Solubility of Felodipine and Nitrendipine in Liquid and Supercritical Carbon Dioxide by Cloud Point and UV Spectroscopy

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The solubility of two calcium channel blockers, felodipine and nitrendipine, was measured in liquid and supercritical carbon dioxide at (298, 308, and 318) K and at pressures between (80 and 250) bar. The solubilites were measured experimentally through two methods: cloud point measurements and UV absorption. At lower pressures, and hence densities, the UV method was more accurate while at higher pressures and densities the solubilities measured by both methods were basically identical. Both of these compounds showed an increase in solubility with increasing temperature and density. The experimentally determined solubility was accurately modeled using an equation, derived from association laws, which had a strong solvent density and temperature dependence.

Introduction

Calcium channel blockers are medications that are prescribed to relax blood vessels and decrease the heart's pumping strength. They work by affecting calcium passages in the muscle cells in the walls of arteries. When calcium flows into these passages, muscle cells contract causing arteries to narrow. Calcium channel blockers prevent calcium from entering the muscle cells and hence keep arteries open and improve circulation. They are commonly used to treat high blood pressure, angina, and some abnormal heart rhythms. The two calcium channel blockers examined in this study were felodipine and nitrendipine, shown in Figure 1. Both of these compounds are pale yellow solids at room temperature.

The motivation for studying the solubility of these calcium channel blockers in liquid and supercritical carbon dioxide is for the future use of carbon dioxide as a carrier for these drugs. Carbon dioxide can dissolve these compounds and then transport them into polymeric drug delivery devices such as transdermal patches or biodegradable sutures. Carbon dioxide has been shown to be an excellent swelling agent for many polymers[1−3] and hence is an ideal choice as a carrier solvent. We have previously used carbon dioxide for the processing of polymeric-based chewing gum and its flavorings.[4−5] Carbon dioxide is also inert, inexpensive, environmentally friendly, and can be recycled in a closed-loop process. Furthermore, carbon dioxide's properties can be tuned easily in the supercritical state with changes in temperature or pressure, and it has favorable transport properties (diffusivity, viscosity, surface tension, and density) for promoting mass transfer.[6] Because of its favorable properties, carbon dioxide has found many uses in the food[7] and pharmaceutical[8] fields where its nontoxic nature is essential. For example, carbon dioxide has been used for the extraction and separation of natural materials,[9] for the particle formation of pharmaceutical compounds,[10] for the creation of drug delivery devices,[11] and as an environmentally friendly solvent replacement for pharmaceutical synthesis.[12] It has also been used to sterilize pharmaceuticals and drug delivery devices.[13]

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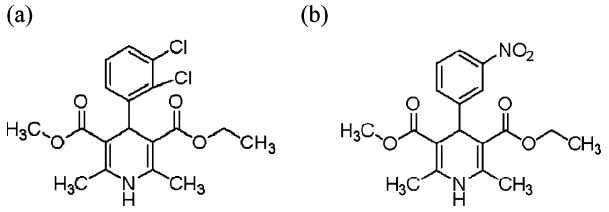

Figure 1. Structures of (a) felodipine and (b) nitrendipine

There are several methods for studying the solubilities of solids 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 solid. The effluent stream is then depressurized, and the solid is collected and analyzed for the compound offline using a variety of analytical techniques.[14−18] This method can often prove to be difficult as during depressurization the solid of interest will tend to drop out of solution and coat valves, lines, and other parts of the apparatus. Although possible with solvent washes, it is often difficult to ensure the accurate sampling during such processes. In addition, the dynamic flow method can lead to carbon dioxide channeling through the bed and spurious solubility data. In this study, we chose to examine two of the more accurate methods for measuring the solubility of a solid in compressed carbon dioxide: cloud point observation and UV absorption.

Experimental Section

Materials. Research grade 5 carbon dioxide with a purity of 99.999 % was supplied by BOC Gases. Nitrendipine was supplied by CSS Chemical (China), and felodipine was supplied by Molekula (United Kingdom). Each had a purity greater than 99.5 % and was used as received. Ethanol (200 proof) was purchased from Pharmco Products and also used as received.

Solubility Measurements by Cloud Point. A system manufactured by Thar Design Technologies (PEA-30ML phase equilibrium analyzer) was used to observe the cloud point of nitrendipine or felodipine at (298, 308, and 318) K over the pressure range of (80 to 250) bar. The PEA system consists of a syringe pump attached to a cylindrical variable volume view

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cell. The view cell has a movable piston with a stirrer attached, which allows the volume of the vessel to be changed under pressure between (5.5 and 30) mL. The view cell is also surrounded by a heating jacket that uses an external circulation bath to maintain a desired temperature inside the view cell. On the bottom of the view cell is a sapphire window, which allows the entire contents of the cell to be viewed by used of a magnifying video camera. The PEA vessel's temperature (± 0.2 K) was monitored by a type K thermocouple and pressure was measured by a Honeywell pressure transducer (± 0.1 %). We have used and published a schematic of this system previously.[19−21]

For an experimental solubility measurement, the PEA vessel was preheated and flushed with low-pressure carbon dioxide while a small amount of solid was weighed with an analytical balance (± 0.05 mg), placed in the bottom of the view cell on the sapphire window, and sealed. More low-pressure carbon dioxide was purged through the view cell, which was then set to the smallest volume. Stirring was initiated, the view cell was pressurized, and the pressure was held constant by the syringe pump while the vessel volume was increased by raising the piston slowly until all the solid was observed to dissolve. The view cell was then isolated from the pump via a valve, and the volume of the vessel was increased slowly until the cloud point was observed by the operator (the point at which material dropped out of solution). When the cloud point was observed, the solubility was calculated using the known amount of solid loaded into the vessel along with the amount of carbon dioxide present in the vessel (by measuring the temperature, pressure, and volume in the view cell and then using the NIST[22] database of carbon dioxide properties). After each cloud point observation, the view cell was vented, thoroughly cleaned, and dried. Each measurement was repeated and found to be within 5 %.

Solubility Measurements by UV Absorption. These measurements were performed in a square, stainless steel, view cell with an internal volume of 2.7 mL and a sapphire window on each face. The path length inside the cell was exactly 1 cm. A Cary 50 Scann UV−vis spectrophotometer was used for absorption measurements. The view cell was jacketed, and heating occurred with an external circulation bath. A small stir bar was placed inside the cell, and mixing was controlled by a magnetic stir plate. Pressurization was achieved by a hand pressure generator (High-Pressure Equipment model 87-6-5), and temperature and pressure were measured as was with the PEA system.

Calibrations for each compound were made using five ethanol solutions of known concentration at room temperature and pressure. Felodipine was measured at 360 nm while nitrendipine was measured at 350 nm. To verify that there was no shifting in the calibrations due from changing to carbon dioxide or the addition of pressure, a known small amount of an ethanol solution of known concentration of the compound was placed inside the view cell, and the cell was pressurized with carbon dioxide and heated, making sure a one-phase solution was obtained. The absorbance was measured, and the calibration was used to calculate the concentration inside the view cell. This calculated concentration was checked against the known concentration (mass of compound added in the ethanol solution/volume of view cell) and found to vary less than 5 % over the pressure and temperature range tested for each compound.

For a solubility measurement, the solid compound was placed inside the view cell with a stir bar, which was sealed and flushed with low-pressure carbon dioxide while it was heated to the desired temperature. After 30 min of temperature equilibration, the cell was pressurized to the lowest desired pressure and left to equilibrate for 30 min after which time the cell was removed from the stir plate and placed in the spectrophotometer for an absorbance measurement. The cell was then returned to the stir plate and left for 30 min after which time another absorbance measurement was made. This process was repeated until three subsequent absorbance measurements were identical (within 2 %). It was important that some solid always remained undissolved and that this solid and the stir bar did not block the UV path. After an accurate absorbance measurement was obtained, the cell was then pressurized to the next lowest desired pressure, and the process was repeated until all measurements were acquired at this temperature. The cell was then vented, cleaned, dried, and made ready for the next set of measurements.

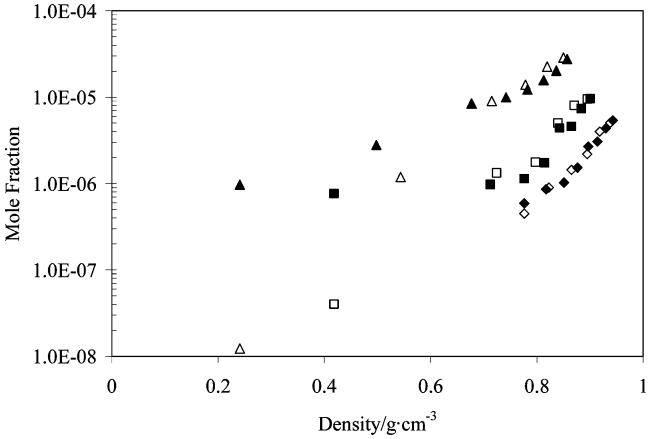

Figure 2. Mole fraction solubility of felodipine: ◆, 298 K cloud point; ■, 308 K cloud point; ▲, 318 K cloud point; ◇, 298 K UV; □, 308 K UV; △, 318 K UV.

Results and Discussion

The solubility of felodipine in liquid and supercritical carbon dioxide at (298, 308, and 318) K and pressures between (80 and 250) bar are presented in Figure 2 and Table 1. The solubility data for nitrendipine is shown in Figure 3 and Table 2. In Figures 2 and 3, solid symbols represent measurements made by cloud point observation while open symbols are the data obtained from UV absorbance measurements. It is important to note that a log scale was used for the clarity of presenting the data since there was a 2 order of magnitude change in the measured solubility over the temperature and pressure range explored. Nitrendipine was slightly more soluble than felodipine under identical conditions, and this is most likely due to the presence of chloride atoms in felodipine as non-fluorine halogen atoms have been known to reduce solubility in carbon dioxide.[23]

There was a strong temperature and density dependence on the solubility of both compounds in condensed carbon dioxide. As temperature was increased at a fixed density, the solubility of each compound was observed to increase. Also, as density was increased at a fixed temperature (by increasing the carbon dioxide pressure), the solubility increased. These are commonly observed trends for the solubility of solids in liquid and supercritical carbon dioxide. The solvating power of carbon dioxide tends to increase with increasing density as there are more molecules of carbon dioxide available for forming a solvating shell around the solid molecule and dissolving it.[21,24−25] This solvating shell of carbon dioxide tends to interact with the solid molecule through weak association interactions such as van der Waals forces and dipole−quadropole interactions[24] and is required for the molecule to dissolve into carbon dioxide. As for the temperature effect, this is most commonly attributed to the fact that, as temperature increases, the sublima-

Table 1. Mole Fraction Solubility (y) of Felodipine in Liquid and Supercritical Carbon Dioxide

$T = 298$ K				$T = 308$ K				$T = 318$ K			
		$y \cdot 10^5$				$y \cdot 10^5$				$y \cdot 10^5$	
P/bar	ρ/g·cm^{-3}	cloud point	UV	P/bar	ρ/g·cm^{-3}	cloud point	UV	P/bar	ρ/g·cm^{-3}	cloud point	UV
80	0.42	0.059	0.045	80	0.42	0.076	0.004	80	0.24	0.097	0.001
101	0.71	0.086		100	0.71	0.097		100	0.50	0.28	
103	0.72		0.090	103	0.72		0.13	103	0.54		0.012
125	0.78	0.10		125	0.78	0.11		125	0.68	0.85	
138	0.80		0.15	138	0.80		0.17	138	0.72		0.91
152	0.82	0.15		151	0.82	0.17		151	0.74	1.0	
172	0.84		0.22	172	0.84		0.50	172	0.78		1.4
175	0.84	0.27		175	0.84	0.44		175	0.78	1.2	
200	0.87	0.31		203	0.87	0.45		202	0.81	1.6	
207	0.87		0.40	207	0.87		.80	207	0.82		2.3
225	0.88	0.44		225	0.88	0.73		226	0.84	2.0	
241	0.90		0.51	241	0.90		0.95	241	0.85		2.9
250	0.90	0.54		248	0.90	0.95		250	0.86	2.8	

Table 2. Mole Fraction Solubility (y) of Nitrendipine in Liquid and Supercritical Carbon Dioxide

$T = 298$ K				$T = 308$ K				$T = 318$ K			
		$y \cdot 10^5$				$y \cdot 10^5$				$y \cdot 10^5$	
P/bar	ρ/g·cm^{-3}	cloud point	UV	P/bar	ρ/g·cm^{-3}	cloud point	UV	P/bar	ρ/g·cm^{-3}	cloud point	UV
80	0.42	0.83	0.33	80	0.42	1.0	0.025	80	0.24	1.0	0.004
99	0.71	0.92		100	0.71	1.7		100	0.50	3.7	
103	0.72		0.64	103	0.72		1.0	103	0.54		0.88
126	0.78	1.7		125	0.78	2.2		125	0.68	4.0	
138	0.80		2.1	138	0.80		2.2	138	0.72		2.6
150	0.82	2.2		150	0.82	2.7		151	0.74	4.6	
172	0.84		3.1	172	0.84		3.9	172	0.78		5.0
175	0.84	2.7		175	0.84	3.9		175	0.78	4.8	
200	0.87	3.5		200	0.87	4.3		202	0.81	5.4	
207	0.87		4.2	207	0.87		6.0	207	0.82		6.0
225	0.88	4.1		225	0.88	6.3		224	0.84	6.5	
241	0.90		5.6	241	0.90		7.6	241	0.85		9.0
250	0.90	5.1		250	0.90	7.4		251	0.86	8.9	

tion pressure of the solid increases, which in turn increases the mole fraction solubility (y_1) of the solid in compressed carbon dioxide as is shown in eq 1:[19]

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

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, P is the system pressure, and $\hat{\phi}_1$ is the fugacity coefficient of the solid in the carbon dioxide phase. Equation 1 equates the fugacity of the pure solid to that of the fugacity of the solid compound dissolved in the carbon dioxide phase.

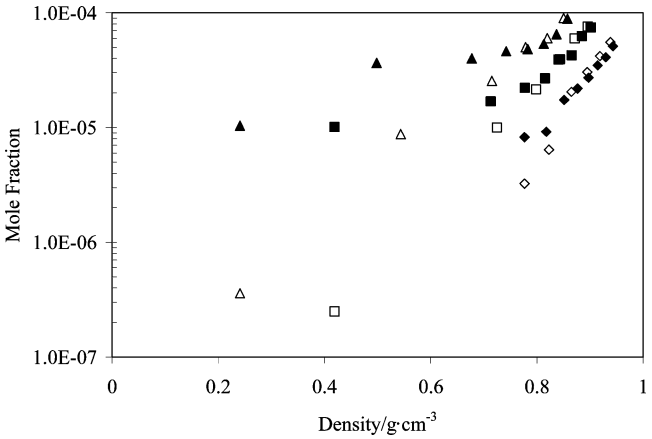

Figure 3. Mole fraction solubility of nitrendipine: ◆, 298 K cloud point; ■, 308 K cloud point; ▲, 318 K cloud point; ◇, 298 K UV; □, 308 K UV; △, 318 K UV.

At the higher densities the cloud point observations and UV measurements produced basically identical solubility measurements. However, at the lower densities, the cloud point measurements predicted solubilities often 1 to 2 orders of magnitude larger than the UV measurements. We have successfully used cloud point measurements to match the solubilities of ketoprofen found in the literature.[19,26] These ketoprofen solubilities were on the order of 10^{-5} mole fraction. However, some of the mole fractions found in this study were on the order of 10^{-6} or 10^{-7} mole fraction for felodipine or nitrendipine. These low mole fractions in this study produced different results between the cloud point and UV measurements. To generate such small mole fractions, the mass of the compound to be added to the PEA vessel was on the same order of the accuracy of the balance and hence the measurements contained significant error. These small masses were also difficult to fully transfer to the PEA. Furthermore, since cloud point measurements are made by visible observation, at these low quantities, it is often difficult to observe when they fully dissolve. Therefore, at low densities with low solubilities (on a mass basis), the cloud point method is not as accurate and the UV method should be trusted. We[20] and others[27] have observed this phenomena before with cloud point observations of other compounds in carbon dioxide.

We were unable to find any other solubility data of felodipine in carbon dioxide in the literature, although some have examined its ability to be crystallized into small particles with the use of carbon dioxide through an anti-solvent process.[28] There was one study of nitrendipine solubility in compressed carbon dioxide. Knez et al.[29] examined the solubility of nitrendipine at (333, 353, and 373) K at pressures between (117 and 300) bar. Their data showed similar trends to our lower temperature data.

Table 3. Fitted Model Parameters

calcium blocker	*k*	*A*	*b*
felodipine	8.8	−14318	−15.7
nitrnedipine	14.9	−11140	−65.4

Modeling

It would be difficult to model the solubilites using a traditional equation of state-fugacity approach as shown in eq 1. First of all, equation of state parameters, while known for pure carbon dioxide, are not available for the two calcium blockers. Most likely binary interaction parameters would also be required, which are not available either. Finally, the sublimation pressures of the solids would be required as a function of temperature to accurately use the equation of state-fugacity approach to model and predict solubilites, and again this property for the pure calcium blockers is not available or accurately predicted.

Instead of using a rigorous equation of state-based model, we have found a model developed by Chrastil,[24] which shows heavy dependence on both the density and temperature of carbon dioxide. Density and temperature have a strong influence on the solubilities of felodipine and nitrendipine in liquid and supercritical carbon dioxide. Chrastil's model is based on the assumption that when a molecule of a calcium blocker dissolves into dense carbon dioxide, a specific number of carbon dioxide molecules (*k*) associate closely with the solvated molecule forming a shell that has large interactions with the solvated molecule.[24,25] It is this solvated complex that is in equilibrium with the system rather than pure solid. The association number, *k*, does not have to be an integer as it represents an average number of carbon dioxide molecules required to assist in forming the salvation shell.[24] The final expression derived by Chrastil is given in eq 2:

$$c/\mathrm{g{\cdot}L^{-1}} = (\rho/\mathrm{g{\cdot}L^{-1}})^k \exp\left(\frac{a}{T/\mathrm{K}} + b\right) \quad (2)$$

where c is the concentration of calcium blocker in carbon dioxide, ρ is the density of carbon dioxide, k is the association number, T is the absolute temperature, and a and b are constants. The two constants, a and b, have physical significance as shown in eqs 3 and 4, respectively:

$$a = \frac{-\Delta H}{R} \quad (3)$$

$$b = \ln(M_{\mathrm{DDC}} + M_{\mathrm{CO_2}}) + q - k\ln(M_{\mathrm{CO_2}}) \quad (4)$$

where ΔH is the enthalpy change of solvation and phase change combined, R is the universal gas constant, M_i is the molecular weight of species i, and q is an integration constant when the Clausius equation was applied. The integration constant has some dependence upon the melting points of the solute and solvent. The reader is directed to Chrastil's original work for the details.[24]

We used linear least-squares regression on the UV absorption measured solubility data to derive the three model parameters for each compound. The UV absorption data was chosen as it was deemed to be more accurate (as discussed previously) than the cloud point measurements. The model parameters are presented in Table 3 and were used with eq 2 to fit the data. The model predictions are shown in Figures 4 and 5 for felodipine and nitrendipine, respectively. For both compounds, the model did an excellent job of predicting the solubility over the range of temperatures and densities explored.

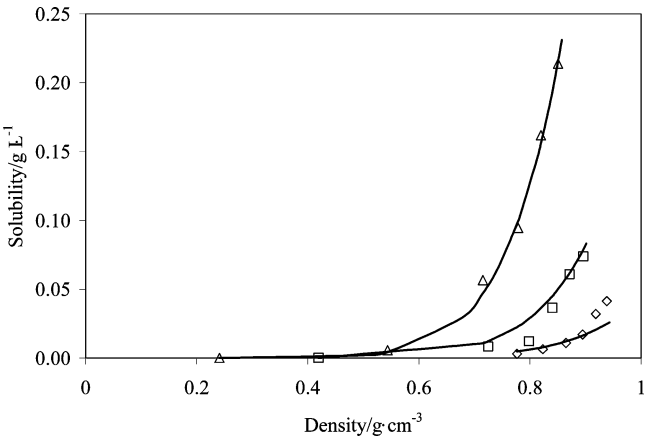

Figure 4. Solubility of felodipine as measured by UV absorption (◇, 298 K; □, 308 K; △, 318 K) and predicted by the model (—).

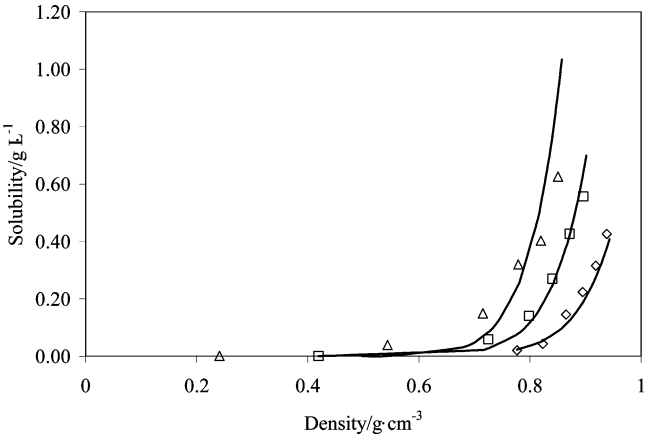

Figure 5. Solubility of nitrendipine as measured by UV absorption (◇, 298 K; □, 308 K; △, 318 K) and predicted by the model (—).

Conclusions

The solubilities of felodipine and nitrendipine were measured in liquid and supercritical carbon dioxide and found to have similar solubilities, with nitrendipine's being slightly higher. The solubilities increased with increasing temperature and density, and a simple association model with temperature and solvent density dependence accurately captured the solubility data. Cloud point measurements and UV absorption measurements were able to both accurately measure the solubility; however, at low densities with low solubilities, only the UV measurements had sufficient accuracy to measure the solubilities of both compounds.

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