that density is the dominate property affecting their solubility. Hence we looked for models heavily dependent on density to model their solubility.

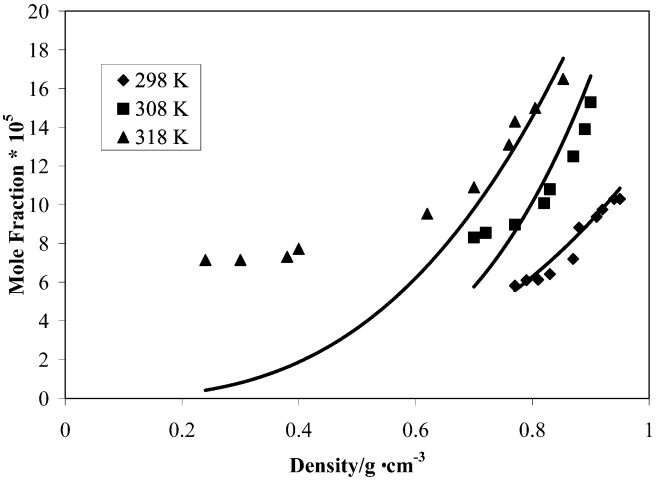

Figure 10. Empirical fit of the solubility of procaine by eq 3 as a function of density in liquid and supercritical carbon dioxide.

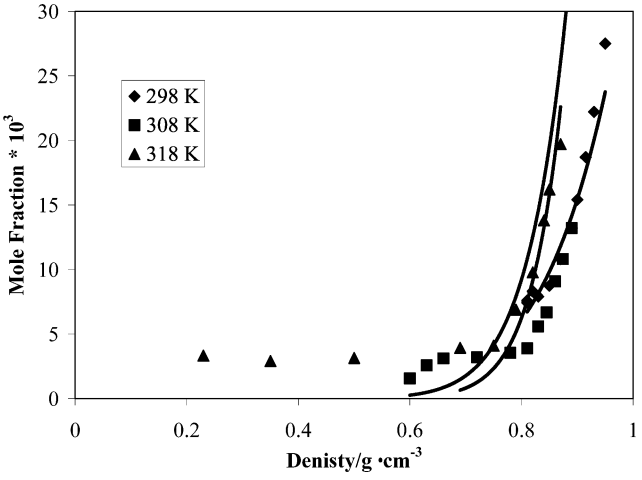

Figure 11. Empirical fit of the solubility of lidocaine by eq 3 as a function of density in liquid and supercritical carbon dioxide.

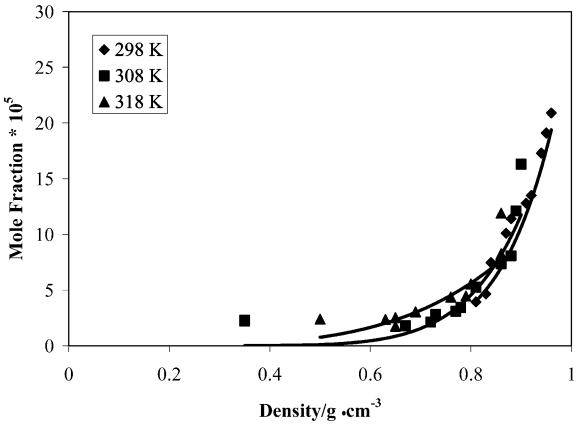

Figure 12. Empirical fit of the solubility of benzocaine by eq 3 as a function of density in liquid and supercritical carbon dioxide.

Procaine's solubility when plotted vs density showed a temperature dependence where higher temperatures produced higher solubilities. Therefore a model which also takes into account temperature affects was required to capture all of the trends in the data. On the basis of these observations, the empirical enhancement factor model was examined as it has a strong temperature and density dependence on the solubility.

The empirical enhancement factor,[38] E, shown in eq 2 is a function of the vapor pressure of the pure solid, which is a strong function of temperature. This temperature dependence is critical to capture the solubility trends of procaine. The enhancement factor is the ratio of the solute partial pressure in the supercritical phase (y_1P) to the sublimation pressure of the pure solute at the same temperature

$$E = \frac{y_1 P}{P^{\mathrm{sub}}} \tag{2}$$

The natural log of the enhancement factor can then be fitted to a linear function of density, ρ

$$\ln E = A + c\rho \tag{3}$$

where A and c are constants. The sublimation pressure was estimated using a modified Clausius−Clapeyron equation (eq 4),[20,21] where the critical temperature (T_c), critical pressure (P_c), and normal boiling temperature (T_b) were calculated by the Marrero and Pardillo estimation method[21,37]

$$\ln P^{\mathrm{sub}} = \frac{T_b \ln P_c}{T_c\left(1 - \frac{T_b}{T_c}\right)}\left(1 - \frac{T_c}{T}\right) \tag{4}$$

The two constants in eq 3 were fit from a linear least squares regression of the experimental data.

Figures 10−12 show how eq 3 fits the experimental data. The empirical correlation can capture the trend as well as the actual values of the experimental data at the higher densities (above 0.8 g•cm^{-3}), while it tended to underpredict the solubility at the lower densities. In all cases, the fit was much better than when attempted with the Peng−Robison equation of state.

Finally, the solubility of procaine hydrochloride and lidocaine hydrochloride was also tested. Experiments were run at the same temperatures and pressure range as the free-base compounds. Neither hydrochloride showed any measurable solubility. We note that benzocaine cannot form a hydrochloride salt.

Conclusions

The solubility measurements of lidocaine, benzocaine, procaine, lidocaine hydrochloride, and procaine hydrochloride in carbon dioxide have been determined at (298, 308, and 318) K from (70 to 280) bar. It was determined that the solubility increases with the system pressure. Lidocaine produced the highest solubility, followed by benzocaine, and then procaine. Procaine hydrochloride and lidocaine hydrochloride showed essentially no solubility over the conditions tested. It was found that the relationship between solubility and density could be represented well for lidocaine and benzocaine, while procaine showed a temperature and density dependence. The solubilities could be accurately modeled by a simple enhancement factor which was a function of system density and the vapor pressure of the solid.

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Literature Cited

(1) Anklam E.; Berg, H.; Mathisasson, L.; Sharman, M.; Ulberth, F. Supercritical Fluid Extraction (SFE) in Food Analysis: A Review. *Food Addit. Contam.* **1998**, *15*, 729−750.
(2) Subramaniam, B.; Rajewski, R. A.; Snavely, K. Pharmaceutical Processing with Supercritical Carbon Dioxide. *J. Pharm. Sci.* **1997**, *86* (8), 885−890.

(3) Medina, I.; Bueno, J. L. Solubilities of 2-Nitroanisole and 3-Phenyl-1-propanol in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2000**, *45*, 298−300.
(4) Medina, I.; Bueno, J. L. Solubilities of Zopiclone and Nimodipine in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2001**, *46*, 1211−1214.
(5) Bristow, S.; Shekunov, B. Y.; York, P. Solubility Analysis of Drug Compounds in Supercritical Carbon Dioxide Using Static and Dynamic Extraction Systems. *Ind. Eng. Chem. Res.* **2001**, *40*, 1732−1739.
(6) Kery, A.; Ronyai, E.; Simandi, B.; Lemberkovics, E.; Keve, T.; Deak, A.; Kemeny, S. Recovery of a Bioactive Sesquiterpene Lactone from Tanacetum Parthenium by Extraction with Supercritical Carbon Dioxide. *Chromatographia* **1999**, *49*, 503−508.
(7) Debenedetti, P. G.; Tom, J. W.; Yeo, S.-D.; Lim, G.-B. Application of Supercritical Fluids for the Production of Sustained Delivery Devices. *J. Controlled Release* **1993**, *24*, 27−44.
(8) Van Hees, T.; Piel, G.; Evrard, B.; Otte, X.; Thunus, L.; Delattre, L. Applications of Supercritical Carbon Dioxide for the Preparation of a Proxicam-B−Cyclodextrin Inclusion Compound. *Pharm. Res.* **1999**, *16*, 1864−1870.
(9) Mishima, K.; Matsuyama, K.; Tanabe, D.; Yamauchi, S.; Young, T. J.; Johnston, K. P. Microencapsulation of Proteins by Rapid Expansion of Supercritical Solution with a Nonsolvent. *AIChE J.* **2000**, *46*, 857−865.
(10) Wang, S.; Kienzle, F. The Synthesis of Pharmaceutical Intermediates in Supercritical Fluids. *Ind. Eng. Chem. Res.* **2000**, *39*, 4487−4490.
(11) Mesiano, A. J.; Beckman, E. J.; Russell, A. J. Supercritical Biocatalysis. *Chem. Rev.* **1999**, *99*, 623−633.
(12) Cooper, A. I. Polymer Synthesis and Processing Using Supercritical Carbon Dioxide. *J. Mater. Chem.* **2000**, *10*, 207−234.
(13) Kumar, S. K.; Johnston, K. P. Modelling the Solubility of Solids in Supercritical Fluids with Density as the Independent Variable. *J. Supercrit. Fluids* **1988**, *1*, 15−22.
(14) Stahl, E.; Schilz, W.; Schutz, E.; Willing, E. A Quick Method for the Microanalytical Evaluation of the Dissolving Power of Supercritical Gases. *Angew Chem., Int. Ed. Engl.* **1978**, *17*, 731−738.
(15) Macnaughton, S. J.; Kikic, I.; Foster, N. R.; Alessi, P.; Cortesi, A.; Colombo, I. Solubility of Antiinflammatory Drugs in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **1996**, *41*, 1083−1086.
(16) 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.
(17) Mendez-Santiago, J.; Teja, A. S. The Solubility of Solids in Supercritical Fluids. *Fluid Phase Equilib.* **1999**, *158−160*, 501−510.
(18) Garnier, S.; Neau, E.; Alessi, P.; Cortesi, A.; Kikic, I. Modeling Solubility of Solids in Supercritical Fluids using Fusion Properties. *Fluid Phase Equilib.* **1999**, *158−160*, 491−500.
(19) Clifford, T. *Fundamentals of Supercritical Fluids*; Oxford University Press: New York, 1999.
(20) Stassi, A.; Bettini, R.; Gazzaniga, A.; Giordano, F.; Schiraldi, A. Assessment of Solubility of Ketoprofen and Vanillic Acid in Supercritical CO_2 under Dynamic Conditions. *J. Chem. Eng. Data* **2000**, *45*, 161−165.
(21) Poling, B. E.; Prausnitz, J. M.; O'Connell, J. P. *The Properties of Gases and Liquids*, 5th ed.; McGraw-Hill: New York, 2001.
(22) Neau, E.; Garnier, S.; Avaullee, L. A Consistent Estimation of Sublimation Pressures Using a Cubic Equation of State and Fusion Properties. *Fluid Phase Equilib.* **1999**, *164*, 173−186.
(23) Yamani, Y.; Hassan, J.; Haghgo, S.; Solubilities of Some Nitrogen-Containing Drugs in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2001**, *46*, 451−455.
(24) Yamani, Y.; Bahramifar, N.; Hassan, J. Solubilities of Pure and Mixed 2-Methylacnthracene and 9-Nitroanthracene in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2002**, *47*, 329−332.
(25) Asghari-Khiavi, M.; Yamini, Y. Solubility of the Drugs Bisacodyl, Methimazole, Methylparaben, and Iodoquinol in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2003**, *48*, 61−65.
(26) Guney, O.; Akgerman, A. Solubilities of 5-Fluorouracil and *β*-Estradiol in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2000**, *45*, 1049−1052.
(27) Xing, H.; Yang, Y.; Su, B.; Huang, M.; Ren, Q. Solubility of Artemisinin in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2003**, *48*, 330−332.
(28) Garcia-Gonzalez, J.; Molina, M. J.; Rodriguez, F.; Mirada, F. Solubilities of Phenol and Pyrocatechol in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2001**, *46*, 918−921.
(29) Lee, L.-S.; Fu, J.-H.; Hsu, H.-L. Solubility of Solid 1,4-Dimethoxybenzene in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2000**, *45*, 358−361.
(30) Paulaitis, M. E.; McHugh, M. Solid Solubilities of Naphthalene and Biphenyl in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **1980**, *25*, 326−329.
(31) Gurdial, S.; Foster, R. Influence of Chemical Modifiers on the Solubility of *o*- and *m*-Hydroxybenzoic Acid in Supercritical CO_2. *Ind. Eng. Chem. Res.* **1993**, *9*, 82−87.
(32) Dandge, D. K.; Heller, J. P.; Wilson, K. V. Structure Solubility Correlations: Organic Compounds and Dense Carbon Dioxide Binary Systems. *Ind. Eng. Chem. Prod. Res. Dev.* **1985**, *24*, 162−166.
(33) Tester, J. W.; Modell, M. *Thermodynamics and Its Applications*, 3rd ed.; Prentice Hall: New Jersey, 1997.
(34) Peng, D.-Y.; Robinson, D. B. New Two-Constant Equation of State. *Ind. Eng. Chem. Fundam.* **1976**, *15*, 59−64.
(35) Joback, K. G. A Unified Approach to Physical Property Estimation Using Multivariate Statistical Techniques. S. M. Thesis, Department of ChE, M.I.T., Cambridge, MA, 1984.
(36) Joback, K. G.; Reid, R. C. Estimation of Pure-Component Properties from Group Contributions. *Chem. Eng. Comm.* **1987**, *57*, 233−243.
(37) Marrero-Marejon, J.; Pardillo-Fontdevila. Estimation of Pure Compound Properties Using Group-Interaction Contributions. *AIChE J.* **1999**, *45*, 615−621.
(38) Johnston, K. P.; Peck, D. G.; Kim, S. Modeling Supercritical Mixtures: How Predictive Is It? *Ind. Eng Chem. Res.* **1989**, *28*, 1115−1125.

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