Solubility of Polycaprolactone in Supercritical Carbon Dioxide with Ethanol as Cosolvent

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The solubility of a polycaprolactone polymer with molecular weight of 1000 g·mol^{-1} (CAPA 2101A) in supercritical carbon dioxide with ethanol as cosolvent has been measured with a variable volume view cell according to the synthetic method. Three isotherms with temperatures ranging from (303 to 330) K were measured in the pressure range of (10 to 25) MPa, maintaining a constant ethanol molar fraction of 0.075. Polycaprolactone solubilities up to 0.2 % in mass were observed. Additionally, the perturbed hard-sphere-chain equation of state (PHSC EoS) has been used to correlate the experimental data.

Introduction

A new dimension for the use of polymeric materials as drug delivery devices involves the incorporation of biodegradability into the system. A number of degradable polymers are potentially useful for this purpose, including a variety of synthetic and natural substances. The use of degradable polymers in medicine has been highlighted as a platform for drug delivery systems. There are two main devices for controlled drug release: the production of a composite with the drug dispersed into a polymeric matrix, which controls the drug release, and the coating or encapsulation of micro- and nanoparticles of the active substance.[1]

Polyesters, such as poly(lactic acid) (PLA), poly(glycolic acid) (PLG), and homo- and copolymers derived from them, have been widely employed in preparing carriers for controlled release of drugs and proteins. These polymers degrade by bulk hydrolysis of ester bonds, and their rate of degradation depends on several parameters such as chemical structure, crystallinity, hydrophobicity, and molecular weight.[2] Their therapeutic value has been enormously increased by the possibility of processing them as micro- and nanoparticles, which have distinct advantages for oral and parenteral administration. The successful use of these polymers in pharmaceutical applications has led to the evaluation of other aliphatic polyesters such as poly(ε-caprolactone) (PCL).

PCL is a synthetic biocompatible semicrystalline polymer. The linear aliphatic structure of its monomer is shown in Figure 1. PCL exhibits a low glass-transition temperature (from (−60 to −10) °C, depending on its molecular weight) that imparts a rubbery characteristic to the material, which results in high permeability. This property has been exploited for the delivery of low-molecular-weight drugs such as steroids and vaccines.[3] It has also been used as a platform for high-molecular-weight substances such as proteins, where protection against degradation has been proven to be better than the protection achieved with other polyesters.[4,5]

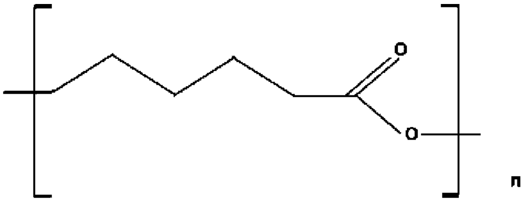

Figure 1. Caprolactone monomer.

Supercritical-fluid (SCF)-based technologies for the production of composites and encapsulates with biopolymers show several important advantages, such as the possibility of operating at mild temperatures without degradation or contamination of the product or the capacity to achieve a better control of product characteristics. Several of these formulation technologies have been proposed and developed in which the SCF plays different roles as solvent, antisolvent, or plasticizing and swelling agent.[6] For the development of all of these processes, knowledge of the phase behavior of the substances involved (supercritical fluid, active substance, and carrier) is essential.

Previous works about the study of the phase behavior of polycaprolactone−supercritical fluid systems are scarce. Cotugno et al.[7] reported the solubility of near-critical CO_2 in PCL (molecular weight, 80 000 g·mol^{-1}; melting temperature, 58 °C) at high temperature (from (70 to 85) °C). Leeke et al.[8] measured the solubility of supercritical CO_2 in the polymer in the temperature range from (40 to 60) °C with pressures up to 20 MPa. Domingo et al.[9] measured the solubility of a polymer blend (PMMA/PCL) in supercritical CO_2 without and with cosolvents (acetone, dichloromethane, and ethanol).

In this work, the solubility of PCL (molecular weight, 1000 g·mol^{-1}) in supercritical CO_2 using ethanol as cosolvent is reported. Moreover, a correlation of experimental data using the perturbed hard-sphere-chain equation of state (PHSC EoS) is presented.

Experimental Section

Materials. Carbon dioxide (purity, 99.5 %) was provided by S. E. Carburos Metálicos S. A. (Spain). The cosolvent, absolute ethanol (purity > 99.9 %), was purchased from Panreac S.A. (Spain). Polycaprolactone (CAPA 2101A; molecular weight, 1000 g·mol^{-1}; melting point interval, (30 to 40) °C) was kindly supplied by Solvay Caprolactones (Solvay Interox, United Kingdom). All products were used as received.

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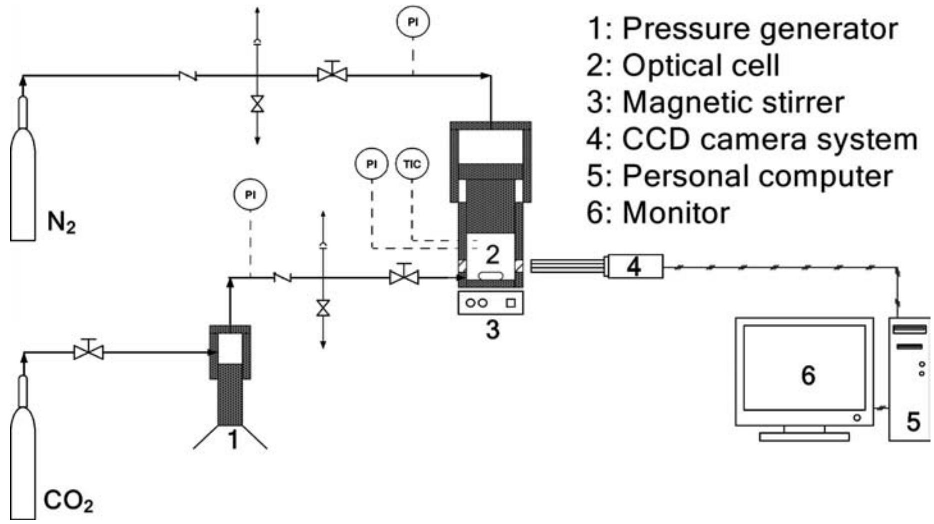

Figure 2. Schematic diagram of the solubility measurement equipment.

Differential scanning calorimetry tests (DSC822e Mettler Toledo, sensor FRS5) were performed in polycaprolactone samples to verify the melting point data provided by the supplier. A melting endotherm in the temperature interval of (23.0 to 51.5) °C and a peak at 38.5 °C were observed in the thermograms.

Equipment. A schematic diagram of the equipment used for solubility determinations is shown in Figure 2. The main part of the equipment was an optical cell (SITEC 740.2120) with a variable volume between (11 and 25) mL controlled by a piston displaceable by pressurized nitrogen. The maximum operating conditions inside the cell were 50 MPa and 200 °C. The cell had two opposite sapphire windows; through one of them a cold light lamp was situated to allow the visualization of the different processes taking place inside the cell aided by a CCD camcorder (Eurotechnica Ingenieurbüro GMBH) connected to a personal computer. The internal temperature of the cell was controlled by a PID temperature controller (Omron E5GN) acting over an electrical jacket and measuring the temperature with a J-type thermocouple (SITEC 770.5131-22; accuracy, 0.1 K). Pressure was measured with a membrane pressure meter (Desin TPR-18/V2; accuracy, 0.01 MPa). The system also had a manual pressure generator (SITEC 750.1060), used either to inject the CO_2 directly into the cell or to fill a gas cylinder with CO_2, and a magnetic stirrer (Agimatic S).

Method. We measured the solubility of the polycaprolactone in the fluid by visually determining the dew pressure at a certain temperature for a fixed mixture composition according to the synthetic method. In each experiment, a known quantity of solution (PCL in ethanol) was introduced with a syringe inside the optical cell, which was previously flushed with CO_2 to remove air. The amount and composition of this solution was determined by weight with an analytical balance (accuracy, 0.0001 g). Afterward, a known amount of CO_2 was introduced with the aid of a gas cylinder. This amount was also determined by weight with a precision balance (accuracy, 0.1 g). Then, the stirring and the electrical jacket were connected to have a homogeneous mixture at the desired operation temperature. During the experiment, the PID temperature controller maintained the temperature at the set point within ± 1 K. When the temperature was stable, the pressure was slowly increased by the displaceable piston until a single phase was visualized. Then, pressure was slowly decreased until the formation of liquid solution was observed (dew point). The process was repeated several times to reduce the pressure interval where the phase change occurred and to ensure the reproducibility of the result. This visual method allowed us to determine the dew point pressure within a pressure interval of ± 0.5 MPa. Experiments were performed at temperatures ranging from (310 to 330) K. The molar fraction of ethanol in the fluid was kept around 0.075 in all experiments with small fluctuations in the composition that were unavoidable with the method used to prepare the mixtures. Pressure was varied between (15 and 25) MPa.

Table 1. Solubility of Polycaprolactone Expressed in Molar Fraction (y) in Supercritical CO_2−Ethanol Mixtures as a Function of Temperature (T) and Pressure (P)

T	P		
K	MPa	y_{EtOH}	$y_{\mathrm{PCL}}\cdot 10^4$
310	16.2 ± 0.5	0.0745	0.342
310	16.6 ± 0.5	0.0775	0.508
310	16.9 ± 0.5	0.0761	0.525
310	16.2 ± 0.5	0.0768	0.707
310	16.8 ± 0.5	0.0751	0.778
310	18.1 ± 0.5	0.0738	0.848
320	17.8 ± 0.5	0.0745	0.342
320	20.4 ± 0.5	0.0761	0.525
320	19.2 ± 0.5	0.0774	0.622
320	19.9 ± 0.5	0.0768	0.707
320	21.4 ± 0.5	0.0751	0.778
330	21.1 ± 0.5	0.0745	0.342
330	21.8 ± 0.5	0.0774	0.622
330	23.2 ± 0.5	0.0768	0.707

Results and Discussion

The experimental results obtained in this work are presented in Table 1 and Figure 3. It can be seen that the molar fraction solubility of PCL reaches values of up to $0.85 \cdot 10^{-4}$, which corresponds to a mass fraction solubility of $0.19 \cdot 10^{-2}$. As expected, the solubility increases with increasing pressure. The solubility decreases with increasing temperature, meaning that the operation pressures are below the crossover point of the system, as expected because of the high molecular weight of PCL.[10] It must be mentioned that some of the scatter in experimental data that can be observed in Figure 3 is due to the small variations in ethanol concentrations between experiments, as displayed in Table 1.

For the correlation of this data, a phase equilibrium model of the ternary system CO_2−ethanol−PCL has been developed. This model is based on the PHSC EoS.[11] This type of equation

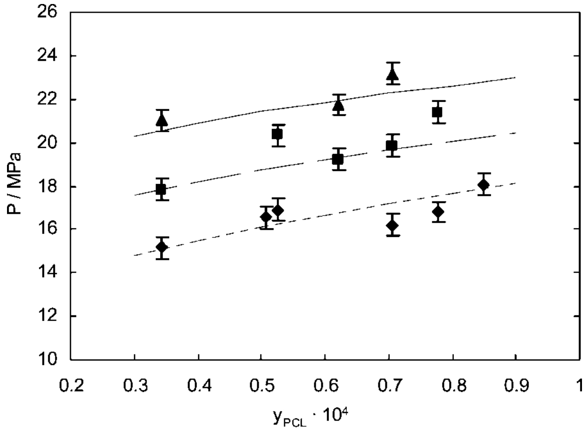

Figure 3. Comparison of experimental solubility data and PHSC model values expressed in molar fraction (y) of CAPA 2101A in an ethanol + CO_2 mixture ($y_{\mathrm{ethanol}} = 0.075$). Experimental isotherms: ◆, $T = 310$ K; ■, $T = 320$ K; ▲, $T = 330$ K. Calculated isotherms: ---, $T = 310$ K; — —, $T = 320$ K; —, $T = 330$ K.

Table 2. PHSC EoS Pure Component Parameters

substance	r	σ m	ε/k_B K
CO_2	4.275	$2.228 \cdot 10^{-10}$	121.7
ethanol	4.259	$2.030 \cdot 10^{-10}$	154.5
PCL	7.14·MW	$3.465 \cdot 10^{-10}$	203.6

is especially recommended for systems with normal fluids and polymers.[12−14] The PHSC EoS is presented in eq 1

$$\frac{P}{\rho n k_B T} = 1 + r^2 b \rho n g(d^+) - (r-1)[g(d^+) - 1] - \frac{r^2 a \rho n}{k_B T} \tag{1}$$

where P is the pressure in MPa, T is the temperature in K, ρ is the molar density in $\mathrm{mol \cdot m^{-3}}$, k_B is the Boltzmann constant in J/K, n is the number of molecules, and $g(d^+)$ is the pair radial distribution function of hard spheres at contact. Each pure component is defined by three segment-based parameters: r is the number of segments (effective hard spheres) per molecule, a represents the attraction between two nonbonded segments ($\mathrm{kPa \cdot cm^6 \cdot mol^{-2}}$), and b is the van der Waals parameter for the calculation of the covolume per segment (cubic centimeters per mole).

These latter parameters are a function of the temperature, the depth of the minimum in the pair potential (ε/J), and the distance between segments centers at this minimum (σ/m). The applicability of this equation in systems with polymers is a consequence of the clear physical meaning of these parameters for these substances.

With this equation of state, no mixing rules are required for the reference term, and the attractive term requires only van der Waals one-fluid mixing rules. No combining rule is needed for σ because of the additivity of the hard-spheres diameter. For the ε parameter, one interaction parameter, k_{ij}, is used for each binary pair, as presented in eq 2

$$\varepsilon_{ij} = (\varepsilon_i \varepsilon_j)^{0.5}(1 - k_{ij}) \tag{2}$$

The pure component parameters for the system CO_2−ethanol−PCL are presented in Table 2. CO_2 parameters have been obtained from the literature,[11] whereas ethanol parameters have been calculated by correlation of PVT and vapor pressure data of ethanol retrieved from the NIST database.[15] In the case of PCL, direct calculation of pure component parameters is not possible because detailed PVT and vapor pressure data of this substance are not available. For this reason, the parameters of PCL have been calculated by a group contribution method.[13] As presented in this table, the r parameter of PCL depends on the molecular weight (MW) of the polymer, whereas all remaining model parameters remain constant for PCLs of different molecular weight. Therefore, it is possible to use the thermodynamic model to estimate the solubility of PCLs of different molecular weight.[11]

Table 3. Binary Interaction Parameters, k_{ij}, of the PHSC EoS

	CO_2 (1)	ethanol (2)	PCL (3)
CO_2 (1)		0.0814	0.0982
ethanol (2)	0.0814		−0.1067
PCL (3)	0.0982	−0.1067	

The binary interaction parameters required by the PHSC EoS are presented in Table 3. The interaction parameter between CO_2 and ethanol, k_{12}, has been calculated by correlation of experimental vapor−liquid equilibrium data at 313 K.[16] We have performed the calculation by finding the optimum value of the interaction parameter that minimizes the deviation between experimental and calculated equilibrium pressures, quantified with the objective function presented in eq 3. For the optimization, the Nedler−Mead unconstrained nonlinear minimization algorithm implemented in the fminsearch function of Matlab 7.3 has been used. With the interaction parameter presented in Table 3, the PHSC EoS is able to calculate the vapor−liquid equilibrium of CO_2 + ethanol with an average error of average absolute pressure deviation (AAPD) of 3.9 %.

$$\mathrm{AAPD}\ \% = \sum_i \frac{|P_i^{\mathrm{exptl}} - P_i^{\mathrm{calcd}}|}{P_i^{\mathrm{exptl}}} 100 \tag{3}$$

The binary interaction parameters between CO_2 and PCL, k_{13}, and between ethanol and PCL, k_{23}, have been calculated by correlation of the solubility data presented in this work. This calculation has also been performed by minimization of the deviation between experimental and calculated dew point pressures (eq 3). With the obtained parameters, the average error between experimental and calculated dew pressures is only AAPD = 2.9 %. Figure 3 shows the results of the calculations of the model together with experimental data. For the calculations presented in this Figure, a constant ethanol molar fraction of 0.075 has been considered.

Conclusions

The solubility of polycaprolactone CAPA 2101A (molecular weight, 1000 $\mathrm{g \cdot mol^{-1}}$) in mixtures of supercritical CO_2 + ethanol has been determined. A maximum solubility of $0.848 \cdot 10^{-4}$ in molar fraction (0.0019 in mass fraction) was observed at 330 K and 22.4 MPa. Solubility data were correlated using the PHSC EoS with an average absolute pressure deviation between experiment and calculations of 2.9 %.

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