Solubilities of Zopiclone and Nimodipine in Supercritical Carbon Dioxide

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Solubility measurements for two pharmaceutical products, zopiclone and nimodipine, in supercritical carbon dioxide are reported over the temperature range (313 to 333) K and pressure range (10.0 to 25.0) MPa. The solubilities were measured using a continuous flow apparatus. The measured mole fractions of the two compounds in supercritical carbon dioxide are correlated with the density of the pure solvent, and the solubilities are correlated using the model proposed by Chrastil.

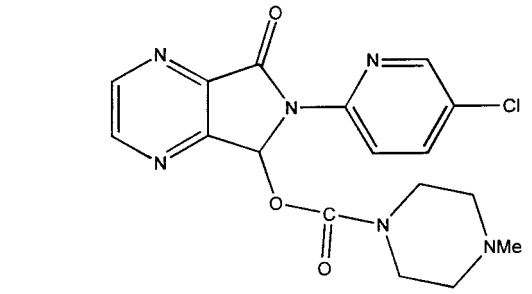
Introduction

Phase equilibrium data and solubility of low-volatile organic compounds in supercritical solvents are of increasing interest for applications in supercritical fluid extraction. The design of supercritical fluid extraction processes requires a detailed knowledge of physical data for all the substances involved. Carbon dioxide is a good solvent for many organic substances. Because of its nontoxicity and low critical temperature, it can be used for extracting natural materials, mainly in the food and pharmaceutical industries.

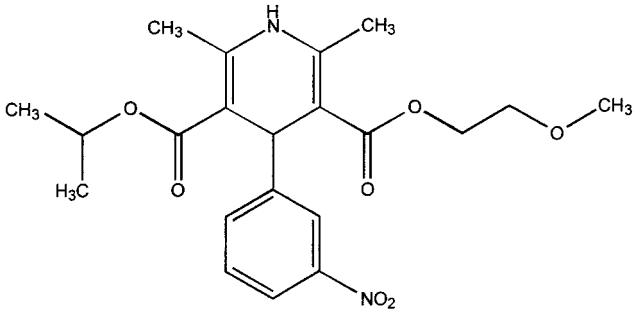
Separations by means of crystallization have played a significant role in the pharmaceutical industry. Many crystalline active substances have to be in a finely divided state for rapid and uniform liberation or solution. Crystallization with supercritical fluids is a new separation process that can control particle size and particle size distribution. A supercritical fluid solution may be expanded rapidly. As a result, nucleation is uniform and narrow particle size distributions have been observed. Pharmaceutical substances have to be made available in the finest and most uniform particle size possible. When pharmaceutical substances are micronized by this procedure, they have very good properties and are superior to those micronized using classical methods.[1,2]

There is relatively little knowledge of the solubilities of pharmaceutical products in supercritical carbon dioxide.[3−6] This paper reports the results of an experimental study of the solubilities of two pharmaceutical products (zopiclone and nimodipine) in a supercritical fluid (carbon dioxide) at three temperatures between 313 and 333 K and at seven pressures between 10.0 and 25.0 MPa. The experimental solubilities are correlated with the density of the pure solvent by two methods.

Zopiclone is a cyclopyrrolone which is reported to have similar sedative, anxiolytic, muscle relaxant, and anticonvulsant properties to those of the benzodiazepines. It is used as a hypnotic in the short-term management of insomnia.[7] The systematic chemical name of zopiclone is 6-(5-chloro-2-pyridyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]-pyrazin-5-yl 4-methylpiperazine-1-carboxylate. Nimodipine is used for the prevention or treatment of delayed ischaemic dysfunction following subarachnoid hemorrhage, and is currently widely studied in impaired brain function in old age and in senile dementia.[8] The systematic name of the calcium antagonist nimodipine is isopropyl-2-methoxyethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. Chemical structures of zopiclone and nimodipine are shown in Figure 1.



zopiclone



nimodipine

Figure 1. Chemical structures of zopiclone and nimodipine.

Experimental Section

Solubility was measured in a Hewlett-Packard supercritical fluid chromatograph (SFC), model G1205A, which was slightly modified. The HP SFC system consists of a pumping module, a mass flow sensor, a column oven, an injection valve, a choice of detectors, and SFC ChemStation software.

The oven module can accommodate fused silica capillary and standard HPLC columns.The HP SFC uses both gas-

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and liquid-phase detectors. In the present work, this unit uses a multiple wavelength UV detector (MWD). The HP SFC uses an electrothermally cooled reciprocating pump to supply supercritical fluids to the system. Electrothermal cooling provides clean, self-contained, quiet, and reliable operation. The pump has feedback control, which compensates for fluid compressibility, minimizes pressure ripple, and provides for more reproducible results. In addition, the use of a reciprocating pump eliminates the inconvenience associated with refilling syringe pumps. The variable restrictor is a programmable, back-pressure control device located inside the pump module. The variable restrictor consists of a pressure transducer and nozzle, which opens and closes accordingly, releasing the mobile phase to control pressure. The SFC ChemStation consists of a PC and HP SFC software. The SFC ChemStation enables instrument control and data handling on a Microsoft Windows-based platform. The mass flow sensor is a device located inside the pumping module.

Zopiclone and nimodipine were supplied by Astur Pharma (Asturias, Spain) and they were obtained by chemical synthesis. Some grams were synthesized in the laboratory of their Research and Development Department and a few grams of high purity (100%) were then isolated by preparative HPLC.[7,8] The carbon dioxide was supplied by Air Liquide and had a minimum purity of 99.998%.

The experimental data were obtained by using a high-pressure cell. The equilibrium cell is 1 cm in internal diameter, 20 cm in length, and about 15 cm^3 in internal volume. The equilibrium cell and the chromatograph are designed for a maximum working temperature of 700 K and maximum working pressure of 40 MPa. Temperature was measured to within ±1 K and pressure within ±0.1 MPa.

The experimental procedure of the solubility measurement was as follows. The pharmaceutical product is placed in the cell and mixed with glass beads to prevent channeling. The traces of dissolved air are removed by charging the cell with carbon dioxide and evacuation. The carbon dioxide is introduced into the cell from the bottom to the top using the high-pressure pump. The mixture in the cell is kept at a given temperature and pressure for 2 to 3 h until equilibrium is achieved. After leaving the equilibrium cell, the carbon dioxide stream is passed through the multiple wavelength UV detector. When the absorbance reading becomes constant with time, the equilibrium between the solute and the supercritical carbon dioxide is reached. The determination of solubility was based on the mass of solute trapped at the outlet of the variable restrictor and the corresponding mass of carbon dioxide. The typical mass of solute that was collected in each experiment was greater than 100 mg. The solid collected was weighed by an analytical balance.

Results and Discussion

Initially, some experiments were carried out at different flow rates to verify that equilibrium was being reached in the cell. It was found that the solubility obtained was at the same flow rates of (0.1, 0.2, and 0.3) g·min^{-1}. A flow rate of 0.2 g·min^{-1} was then used. For these flows, the tests performed demonstrated that the measured solubilities were not affected by the contact time between supercritical carbon dioxide and the solute. This shows that the solubilities of the solutes were measured under equilibrium conditions in the flow type apparatus.

The reliability of the apparatus was tested by measuring the solubilities of naphthalene in supercritical carbon dioxide at 308 K. The solubilities obtained were in good agreement with those reported by Kurnik and Reid,[9] Iwai et al.,[10] and Fat'hi et al.[11] to within an average of 5%. Also, the accuracy was checked by measuring the solubility of nitrendipine in supercritical carbon dioxide at 353 K and 100 bar. Nitrendipine was isolated by preparative HPLC.[12] The measured solubility agreed with the data reported by Knez et al.[4] within 7%.

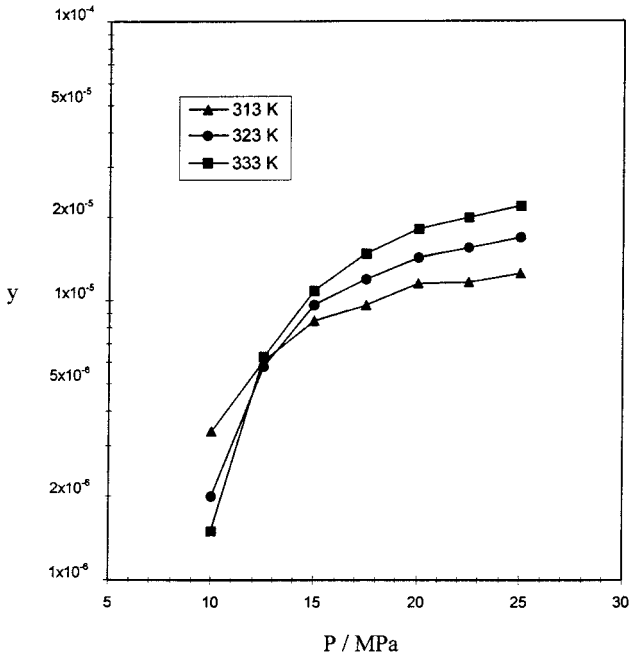

Figure 2. Mole fraction solubility of zopiclone as a function of pressure in supercritical carbon dioxide.

Table 1. Solubilities of Zopiclone and Nimodipine in Supercritical Carbon Dioxide

		zopiclone		nimodipine	
T	P	y	S	y	S
K	MPa	10^5	10^3 g·L^{-1}	10^5	10^3 g·L^{-1}
313	10.0	0.34	19.00	0.50	31.14
	12.5	0.61	39.58	0.74	53.51
	15.0	0.85	58.68	1.03	79.25
	17.5	0.96	69.24	1.25	100.48
	20.0	1.15	85.38	1.33	110.05
	22.5	1.17	89.13	1.52	129.06
	25.0	1.26	97.88	1.62	140.26
323	10.0	0.20	7.03	0.18	7.05
	12.5	0.58	31.80	0.61	37.27
	15.0	0.96	59.58	1.11	76.77
	17.5	1.20	79.45	1.65	121.76
	20.0	1.42	98.40	2.04	157.56
	22.5	1.56	111.96	2.39	191.18
	25.0	1.69	124.57	2.44	200.46
333	10.0	0.15	3.88	0.06	1.73
	12.5	0.63	27.36	0.46	22.27
	15.0	1.09	58.60	1.20	71.90
	17.5	1.48	88.84	2.21	147.86
	20.0	1.81	116.16	2.95	211.01
	22.5	2.00	134.00	3.64	271.83
	25.0	2.19	152.34	4.23	327.96

The solubilities of pure zopiclone and nimodipine in supercritical carbon dioxide were measured over the temperature and pressure ranges (313 to 333) K and (10.0 to 25.0) MPa, respectively. The mole fractions of zopiclone and nimodipine in supercritical carbon dioxide are given in Table 1 and Figures 2 and 3. Also, Table 1 reports the solubilities in terms of grams of solute per liter of solvent (S). Each data point is the average of at least three measurements. The absolute relative deviation (ARD)

Table 2. Correlation of Solubility Data with Equations 1 and 2

		eq 1			eq 2			
solute	*T* (K)	*A*	*B*	AARD (%)	*k*	*a* (K)	*b*	AARD (%)
zopiclone	313	−38.79	4.06	2.88	4.232	-51313	129.38	13.22
	323	−30.66	2.92	5.29				
	333	−28.82	2.71	2.77				
nimodipine	313	−35.99	3.68	3.47	4.883	16632	82.29	15.01
	323	−35.07	3.63	11.45				
	323	−39.07	4.34	7.21				

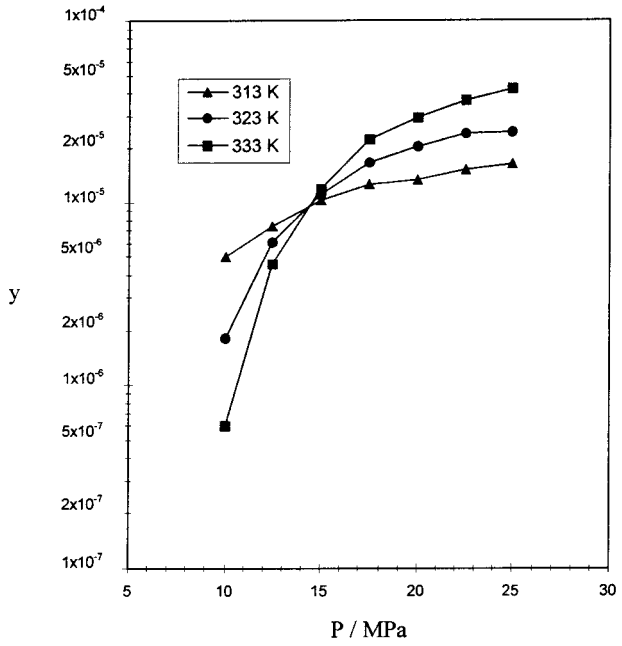

Figure 3. Mole fraction solubility of nimodipine as a function of pressure in supercritical carbon dioxide.

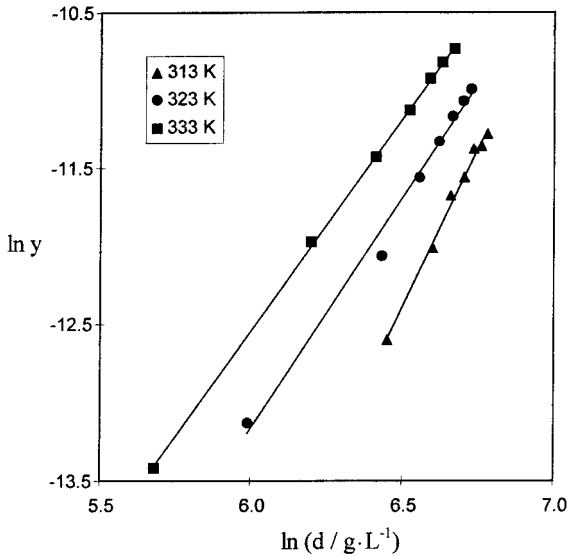

Figure 4. Mole fraction solubility of zopiclone as a function of the carbon dioxide density. Lines represent regression fits of eq 1 to the data.

ranged from (1.5 to 5.9)%, with an average absolute relative deviation (AARD) of 3.6%. The less accurate measurements were obtained at the lower pressures. For both solutes the lowest solubility was found at a temperature of 333 K and a pressure of 10.0 MPa and the highest one at a temperature of 333 K and a pressure of 25.0 MPa. The measured solubilities of zopiclone are of similar order of magnitude and, generally, lower than that reported for nimodipine.

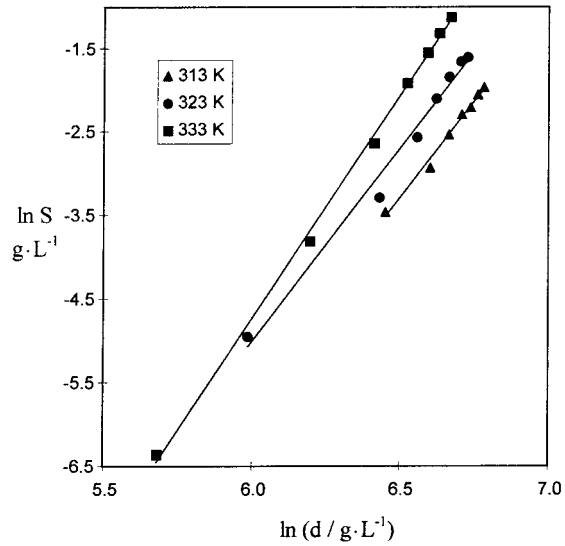

Figure 5. Nimodipine solubility *S* as a function of the carbon dioxide density. Lines represent regression fits of eq 2 to the data.

The results exhibit trends that are typical of the solubility of nonvolatile organic molecules in supercritical CO_2. In Figures 2 and 3, solubilities in terms of the mole fraction of solute are plotted as a function of pressure at three temperatures. The solubility shows a tendency to rise with increasing pressure at three temperatures. By observing the effect of the temperature on the solubilities, the measurements allowed the localization of a solubility crossover point at about 13.0 MPa for zopiclone and 14.0 MPa for nimodipine. At 10.0 and 12.5 MPa, the solubilities were higher with decreasing temperature, and at (15.0 to 25.0) MPa, the solubilities were higher with increasing temperature.

The main problem for correlating solubility data of pharmaceutical compounds in supercritical fluids is the knowledge of the pure component properties of the compound in question. The solubility behavior is similar to other solutes and can be correlated against solvent density. The experimental solubilities of zopiclone and nimodipine obtained in this work have been correlated with two methods.

In the first method, the mole fraction of solute, *y*, was related to the density of pure solvent, ρ, by a linear relation,

$$\ln y = A + B \ln(\rho/\mathrm{g{\cdot}L^{-1}}) \qquad (1)$$

where *A* and *B* are two empirical constants. The optimum values of *A* and *B* for each compound at each temperature are listed in Table 2.

The second method is the model proposed by Chrastil.[13] This model is based on the hypothesis that each molecule of a solute associates with *k* molecules of supercritical solvent to form a solvato complex which is in equilibrium with the gas. The relationship is expressed as

$$\ln(S/\mathrm{g{\cdot}L^{-1}}) = k \ln(\rho/\mathrm{g{\cdot}L^{-1}}) + a(\mathrm{K})/T + b \qquad (2)$$

where S is the solubility, T is the absolute temperature, k is an association number, a is dependent on the enthalpy of solvation and enthalpy of vaporization of the solute, and b is dependent on the molecular weights of the solvent and the solute. The optimum values of k, a, and b for zopiclone and nimodipine were obtained by least-squares analysis and are listed in Table 2. In any case, the results obtained with eq 2 are similar to those using eq 1. The solubilities of these substances can be correlated with fairly good accuracy. Figures 4 and 5 are a comparison of correlated solubilities with the two methods. The average absolute relative deviation (AARD) from the correlations is given in Table 2.

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Literature Cited

(1) McHugh, M.; Krukonis, V. *Supercritical Fluid Extraction*; Butterworths: Stoneham, MA, 1986.

(2) Stahl, E.; Quirin, K. W.; Gerard, D. *Dense Gases for Extraction and Refining*; Springer-Verlag: Berlin, 1988.

(3) Tin, 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.

(4) Knez, Z.; Skerget, M.; Sencar-Bozic, P.; Rizner, A. Solubility of Nifedipine and Nitrendipine in Supercritical CO_2. *J. Chem. Eng. Data* **1995**, *40*, 216−220.

(5) Macnaughton, S. J.; Kikic, I.; Foster, N. R.; Alessi, P.; Cortesi, A.; Colombo, I. Solubility of Anti-inflammatory Drugs in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **1996**, *41*, 1083−1086.

(6) Alessi, P.; Cortesi, A.; Kikic, I.; Foster, N. R.; Macnaughton, S. J.; Colombo, I. Particle Production of Steroid Drugs Using Supercritical Fluid Processing. *Ind. Eng. Chem. Res.* **1996**, *35*, 4718−4726.

(7) Medina, I. Purification of Zopiclone by Preparative High-Performance Liquid Chromatography. *J. Liq. Chromatogr. Relat. Technol.* **1998**, *21* (17), 2689−2698.

(8) Medina, I. Purification of 2-Methoxyethyl 1-methylethyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3, 5 dicarboxylate by Preparative High-Performance Liquid Chromatography. *Analusis* **1999**, *27*, 447−451.

(9) Kurnik, R. T.; Reid, R. C. Solubility of Solid Mixtures in Supercritical Fluids. *Fluid Phase Equilibr.* **1982**, *8*, 93−105.

(10) Iwai, Y.; Fukuda, T.; Koga, Y.; Aral, Y. Solubilities of Myristic Acid, Palmitic Acid, and Cetyl Alcohol in Supercritical Carbon Dioxide at 35 °C. *J. Chem. Eng. Data* **1991**, *36*, 430−432.

(11) Fat'hi, M. R.; Yamini, Y.; Shargi, H.; Shamsipur, M. Solubilities of Some 1,4-Dihydroxy-9,10-anthraquinone Derivatives in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **1998**, *43*, 400−402.

(12) Medina, I. Preparative High-Performance Liquid Chromatography for the Purification of Nitrendipine and its Dimethylester. *J. Liq. Chromatogr. Relat. Technol.* **1999**, *22* (17), 2689−2698.

(13) Chrastil, J. Solubility of Solids and Liquids in Supercritical Gases. *J. Phys. Chem.* **1982**, 86, 3016−3021.

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