

Solubility of Acetazolamide in Supercritical Carbon Dioxide in the Presence of Ethanol as a Cosolvent

Ana Rita C. Duarte,[†] Susana Santiago,[‡] Hermínio C. de Sousa,[‡] and Catarina M. M. Duarte^{*†}

Nutraceuticals and Delivery Laboratory, ITQB/IBET, Apartado 12 – 2781-901 Oeiras, Portugal, and Departamento de Engenharia Química, FCT, Universidade de Coimbra, Pólo II – Pinhal de Marrocos, 3030-290 Coimbra, Portugal

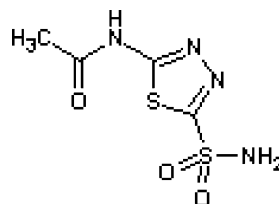
Equilibrium solubility of acetazolamide, a carbonic-anhydrase inhibitor, in supercritical carbon dioxide in the presence of a cosolvent was measured by a static analytical method for three mole fractions of ethanol (5, 7.5, and 10) % at 313.0 K from (13.0 to 21.0) MPa and at 323.0 K from (13.0 to 21.0) MPa for a mole fraction of 5% ethanol. The presence of a cosolvent (ethanol) was essential for the solubilization of the bioactive compound in supercritical carbon dioxide. The results obtained are useful for the design of supercritical processes with this drug. Experimental solubility data were correlated with two enhanced density-based models (Chrastil, I. Solubility of Solids in Supercritical Gases. *J. Phys. Chem.* **1982**, *86*, 3016–3021; Santiago, J. M.; Teja, A. S. The solubility of solids in supercritical fluids. *Fluid Phase Equilib.* **1999**, *158–160*, 501–510).

Introduction

This work is part of a research project designed for the development of polymeric controlled drug release systems (CDRS) for ophthalmic applications, namely, for glaucoma and several other corneal pathologies treatments, using “clean and environmental friendly” supercritical processes.

Glaucoma is the term used for a group of ophthalmic disorders characterized by an increase in intraocular pressure, which results in damage to the optic disk and visual field disturbances. It is the leading cause of irreversible blindness in the world. Agents used to treat glaucoma are designed to decrease intraocular pressure. Various classes of drugs used in the treatment of glaucoma include, among others, carbonic anhydrase inhibitors (CAIs). Acetazolamide (*N*-5-sulfamoyl-1,3,4-thiadiazol-2-yl)-acetamide (Figure 1) is a CAI and has been an integral part of antiglaucoma treatment for more than 40 years. However, it presents several systemic side effects. Controlled drug release systems for glaucoma treatment can prolong the drug duration action, increase ocular bioavailability, and avoid ocular and nonocular side effects as well as large fluctuation in ocular drug concentration.¹

The preparation of these controlled release systems can involve the use of supercritical fluid technology by taking advantage of its properties. In products for medical and pharmaceutical applications, the presence of residual organic solvents is rigorously controlled by international safety regulations. Thus, it is necessary to warrant the complete removal and absence of these substances without exposing the polymers and drugs contained in a typical polymeric controlled drug release system to high temperatures that could degrade them. In this sense, supercritical fluids (SCFs) can be very attractive solvents. Supercritical carbon dioxide ($t_c = 31\text{ °C}$ and $p_c = 73\text{ bar}$), because of its relatively low critical temperature, is less likely to degrade thermally labile substances. SC carbon dioxide has other



acetazolamide

MW = 222.25 g.mol⁻¹

m.p. = 258–259 °C

Figure 1. Chemical structure of acetazolamide, CAS [59-66-5], (*N*-5-sulfamoyl-1,3,4-thiadiazol-2-yl)-acetamide.

import advantages, including its nontoxicity, nonflammability, and inexpensiveness. Some CDRS and other medical applications have been developed using techniques involving SC CO₂.^{2–9} The design of chemical and pharmaceutical processes based on SCFs and the determination of their best operating conditions require a knowledge of phase equilibria and drug solubility in a supercritical fluid. In the last two decades, the solubility of a large number of different low-volatility compounds in SCFs has been measured, reported, and reviewed.^{10–18} However, the development of new supercritical processes and new applications for existing substances has maintained the need for new experimental solubility determinations.

For organic compounds having high molecular masses, supercritical solubility is usually low. Thus, high temperatures and pressures are required for substantial solid loadings in a supercritical phase. For example, although carbon dioxide is the most common SCF used by industry, it does have limitations due to its lack of polarity and its associated deficiency of specific solvent–solute interactions that would lead to high loading and/or selectivity for polar organic compounds. To improve polarity/selectivity, it was found that the addition of small amounts of a so-called cosolvent or entrainer (usually a polar substance) to a SCF can produce dramatic effects on its solvent power, some-

* To whom correspondence should be addressed. E-mail: eduarte@itqb.unl.pt. Fax: +351 21 4421161.

[†] ITQB/IBET.

[‡] Universidade de Coimbra.

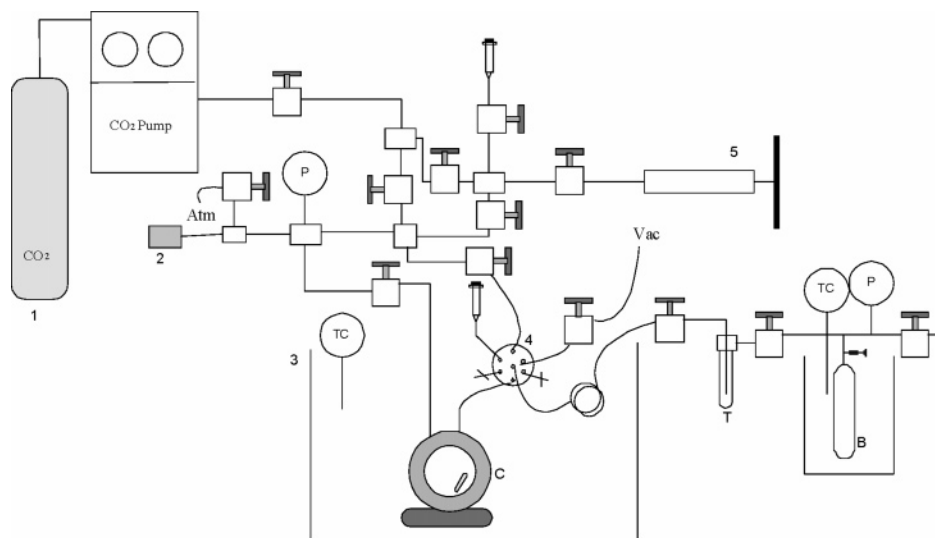


Figure 2. High-pressure apparatus for solubility measurements: (1) CO₂ compressor; (2) rupture disk; (3) thermostatic water bath; (4) six-port sampling HPLC valve; (5) manual syringe; (P) pressure transducer; (TC) temperature controller; (C) equilibrium cell with sapphire windows; (T) glass trap; (B) expansion calibrated cylinder.

times up to several hundred percent solubility enhancement.^{19,20} The entrainer can be a gas, a liquid, or a supercritical fluid.²¹

In this work, the equilibrium solubility of acetazolamide in supercritical carbon dioxide in the presence of a cosolvent was measured for three mole fractions of ethanol (5, 7.5, and 10%) at 313.0 K from (13.0 to 21.0) MPa and at 323.0 K from (13.0 to 21.0) MPa for a mole fraction of ethanol of 5%. The static analytical apparatus used for solubility measurements is briefly described, and the experimental procedure is presented. Solubility data results were correlated by applying the Chrastil and Mendez-Santiago and Teja empirical density-based model.

Experimental Section

Materials. Acetazolamide, (*N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide, CAS [59-66-5] (99% purity), was purchased from Sigma-Aldrich. Dimethyl sulfoxide, CAS [67-68-5] (99.9% purity), was purchased from Sigma-Aldrich. Ethanol, CAS [64-17-5] (99.8% purity), was purchased from Riedel-de Hën. Carbon dioxide (99.998 mol %) was supplied by Air Liquide. All chemicals were used without any further purification.

Experimental Procedures. The solubility of acetazolamide in the presence of a cosolvent was measured using a static analytical high-pressure apparatus, schematically presented in Figure 2. The determination of the solubility was performed in a similar manner similar to that described by Matias et al.²² A stainless steel equilibrium cell equipped with two sapphire windows, with an internal volume of approximately 30 cm³, is immersed in a thermostatic water bath, heated by means of a controller that maintained temperature within ± 0.1 °C. The cell is initially loaded with the solid and a magnetic internal stirrer. A manual syringe pump (HIP, model 87-6-5) was coupled to the system and was kept at constant temperature with circulating water coming from a thermostatic bath. The volume of ethanol necessary to prepare a mixture with a predetermined ethanol mole fraction was iteratively calculated, on the basis of the density of the cosolvent and the amount of CO₂ present in the syringe, at the operational (*p*, *T*) conditions. The quantity of carbon dioxide was calculated using the EOS for this fluid.²³

The syringe is then loaded with this volume of ethanol (± 1 μ L) and pressurized with fresh CO₂. In all of the

experiments, the cell was pressurized with the mixture of ethanol and carbon dioxide inside this syringe pump. The pressure inside the cell is measured with a pressure transducer (SETRA, model 204, (0 to 34.40 \pm 0.04) MPa), calibrated between (0 and 20.6) MPa.

The mixture of CO₂ + ethanol + acetazolamide is stirred for 1 h, a typical equilibration time. After 30 min of rest for equilibration, samples from the gas (top) phase are taken through a six-port sampling HPLC valve. These samples were collected by a quick depressurization and expansion into a small glass trap. The gas in the samples is expanded into calibrated volumes, and the amount of CO₂ in each sample is calculated from the measurement of the resulting subatmospheric pressure increase at the working temperature.

Pressure, after the expansion, was measured with a pressure transducer (SETRA, model 204, (0 to 0.17 \pm 2.0 $\times 10^{-4}$) MPa). To ensure that all solute is recovered in the trap, dimethyl sulfoxide is injected through the sample loops and expansion lines. Finally, the lines are cleaned with fresh carbon dioxide that has been smoothly pressurized.

Analytical Method. The collected samples were diluted in dimethyl sulfoxide to a convenient volume. Dimethyl sulfoxide was chosen because the solubility of the drug in this solvent is higher than in any other one. To determine the amount of acetazolamide ($\pm 0.5\%$), the resulting solutions were analyzed by UV spectrophotometry in a UV-vis spectrometer (Cary 3E, Varian). Acetazolamide absorbs in the UV region, with a maximum absorbance at 265 nm. Calibration was obtained by using standard samples with concentrations between (4.0×10^{-5} and 2.0×10^{-4}) M.

Each data point is the average of at least four measurements with an average absolute relative deviation, AARD, of 1%.

$$\text{AARD}(\%) = \frac{100}{n} \sum_{i=1}^n \frac{|S_{\text{calcd}} - S_{\text{exptl}}|}{S_{\text{exptl}}} \quad (1)$$

where S_{exptl} and S_{calcd} are the experimental and calculated solubilities for *n* data points.

Results and Discussion

Ethanol is one of the few organic solvents considered suitable for contact with products for human consumption,

Table 1. Solubilities of Acetazolamide in Supercritical Carbon Dioxide in the Presence of Ethanol

T/K	$x_3/\%$	p/MPa	$\rho^a/\text{kg}\cdot\text{m}^{-3}$	$10^5 y_2$	$S/\text{g}\cdot\text{L}^{-1}$
313	5	15.0	829.2	0.570	0.023
		17.2	853.8	0.669	0.027
		18.1	864.1	0.726	0.030
		20.2	883.8	0.888	0.038
	7.5	15.0	856.6	0.830	0.033
		17.1	875.7	0.842	0.035
		18.2	885.2	1.011	0.042
	10	13.1	860.2	1.050	0.046
		15.1	878.0	1.190	0.047
		17.1	893.3	1.277	0.052
		18.1	900.7	1.266	0.053
		20.1	914.3	1.392	0.059
323		5	15.1	759.1	0.735
		17.1	788.9	0.799	0.030
		18.1	802.6	0.839	0.032
		20.1	825.9	0.898	0.036

^a The densities of the mixture ($\text{CO}_2 + \text{ethanol}$) were calculated using the phase equilibria program developed in Professor Gerd Brunner's department "Thermische Verfahrenstechnik" at the University of Hamburg–Harburg.

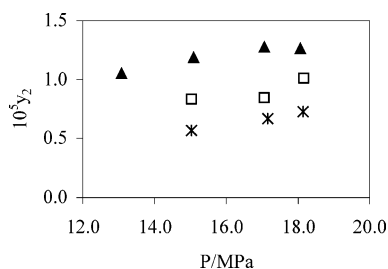


Figure 3. Mole fraction solubility of acetazolamide as a function of pressure in supercritical CO_2 in the presence of ethanol at 313 K: *, 5% ethanol; □, 7.5% ethanol; ▲, 10% ethanol.

at moderate concentrations. In this work, the solubility of acetazolamide in carbon dioxide in the presence of ethanol was determined for three mole fractions of ethanol (5, 7.5, and 10) % at 313.0 K from (13.0 to 21.0) MPa and at 323.0 K from (13.0 to 21.0) MPa for a mole fraction of 5% ethanol. In Table 1 and Figure 3, the solubility of acetazolamide is expressed in terms of the acetazolamide mole fraction ($y_{\text{acetazolamide}}$) and in terms of the mass of solute per unit volume of supercritical CO_2 .

At the two temperatures, the effect of pressure on the solute solubility follows the expected trend. The solvent capacity increases with pressure at constant temperature. This can be easily explained in simple physical terms. Density increases with increasing pressure, which means that the intermolecular mean distance of the molecules decreases and consequently the specific interaction between the solute and the solvent molecules increases, leading to higher solubility.

The ethanol cosolvent effect on acetazolamide's solubility in supercritical CO_2 was studied at 15.0 MPa and 313.0 K. Three different ethanol mole fractions, (5.0, 7.5, and 10.0)%, were investigated. The results obtained are illustrated in Figure 4, where the solubility of acetazolamide is plotted as a function of ethanol concentration. The ethanol cosolvent effect follows the expected tendency (i.e., the solubility of the compound is higher for a higher mole fraction).

Temperature is a more complex factor affecting solubility because it influences the solute vapor pressure, the solvent density, and the intermolecular interactions in the fluid phase. Whereas solute vapor pressure increases with increasing temperature, the opposite occurs regarding the

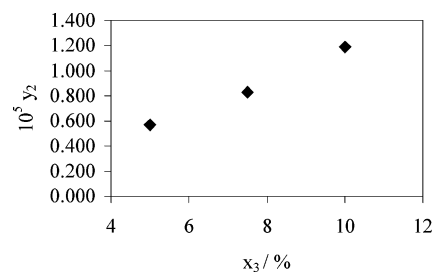


Figure 4. Effect of cosolvent, at 15.0 MPa and 313.0 K, as a function of x_3 .

solvent density. These two factors compete with each other, leading to an increase or decrease of the solubility with the increase in temperature depending on which one prevails. In this work, for the same ethanol composition the solubility increases with increasing temperature, meaning that the solute vapor pressure effect overlays the solvent density effect.

Correlation of Experimental Solubility Data. Because of the lack of information on the thermophysical data of the substances, the correlation of solubility data is, in most cases, done using simple empirical correlations such as density-based equations. These empirical models are based on simple error minimization using least-squares methods, and for the majority of them, there is no need to estimate and use thermophysical properties. The most commonly used model is Chrastil's model,²⁴ which correlates the solubility of a solute in a supercritical solvent to the density and temperature. This model is based on the hypothesis that each molecule of a solute associates with k molecules of a supercritical solvent to form a solvato complex, which is in equilibrium with the system. The Chrastil relationship between solubility and density can be expressed as

$$\ln S = k \ln \frac{\rho}{\rho_0} + \frac{a}{T} + b \quad (2)$$

where S is the solubility of the compound in scCO_2 , ρ is the density of the pure CO_2 ($\rho_0 = 1 \text{ g}\cdot\text{L}^{-1}$) at the experimental absolute temperature T and pressure p . The constant k expresses an average equilibrium association number, which is a characteristic constant for a given gas–solute system. The parameter a is defined as $\Delta H/R$, where ΔH is the sum of the enthalpies of vaporization and solvation. Finally, the parameter b is dependent on the molecular weights of solvent and solute.

The Chrastil model is usually applied to pure fluids; however, it can be applied to mixtures at constant composition, with the hypothesis that these mixtures behave like pure fluids.²⁵ It is important to notice that the density now does not correspond to the density of the pure fluid but it corresponds to the density of the mixture ($\text{CO}_2 + \text{cosolvent}$). The density of the mixture was calculated using a phase equilibria computer program. In this case, the constant k corresponds to the sum of the number of molecules of solvent and cosolvent associated with one molecule of the solute.

Mendez-Santiago and Teja have presented another empirical model based on the theory of infinitely dilute solutions.¹⁵ An equation that follows a simple relationship for the solubility of solids in supercritical fluids was deduced:

$$T \ln \frac{y_2 p}{P_2^{\text{sub}}} = A + B\rho \quad (3)$$

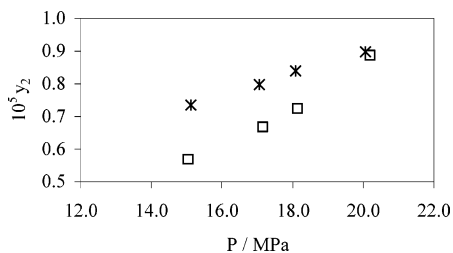


Figure 5. Effect of temperature on the solubility of acetazolamide for a mole fraction of ethanol of 5%: □, 313 K; *, 323 K.

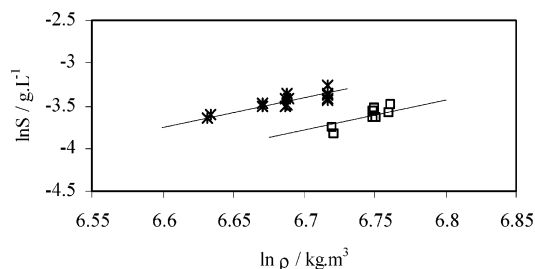


Figure 6. Logarithmic relationship between the solubility of acetazolamide and the density of the mixture (CO₂ + ethanol): □, 313 K; *, 323 K. The lines represent the regression fit using the Chrastil equation.

where T is the temperature, y_2 is the solubility of the compound in terms of mole fraction, p is the pressure, p_2^{sub} is the sublimation pressure of the solid at temperature T , ρ the density of the fluid, and A and B are constants independent of the temperature.

Because the sublimation pressures are not often available, a Clausius–Clapeyron-type expression for the sublimation pressure was incorporated, and a semiempirical relation, with three adjustable parameters, for the solid solubility was derived:²⁵

$$T \ln \frac{y_2 p}{p^{\text{std}}} = A_1 + B_1 \rho_1 + C_1 T \quad (4)$$

where p^{std} is the standard pressure and ρ_1 is the density of the ethanol + carbon dioxide mixture.

A similar equation, with four parameters, can be rewritten to correlate the effects of density, temperature, and cosolvent composition at the same time:²⁵

$$T \ln \frac{y_2 p}{p^{\text{std}}} = A_2 + B_2 \rho_1 + C_2 T + D_2 x_3 \quad (5)$$

where x_3 is the mole fraction of cosolvent.

The correlation of the solubility of acetazolamide in supercritical CO₂ is very important for the application of supercritical fluid technology in processing this bioactive compound. In this work, the experimental solubility data for acetazolamide were correlated using the previously described semiempirical models.

In the Chrastil model, the logarithmic solubility–density relationship shows a linear behavior for all the isotherms, as illustrated in Figure 6. By performing a multiple linear regression on $\ln S$ as a function of $\ln \rho$ and $1/T$, one obtains $k = (3.4 \pm 0.4)$, $a = (-3981 \pm 407)$ K, and $b = (-14.2 \pm 2.0)$. The thermodynamic quantity ΔH can be calculated directly from a , resulting, for the studied system, in a value of -62.98 kJ mol⁻¹. The average absolute relative deviation of the fitted Chrastil equation from experimental data was 5%.

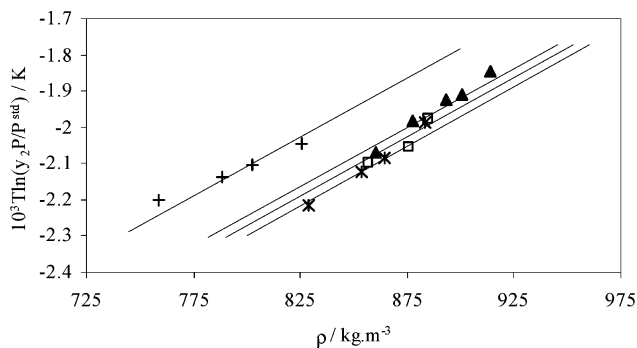


Figure 7. $T \ln(y_2 p / p^{\text{std}})$ as a function of ρ at 313 K: *, 5% ethanol; □, 7.5% ethanol; ▲, 10% ethanol. At 323 K, +, 5% ethanol: experimental solubility data correlated with eq 5.

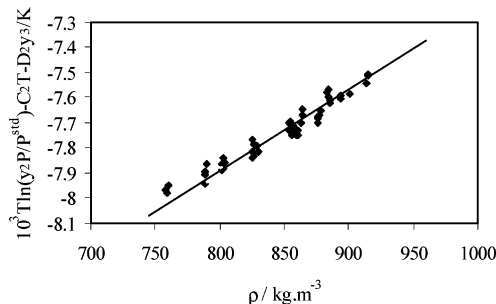


Figure 8. $T \ln(y_2 p / p^{\text{std}}) - C_2 T - D_2 x_3$ vs ρ : experimental solubility data correlated with eq 5.

The parameters of the correlation by Mendez-Santiago and Teja are the following: A_2 , B_2 , C_2 , and D_2 were obtained by performing a multiple linear regression to $T \ln(y_2 p / p^{\text{std}})$ as a function of ρ , T , and x_3 . In a first attempt, the solubility data were treated independently for each ethanol composition (Figure 7). $A_2 = (-10\,236 \pm 541)$ K, $B_2 = (3.0 \pm 0.2)$ K·m³·kg⁻¹, $C_2 = (7.6 \pm 1.3)$, and $D_2 = (1736 \pm 223)$ K. Data are well fit with an AARD of about 10%. Furthermore, solubility data can be gathered and correlated with the same equation, and the results are presented in Figure 8.

Conclusions

The equilibrium solubility of acetazolamide in supercritical CO₂ in the presence of ethanol was measured by a static analytical method for three mole fractions of ethanol (5, 7.5, and 10%) at 313.0 K from (13.0 to 21.0) MPa and at 323.0 K from (13.0 to 21.0) MPa for a mole fraction of ethanol of 5%. Equilibrium solubility data, expressed in terms of acetazolamide's mole fraction, range from $(0.5 \text{ to } 1.5) \times 10^{-5}$, with an average absolute relative deviation, AARD, of 1%. At a constant temperature, the solvent capacity increases with increasing pressure. For the same ethanol composition, the solubility increases with increasing temperature.

The ethanol cosolvent effect on acetazolamide's solubility in supercritical CO₂ was studied at 15.0 MPa and 313.0 K. Three different ethanol concentrations (5.0, 7.5, and 10.0) mol % were investigated. The solubility of acetazolamide in supercritical CO₂ + ethanol increases with increasing ethanol mole fraction.

Application of Chrastil's density-based model to the experimental data leads to values of $k = (3.4 \pm 0.4)$, $a = (-3981 \pm 407)$ K, $b = (-14.2 \pm 2.0)$, and $\Delta H = -33.06$ kJ·mol⁻¹. These data were correlated with a maximum AARD of 5%.

The Mendez-Santiago and Teja model was also applied, and the parameters determined were $A_2 = (-10\,236 \pm 541)$

K , $B_2 = (3.0 \pm 0.2) \text{ K} \cdot \text{m}^3 \cdot \text{kg}^{-1}$, $C_2 = (17.6 \pm 1.3)$, and $D_2 = (1736 \pm 223) \text{ K}$. Data are well fit with an AARD of about 10%.

The solubility results obtained in this work are very promising for the development of supercritical processes for pharmaceutical applications based on this drug.

Literature Cited

- (1) Kaur, I. P.; Smitha, R.; Aggarwal, D.; Kapil, M. Acetazolamide: future perspectives in topical glaucoma therapeutics. *Int. J. Pharm.* **2002**, *248*, 1–14.
- (2) Kikic, I.; Sist, P. Applications of Supercritical Fluids to Pharmaceuticals: Controlled Drug Release Systems. In *Supercritical Fluids: Fundamentals and Applications*, Proceedings of the 2nd NATO ASI on Supercritical Fluids; NATO Science Series; Kiran, E., Debenedetti, P. G., Peters, C. J., Eds.; Kluwer: Dordrecht, The Netherlands, 2000; pp 291–306.
- (3) Foster, N.; Mammucari, R.; Dehgahani, F.; Barrett, A.; Benzanehtak, K.; Coen, E.; Combes, G.; Meure, L.; Ng, A.; Regtop, H. L.; Tandaya, A. Processing Pharmaceutical compounds using dense gas technology. *Ind. Eng. Chem. Res.* **2003**, *42*, 6476–6493.
- (4) Guney, O.; Akgerman, A. Synthesis of controlled-release products in supercritical medium. *AIChE J.* **2002**, *48*, 856–866.
- (5) Kazarian, S. G. Polymer processing with supercritical fluids. *Polym. Sci. Ser. C* **2000**, *42*, 78–101.
- (6) Knez, Z.; Weidner, E. *Precipitation of Solids with Dense Gases, in High-Pressure Process Technology: Fundamentals and Applications*; Bertuccio, A., Vetter, G., Eds.; Elsevier Science: Amsterdam, The Netherlands, 2001; pp 587–611.
- (7) Sproule, T. L.; Lee, J. A.; Li, H.; Lannutti, J. J.; Tomasko, D. L. Bioactive polymer surfaces via supercritical fluids. *J. Supercrit. Fluids* **2004**, *28*, 241–248.
- (8) Jung, J.; Perrut, M.; Particle design using supercritical fluids: literature and patent survey. *J. Supercrit. Fluids* **2001**, *20*, 179–219.
- (9) Kikic, I.; Vecchione, F. Supercritical impregnation of polymers. *Curr. Opin. Solid State Mater. Sci.* **2003**, *7*, 399–405.
- (10) Burgos-Solórzano, G. I.; Brennecke, J. F.; Stadtherr, M. A. Solubility measurements and modeling of molecules of biological and pharmaceutical interest with supercritical CO₂. *Fluid Phase Equilib.* **2004**, *220*, 55–67.
- (11) Li, Q.; Zhang, Z.; Zhong, C.; Liu, Y.; Zhou, Q. Solubility of solid solutes in supercritical carbon dioxide with and without cosolvents. *Fluid Phase Equilib.* **2003**, *207*, 183–192.
- (12) Duarte, A. R. C.; Coimbra, P.; Sousa, H. C. De; Duarte, C. M. M. Solubility of Flurbiprofen in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2004**, *49*, 449–452.
- (13) Dohrn, R.; Brunner, G. High-pressure fluid phase equilibria: Experimental methods and system investigated (1988–1993). *Fluid Phase Equilib.* **1995**, *106*, 213–282.
- (14) 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.
- (15) Santiago, J. M.; Teja, A. S. The solubility of solids in supercritical fluids. *Fluid Phase Equilib.* **1999**, *158–160*, 501–510.
- (16) Lucien, F. P.; Foster, N. R. Solubilities of solid mixtures in supercritical carbon dioxide: a review. *J. Supercrit. Fluids* **2000**, *17*, 111–114.
- (17) Jouyban, A.; Chan, H.-K.; Foster, N. R. Mathematical representation of solute solubility in supercritical carbon dioxide using empirical expressions. *J. Supercrit. Fluids* **2002**, *24*, 19–35.
- (18) Saucéau, M.; Letourneau, J.-J.; Freiss, B.; Richon, D.; Fages, J. Solubility of eflucimibe in supercritical carbon dioxide with or without a cosolvent. *J. Supercritical Fluids* **2004**, available online.
- (19) Brunner, G. Selectivity of supercritical compounds and entrainers with respect to model substances. *Fluid Phase Equilib.* **1983**, *10*, 289–298.
- (20) Eckert, C. A.; Knutson, B. L.; Debenedetti, P. G. Supercritical fluids as solvents for chemical and materials processing. *Nature* **1996**, *383*, 313–318.
- (21) Schmitt, W. J.; Reid, R. C. The use of entrainers in modifying the solubility of phenanthrene and benzoic acid in supercritical carbon dioxide and ethane. *Fluid Phase Equilib.* **1986**, *32*, 77–99.
- (22) Matias A. A.; Nunes A. V. M.; Casimiro T.; Duarte C. M. M. Solubility of Coenzyme Q10 in Supercritical Carbon Dioxide. *J. Supercrit. Fluids* **2004**, *28*, 201–206.
- (23) *Thermodynamic Properties of Fluids*. Program from the Center of Applied Thermodynamic Studies, College of Engineering, University of Idaho, Moscow, Idaho, 1991.
- (24) Chrastil, I. Solubility of Solids in Supercritical Gases. *J. Phys. Chem.* **1982**, *86*, 3016–3021.
- (25) Saucéau, M.; Letourneau, J.-J.; Richon, D.; Fages, J. Enhanced density-based models for solid compound solubilities in supercritical carbon dioxide with cosolvents. *Fluid Phase Equilib.* **2003**, *208*, 99–113.

Received for review July 28, 2004. Accepted October 20, 2004. A.R.C.D. is grateful for financial support from a SFRH/BD/10780/2002 grant. This work was financially supported by FCT-MCES and FEDER, Portugal, under contract POCTI/FCB/38213/2001.

JE049722M