Solubilities of 5-Fluorouracil and β-Estradiol in Supercritical Carbon Dioxide

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Controlled release drug products are gaining importance in the pharmaceutical industry. Impregnation via supercritical fluids is a potential technique for the production of these products. The solubilities of the drugs in supercritical carbon dioxide are being measured, since they control the amount of drug component that can be carried by the mobile phase and therefore the impregnation period and extent. The solubilities of 5-fluorouracil and β-estradiol, used in chemotherapy and estrogen hormone therapy, respectively, are measured at pressures ranging from 100 bar to 220 bar and at 308 K to 328 K. These drugs have mass fraction solubilities of the order 10^{-6} to 10^{-4}, which are high enough to make the supercritical impregnation process a feasible alternative to impregnation employing organic solvents. The solubilities are presented as a function of solvent density and indicate higher solubilities at higher temperatures for both of the drugs. Solubilities of β-estradiol are also reported at select conditions with ethanol as a cosolvent.

Introduction

Controlled release drug systems are being used for the treatment of diseases ranging from diabetics to cancer. With the help of these new products, the total amount of effective drug is reduced, and its effect is prolonged. This avoids the problems that can originate by the introduction of excessive dosages to keep the effect as long with the traditional pharmaceutical methods. The formulation of controlled release pharmaceutical products requires the introduction of the drug to a matrix capable of releasing the active drug. The matrix in controlled drug release systems is consequently a biocompatible and biodegradable polymer. Almost exclusively, organic solvents, such as aromatics, ketones, chlorinated solvents, alcohols, tetrahydrofuran, and dimethyl sulfoxide, are used as the mobile phase to carry the drug component and, in addition, are used as the swelling agent for the polymer matrix. There are stringent regulations regarding the amount of residual organic solvents in products for human consumption, such as pharmaceuticals and food additives. Hence, there is a great incentive for developing alternative production techniques. Switching to nontoxic liquid solvents is the first alternative, but the costly solvent removal process cannot be avoided. These drawbacks are the key factors for a wider introduction of supercritical fluid technologies. Studies so far have focused on using supercritical fluids as vehicles for the formation of particles of biomedical interest (Debenedetti et al., 1993). Two techniques have been extensively studied. Rapid expansion of supercritical solutions (RESS) is an alternative to conventional size-reduction methods and a novel solvent route to solvent-free drug-loaded microspheres. Gas anti-solvent precipitation (GAS) uses supercritical fluids as an anti-solvent that causes particle precipitation from a liquid solution. In both approaches the objective has been the coprecipitation of the drug and the polymer matrix from a supercritical solvent and, ultimately, the microencapsulation of the drug in the polymer matrix. There is by now vast literature on the use of similar supercritical techniques (Reverchon, 1999; Winters et al., 1999). More recently, the feasibility of using supercritical carbon dioxide ($SCCO_2$) as a solvent for applying tablet coatings, and the possibility of using $SCCO_2$ saturated with a drug for the impregnation of the polymers for controlled release drug synthesis purposes have been studied (Broadbent et al., 1997; Alessi et al., 1998). Alessi et al. reported that they have successfully impregnated polyvinylpyrrolidone using $SCCO_2$ saturated with the drugs ketoprofen, nimesulide, and piroxicam. Another recent study reports on the successful preparation of drug delivery systems through impregnation with supercritical fluids (Kikic, 2000).

Controlled delivery products are synthesized by the impregnation of a polymer matrix with a drug component, which is a process governed by the solubilities of the desired components in the supercritical fluid and the adsorption isotherms in the presence of supercritical fluids and/or the partition coefficient of the drug between the polymer and supercritical phases. The supercritical fluid loaded with the drug component is passed over the polymer. During this process the drug either diffuses into the pores of the polymer matrix, where the drug component is adsorbed on the polymer, or is partitioned between the polymer and supercritical phases and then entrapped as the system is depressurized. The amount of the drug carried in the mobile phase is determined by the solubility of the drug in the supercritical phase. In this study, the solubilities of two drugs, 5-fluorouracil (2,4-dioxo-5-fluoropyrimidine) and β-estradiol (3,17-beta-dihydroxyestra-1,3,5(10)-triene), have been measured in supercritical carbon dioxide.

Experimental Section

Apparatus and Procedures. The solubilities of the drugs in pure carbon dioxide at supercritical conditions were measured using a dynamic measurement technique similar to that developed to determine the solubilities of

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10.1021/je000110l CCC: $19.00
Published on Web 09/09/2000

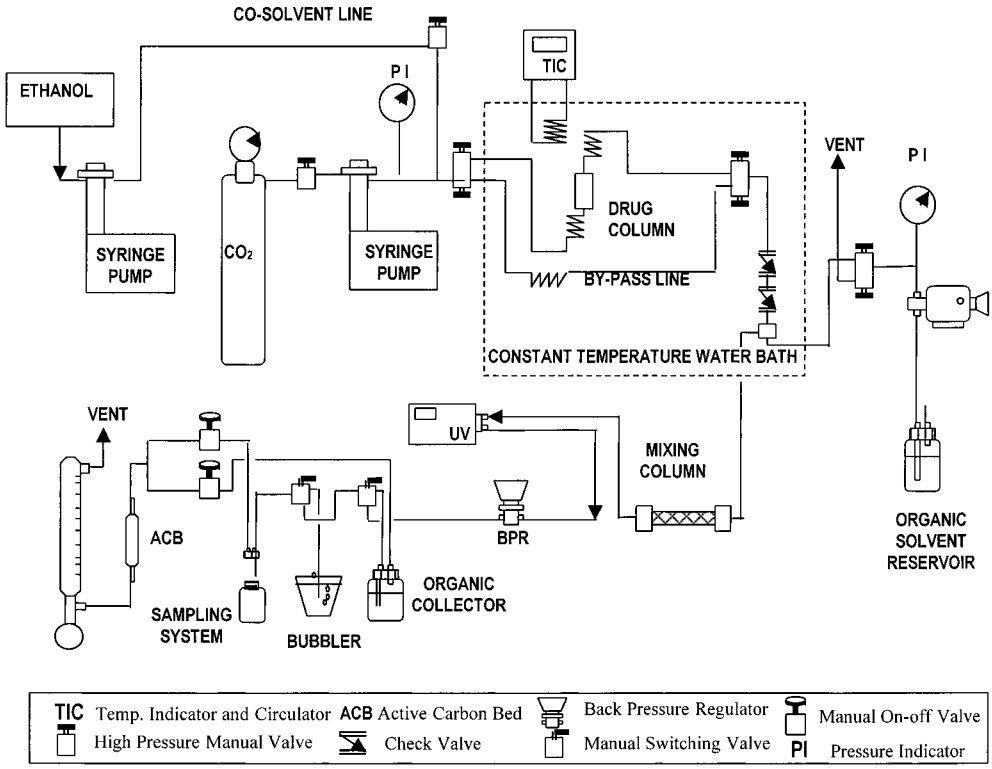

Figure 1. Experimental apparatus for the solubility measurements.

organometallic complexes, chelating agents, and ligands in supercritical carbon dioxide (Cross et al., 1996). The apparatus is shown in Figure 1.

The drug column is packed with the solid drug component and placed in a constant temperature water bath. The temperature of the water bath is controlled to 0.1 °C with an immersion circulator (Tempette Junior TE-8J model FJP8P, Techne). Carbon dioxide (99.8% minimum purity) is then compressed into an ISCO model 260D syringe pump at the desired pressure. An organic solvent is selected on the basis of two important criteria: First, the drug component needs to be soluble in the organic solvent. Second the organic solvent should be invisible to the on-line UV/vis spectrophotometer (DYNAMAX absorbance detector UV-D II) at the detection wavelength. The organic solvents chosen for β-estradiol and 5-fluorouracil solubility measurements are ethyl alcohol (92% purity) and butyl alcohol (99.4% purity), respectively. The organic solvent reservoir is filled with the selected organic solvent.

The supercritical fluid is passed through the system at a constant flow rate controlled to 10^{-2} flow units (mL/h, mL/min, ..., etc.) by the ISCO 260D pump controller. The flow can be directed to either the bypass line or the drug column. The bypass line and the line before the drug column are intentionally coiled, to keep the tube length long enough in order to achieve thermal equilibrium. The supercritical fluid is combined with the organic solvent from the reservoir, which is pumped through a Techne Minipump. Two check valves in series keep the organic solvent from moving toward the drug column. Once the streams are combined, they pass a mixing column packed with glass beads to ensure a one-phase mixed system. This technique of mixing the supercritical fluid with an organic solvent before expansion eliminates the problems associated with clogging due to solute crystallization. During the expansion, the supercritical fluid and the organic solvent form a two-phase system and the solute that crystallizes out of the supercritical phase dissolves in the organic phase.

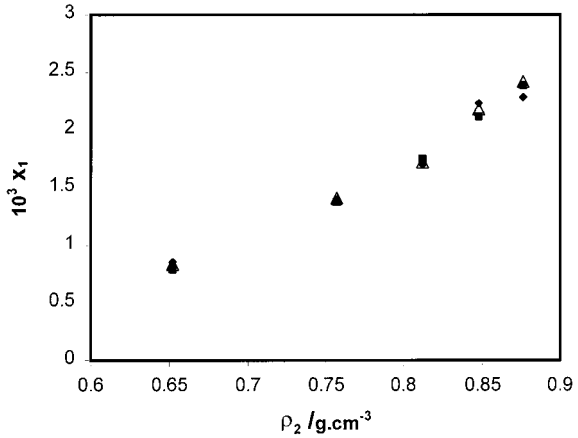

Figure 2. Mole fraction solubility of phenanthrene (1) in supercritical carbon dioxide (2) as a function of density: (◆) Kurnik et al. (1981); (■) Cross et al. (1996); (△) this study.

Initially, the saturation column is bypassed to obtain a baseline at the UV detector and to stabilize the flow rates and reach steady state. Then the supercritical phase flow is directed through the drug-packed column. Due to small volume differences, minor flow adjustments are made after switching to the drug column. While the supercritical stream is being saturated with the drug, the pressure should be steady. When a constant UV response is read, solute saturation is reached. System pressure is released through the back pressure regulator, and a separator is used to vent off the gas and collect samples in the organic solvent. The on-line UV detector serves only in a qualitative manner to determine when the saturation is reached and when sampling should begin. The absorbance data are recorded by the data acquisition system (Quick Log, Strawberry Tree Products) throughout the process. The samples are analyzed off line by another UV/vis detector operating in conjunction with software, where the spectra

Table 1. Mole Fraction Solubilities of Phenanthrene (1) in $SCCO_2$ at 318 K

p	$\rho(CO_2)$	x_1		
bar	g·cm^{-3}	Kurnik et al., 1981	Cross et al., 1996	this study, 1999
265	0.8760	2.28×10^{-3}	2.39×10^{-3}	$2.42 \times 10^{-3} \pm 1.07 \times 10^{-4}$
240	0.8478	2.23×10^{-3}	2.11×10^{-3}	$2.18 \times 10^{-3} \pm 6.43 \times 10^{-5}$
198	0.8118	1.70×10^{-3}	1.75×10^{-3}	$1.72 \times 10^{-3} \pm 4.08 \times 10^{-5}$
160	0.7571	1.40×10^{-3}	1.38×10^{-3}	$1.41 \times 10^{-3} \pm 1.12 \times 10^{-4}$
131	0.6520	8.49×10^{-4}	7.93×10^{-4}	$8.29 \times 10^{-4} \pm 3.24 \times 10^{-5}$

Table 2. Source and Purity of Materials Used

material	source	purity (%)
CO_2	Brazos Valley Welding Supply, Inc.	99.99
ethyl alcohol	EM Science	92 (omnisolv grade)
butyl alcohol	EM Science	99.4 (guaranteed reagent)
5-fluorouracil	Sigma	99 (min)
β-estradiol	Sigma	98 (min)
phenanthrene	Aldrich	98 (min)

Table 3. Physical Properties of the Drugs Used

material	molecular form.	molecular wt	melting point (°C)
5-fluorouracil	$C_4H_3FN_2O_2$	130.08	280−282
β-estradiol	$C_{18}H_{24}O_2$	272.40	173−179

Table 4. Mass Fraction Solubilities for 5-Fluorouracil (1) in $SCCO_2$ (2)

T/K	p/bar	ρ_2/g·cm^{-3}	w_1
308	210	0.8749	$2.05 \times 10^{-6} \pm 2.84 \times 10^{-9}$
	175	0.8433	$1.39 \times 10^{-6} \pm 1.11 \times 10^{-7}$
	145	0.8115	$9.53 \times 10^{-7} \pm 6.41 \times 10^{-8}$
	110	0.7356	$4.55 \times 10^{-7} \pm 4.15 \times 10^{-10}$
328	210	0.7685	$2.86 \times 10^{-6} \pm 7.22 \times 10^{-8}$
	175	0.7106	$2.18 \times 10^{-6} \pm 8.26 \times 10^{-9}$
	145	0.6187	$1.36 \times 10^{-6} \pm 1.47 \times 10^{-9}$
	110	0.3938	$3.72 \times 10^{-7} \pm 7.22 \times 10^{-8}$

for each sample over a wide range of wavelengths are determined. Knowing the organic solvent and supercritical fluid flow rates, the collection time of the organic solvent sample, and the concentration of the solid in this sample, the solubility of the solid in supercritical fluid is calculated.

The reliability and validity of this technique have been determined by measuring the solubility of phenanthrene in supercritical carbon dioxide. There are accurate data in the literature on phenanthrene solubility. As shown in Figure 2 and Table 1, solubility measurements with this new apparatus are in excellent agreement with the data of Kurnik et al. (1981) and Cross et al. (1996).

Materials. The sources and the purities of the chemicals used in this study are listed in Table 2. They were used as supplied.

Results

The supercritical carbon dioxide solubilities of the two drugs, 5-fluorouracil and β-estradiol, were determined, and the values are listed in Table 4 and Table 5. The data in Tables 4 and 5 are plotted as a function of $SCCO_2$ density in Figures 3 and 4, respectively. Each data point in Tables 4 and 5 is the average of up to four repeat runs, all of which are plotted in the figures. The solubility data are reported as the mass fraction of the drug in supercritical carbon dioxide. The variation of $SCCO_2$ density with temperature and pressure is available in the literature (Angus et al., 1976).

The solubility measurements for 5-fluorouracil were performed using butanol, and those for β-estradiol were performed using ethanol as the organic solvent, both at a rate of 94.25 mL/h and at a supercritical carbon dioxide flow rate of 40 mL/h. The results indicated that the solubility is a strong function of the temperature and density of the solvent. The isothermal dependence of drug solubility on solvent density can clearly be seen in Figures 3 and 4. At constant solvent density, the solubility increases with an increase in temperature.

Table 5. Mass Fraction Solubilities for β-Estradiol (1) in $SCCO_2$ (2)

T/K	p/bar	ρ_2/g·cm^{-3}	w_1
308	220	0.8805	$1.26 \times 10^{-4} \pm 9.01 \times 10^{-9}$
	179	0.8450	$7.32 \times 10^{-5} \pm 1.34 \times 10^{-7}$
	140	0.7964	$4.83 \times 10^{-5} \pm 5.84 \times 10^{-8}$
	105	0.7190	$1.05 \times 10^{-5} \pm 1.68 \times 10^{-8}$
318	220	0.8314	$1.81 \times 10^{-4} \pm 7.06 \times 10^{-6}$
	180	0.7838	$1.07 \times 10^{-4} \pm 1.80 \times 10^{-9}$
	153	0.7553	$7.41 \times 10^{-5} \pm 1.61 \times 10^{-6}$
	144	0.7140	$4.70 \times 10^{-5} \pm 1.15 \times 10^{-6}$
	110	0.6132	$2.15 \times 10^{-5} \pm 7.27 \times 10^{-9}$
328	217	0.7750	$3.05 \times 10^{-4} \pm 1.43 \times 10^{-7}$
	181	0.7164	$2.03 \times 10^{-4} \pm 1.95 \times 10^{-7}$
	141	0.5981	$7.78 \times 10^{-5} \pm 4.26 \times 10^{-8}$
	114	0.4277	$1.58 \times 10^{-5} \pm 1.56 \times 10^{-7}$

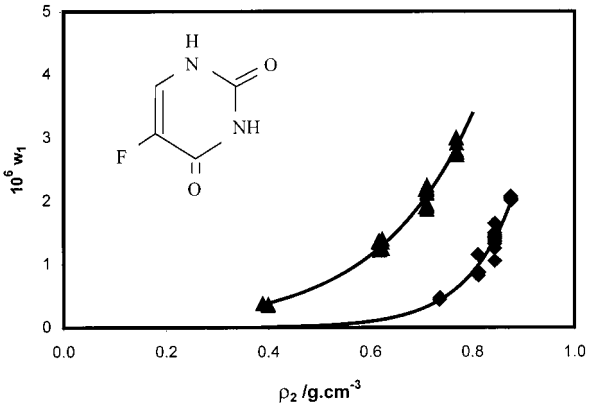

Figure 3. Mass fraction solubility of 5-fluorouracil (1) in supercritical carbon dioxide (2) as a function of density at 308 K (◆) and 328 K (▲).

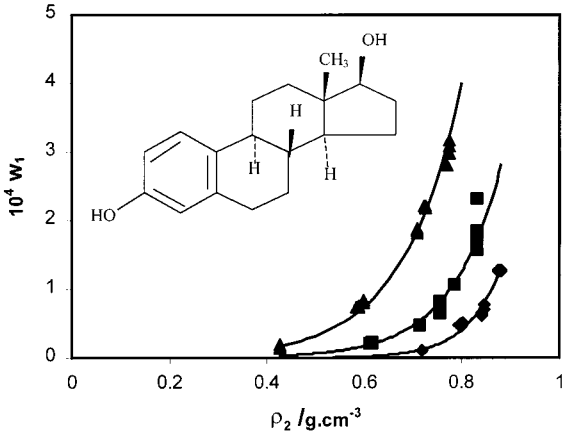

Figure 4. Mass fraction solubility of β-estradiol (1) in supercritical carbon dioxide (2) as a function of density at 308 K (◆), 318 K (■), and 328 K (▲).

Table 6. Mass Fraction Solubilities for β-Estradiol (1) in Ethanol (2) + $SCCO_2$ (3)

T/K	p/bar	$100w_2$	ρ_3/g·cm^{-3}	w_1
323	200	5	0.806 14	3.45×10^{-3}
323	200	0	0.801 85	2.76×10^{-4}
333	172	10	0.724 21	1.09×10^{-3}
333	172	0	0.701 65	1.74×10^{-4}
343	172	12.5	0.727 12	7.77×10^{-4}
343	172	0	0.641 744	1.04×10^{-4}

The mass fraction solubilities of β-estradiol have also been determined using ethanol as a cosolvent. Ethanol is delivered from an ISCO 500LC syringe pump at a constant flow rate and mixed with the pure supercritical carbon dioxide stream before entering the constant temperature heat bath (Figure 1). The experiment follows the same steps as for pure $SCCO_2$. The supercritical fluid densities with ethanol as the cosolvent were determined from data of Pohler and Kiran (1997). The results are the averages of two repeat runs and are tabulated in Table 6 as a function of supercritical fluid density in mass fraction solubility of β-estradiol. The solubilities are up to 20 times higher than the values in pure $SCCO_2$.

Discussion and Conclusion

The solubility measurements for two drugs, 5-fluorouracil and β-estradiol, in supercritical carbon dioxide have been determined. The solubility is a strong function of the temperature and density of the solvent and increases with isochoric increases in temperature for both of the drugs. The solubility of β-estradiol, although it is a much larger molecule and previous studies show that fluorinated compounds have higher solubilities in supercritical carbon dioxide (Laintz and Wai, 1992), is about 2 orders of magnitude higher than that of 5-fluorouracil under the same conditions.

This unpredicted behavior could be explained by the difference between the melting points of the drugs (Krukonis and Kurnik, 1985). The melting point of 5-fluorouracil is >100 °C higher than that of β-estradiol, as shown in Table 3. Dissolution, like melting, involves overcoming the intermolecular forces of the crystal. The more symmetrical a compound, the better it fits into a crystalline lattice. Hence, higher melting point and lower solubility are general effects of molecular symmetry on intracrystalline forces (Morrison and Boyd, 1987).

Although the solubility of β-estradiol in supercritical carbon dioxide has been considerably enhanced by the introduction of a cosolvent, the solubilities of the drugs in pure carbon dioxide were proven to be high enough to carry on impregnation applications on biodegradable polymer matrixes for the synthesis of controlled delivery products.

Literature Cited

Alessi, P.; Cortesi, A.; Kikic I. Effect of Operating Parameters on the Impregnation of Polymers with Drugs. *Proceedings of the 5th Meeting on Supercritical Fluids*, Nice, 1998; pp 373−378.

Angus, P.; Armstrong, B.; DeReuck, K. M. *Carbon Dioxide International Thermodynamic Tables of the Fluid State−3*; IUPAC Project Centre, Imperial College: London, 1976; Vol. 3, pp 266−359.

Broadbent, A.; England, R.; Staniforth, J. N.; Crittenden, B. D. The Potential of Supercritical Carbon Dioxide as a Solvent in the Production of Pharmaceutical Products. *Proceed. 4th Italian Conference on SCFs and their Applications*, Capri, Italy, 1997; pp 11−17.

Cross, W., Jr.; Erkey, C.; Akgerman, A. Determination of Metal-Chelate Complex Solubilities in Supercritical Carbon Dioxide. *Ind. Eng. Chem. Res.* **1996**, *35*, 1765−1770.

Debenedetti, P. G.; Tom, J. W.; Yeo, S.-D.; Lim, G.-B. Application of SCFs for the Production of Sustained Delivery Devices. *J. Controlled Release* **1993**, *24*, 27−44.

Kikic, I. Preparation of Drug Delivery Systems through Impregnation with Supercritical Fluids. *Proceedings of the 5th International Symposium on Supercritical Fluids*, Atlanta, GA, 2000.

Krukonis, V. J.; Kurnik, R. T. Solubility of Solid Aromatic Isomers in Carbon Dioxide. *J. Chem. Eng. Data* **1985**, *30*, 247−249.

Kurnik, R. T.; Holla, S. J.; Reid, R. C. Solubility of Solids in Supercritical Carbon Dioxide and Ethylene. *J. Chem. Eng. Data* **1981**, *26*, 47−51.

Laintz, K. E.; Wai, C. M. Extraction of Metal Ions from Liquid and Solid Materials by Supercritical Carbon Dioxide. *Anal. Chem.* **1992**, *64*, 2875−2878.

Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 5th ed.; Boston, 1987; pp 535−537.

Pohler, H.; Kiran, E. Volumetric Properties of Carbon Dioxide + Ethanol at High Pressures. *J. Chem. Eng. Data* **1997**, *42*, 384−388.

Reverchon, E. Supercritical Antisolvent Precipitation of Micro- and Nano-Particles. *J. Supercrit. Fluids* **1999**, *15*, 1.

Winters, M. A.; Frankel, D. Z.; Debenedetti, P. G. Protein Purification with Vapor-Phase Carbon Dioxide. *Biotech. Bioeng.* **1999**, *62*, 247.

Received for review April 12, 2000. Accepted July 14, 2000.

JE000110L