Macromol. Symp. **2007**, 259, 197–202 DOI: 10.1002/masy.200751323

Sorption and Swelling of Poly(D,L-lactic acid) and Poly(lactic-co-glycolic acid) in Supercritical CO_2

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Summary: The equilibrium sorption and swelling behavior in supercritical CO_2 of poly(D,L-lactic acid) and poly(lactic-co-glycolic acid) has been studied at a temperature of 35 °C and at pressures up to 200 bar. Sorption was measured through a gravimetric technique and swelling by visualization. From these data, the behavior of the different polymers can be compared. In terms of partial molar volume of CO_2 in the polymer matrix, all the polymers exhibit a behavior typical of rubbery systems. The experimental results have been modeled using the Sanchez-Lacombe equation of state, which is able to represent the actual behavior of the polymer-CO_2 systems with reasonable accuracy.

Keywords: biodegradable; PLA; PLGA; sorption and swelling; tissue engineering

Introduction

In tissue engineering, biomaterials are used as precursors for the reparation or even the replacement of damaged tissues. In order to give a mechanical and structural support for the cell proliferation during tissue growth, porous structures of polymeric composites are used, which are called scaffolds. These scaffolds have to be biocompatible and they may also serve to deliver biologically active compounds, such as growth factors, at a specific rate matching the physiological need of the tissue.[1] The control over the scaffold pore structure (porosity and pore sizes), which influence both cell growth behavior and drug release, and the incorporation of the biologically active guest species into the polymer without loss of their activity, represent some of the major technical challenges in the scaffold processing.

Supercritical fluids, and in particular supercritical CO_2 ($scCO_2$) technologies, have been proposed and successfully adopted to overcome these issues.[2–9] The interaction between $scCO_2$ and the polymer leads to a plasticization of the polymer also at low temperatures: a small amount of CO_2 dissolved in the polymer is in fact sufficient to strongly reduce its glass transition temperature and viscosity.[10] Under these conditions, the incorporation of bioactive compounds can be achieved, since the polymer can be easily penetrated. Upon depressurization, CO_2 gets out the polymer and a porous structure is formed. Pore nucleation and growth are mainly influenced by the amount of CO_2 dissolved in the polymer and the rate of CO_2 leaving the polymer. Therefore, the quantitative knowledge of the solubility of CO_2 in the polymer is an important issue towards the successful fabrication of scaffolds with desired characteristics.

Experimental analyses of the solubility of CO_2 in PLA and PLGA polymers have been recently reported.[11–14] In order to be useful for the design of the scaffold processing, these data should be obtained

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at physiological temperatures and should cover a broad pressure range. However, this information is still not complete in the literature, since most of the referred studies do not exceed a maximum pressure of about 100 bar.

In this paper, the solubility of CO_2 in one poly(lactic acid) ($P_{DL}LA$) sample and two poly(lactic-co-glycolic acid) (PLGA) samples, with different lactic acid content, was studied by measuring sorption and swelling at a temperature 35 °C and at pressure up to 200 bar using a gravimetric technique and a visualization method. From the obtained data, the partial molar volume of CO_2 in the polymer matrix was estimated. The Sanchez-Lacombe equation of state was then used for correlating the experimental data.

Materials and Methods

One $P_{DL}LA$ sample (Purac, the Netherlands) and two PLGA samples (PLGA7525 (75 mol% lactic acid, 25 mol% glycolic acid) and PLGA5050 (50 mol% lactic acid, 50 mol% glycolic acid) from Resomer (Germany)) have been investigated in this study. The properties of these polymers (average molecular weight, $M_{w,p}$, polydispersity index of the molecular weight distribution, PDI, glass transition temperature, T_g, density, ρ_0^p, and initial form) are summarized in Table 1. The gases were obtained from Pangas AG (Switzerland), namely CO_2 at a purity of 99.995% and He at a purity of 99.999%.

The solubility of CO_2 in the polymer samples is obtained by combining two different methods, i.e. a gravimetric technique (magnetic suspension balance) to measure the CO_2 sorption and a visualization technique (view cell) to obtain the swelling of the polymer. More details about the two equipments can be found in previous publications,[15–17] whereas the technique is briefly summarized in the following.

The sorption measurements were performed in a magnetic suspension balance (Rubotherm, Germany), equipped with a calibrated sinker for the in-situ measurement of the fluid bulk density ρ^b. The amount of gas dissolved in a known amount of polymer, m_0^p, is obtained by applying the following equation:

$$m^s = M_1 - M_1^0 + \rho^b(V^{met} + V^p) \tag{1}$$

where M_1 and M_1^0 are the balance readings at the operating conditions and under vacuum, respectively. The volume of the basket and of the other metal parts lifted, V^{met}, is known from previous experiments carried out without polymer in the measuring cell. Since the polymer swells with increasing CO_2 pressure, the volume of the polymer sample V^p is not constant, but has to be obtained from a second independent measurement. These experiments are carried out in a high pressure view cell, where digital stop-motion images of the polymer sample placed in a glass beaker are taken at different CO_2 pressures levels. Being a purely visualization method, the swelling can be estimated only once the polymer is completely molten; its volumetric expansion, constrained to the vertical direction only by the beaker, is in fact given by:

$$s = \frac{V^p - V_0^p}{V_0^p} = \frac{h^p - h_0^p}{h_0^p} \tag{2}$$

where V^p and V_0^p are the initial and swollen volume of the polymer, and h_0^p and h^p are the levels of the polymer in the glass beaker at initial and equilibrium conditions, respectively. From the digital image, the level of the polymer sample in the beaker

Table 1.
Properties of the polymers investigated in this study.

Polymer	*Mw,p* [kg/mol]	PDI	*Tg* [°C]	ρ_0^p [g/cm^3]	Form
PDLLA	52	1.87	46.9	1.275	granular
PLGA7525	72	1.75	50.4	1.353	powder
PLGA5050	53	1.59	47.0	1.407	powder

h^p can be read, using a brass holder, whose dimensions are known, as a reference. The initial volume of the sample in the beaker is calculated from initial sample mass and density as measured with a Helium pycnometer AccuPyc1330 (Micromeritics, Belgium). The initial height of the non-swollen polymer is then obtained as $h_0^p = V_0^p/(\pi r^2)$, where r is the internal radius of the beaker. The initial density values, ρ_0^p, are reported in Table 1. In Figure 1 a set of images of the swelling of the $P_{DL}LA$ sample at different CO_2 exposure pressures is shown.

The actual value of the polymer sample volume V^p at each specific condition is thus inserted in Equation (1) and the corresponding sorption $q = m^s/m_0^p$ is evaluated. When the pressure value in the balance does not match exactly the pressure at which the view cell experiments are carried out, the value of the swelling at the required pressure is obtained by interpolating the swelling data through a polynomial fit.

It is worth noting, that the correction brought by taking into account the volume change of the polymer sample is essential to get reliable values of CO_2 solubility, especially at high pressures. In fact, according to Equation (1), the buoyancy correction term $\rho^b(V^{met} + V^p)$ increases with increasing fluid bulk density. This effect is shown in Figure 2, where the sorption of CO_2 in $P_{DL}LA$ is plotted as a function of pressure for two different cases, i.e. by keeping the value of V^p in Equation (1) constant and equal to V_0^p (empty symbols) or correcting it for the swelling (filled symbols). The error made neglecting the swelling effect on sorption increases with pressure and it reaches a value of about 80% at 200 bar.

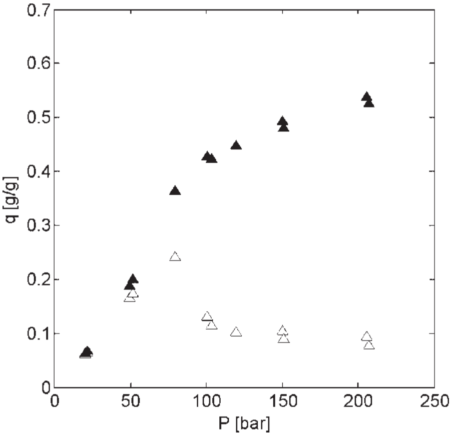

Figure 2.
Effect of the swelling correction on the CO_2 sorption of $P_{DL}LA$ at 35°C. Sorption with swelling correction (▲) and without correction (△).

Results

The equilibrium swelling and sorption behavior of the systems investigated in this work is modeled with the Sanchez-Lacombe (SL) equation of state.[18] In this equation, pressure, density and temperature are related by the following expression:

$$\tilde{\rho} + \tilde{P} + \tilde{T}\left[\ln(1-\tilde{\rho}) + \tilde{\rho}\left(1 - \frac{1}{r^0}\right)\right] = 0 \tag{3}$$

where r^0 is the number of sites occupied by a molecule in the lattice and $\tilde{\rho}$, $\tilde{P}$, $\tilde{T}$ are respectively the reduced density, pressure and temperature. These are reduced by the

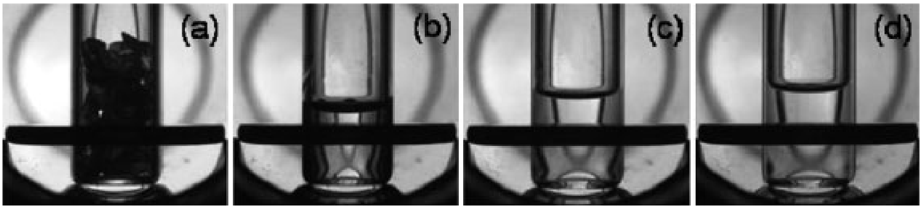

Figure 1.
Visualization of the swelling behavior of the $P_{DL}LA$ sample at 35 °C and different pressures. (a) no CO_2 (b) 50 bar (c) 100 bar (d) 150 bar.

so-called characteristic quantities, as $\tilde{\rho} = \rho/\rho^*$, $\tilde{P} = P/P^*$ and $\tilde{T} = T/T^*$. The procedure described by McHugh[17,19] has been used to extend Equation (3) to mixtures (by applying the van der Waals-1 rules) and to evaluate the chemical potential of each component in the mixture.[17,19] Swelling and sorption have been calculated through the model using the following equations:

$$\begin{aligned} s &= \frac{\rho_0^p}{(1-w_{CO_2})\rho^p} - 1 \quad \text{and} \\ q &= \frac{w_{CO_2}}{(1-w_{CO_2})} \end{aligned} \tag{4}$$

where ρ_0^p and ρ^p are the initial and equilibrium density of the polymer rich mixture, and w_{CO_2} the CO_2 weight fraction in the polymer. The parameter values for pure components have been taken from the literature without adjustment,[17] while the binary interaction parameters have been evaluated by direct fitting of the model predictions to the experimental values. More details about model equations and the complete list of the parameter values can be found elsewhere.[17,19]

The equilibrium sorption and swelling data together with the model predictions are plotted as a function of pressure in Figure 3 and Figure 4, respectively. All the measurements have been carried out at 35 °C. For all polymers, both sorption and swelling increase monotonically with pressure, showing a remarkable change in slope at a pressure of about 75 bar. At this pressure, the transition of the CO_2 rich phase from the gas to the supercritical phase takes place. In terms of CO_2 sorption and swelling, the $P_{DL}LA$ homopolymer and the PLGA7525 copolymer show a similar quantitative behavior, whereas the PLGA5050 copolymer has the lowest affinity to CO_2. This same behavior has been previously reported in the literature.[14]

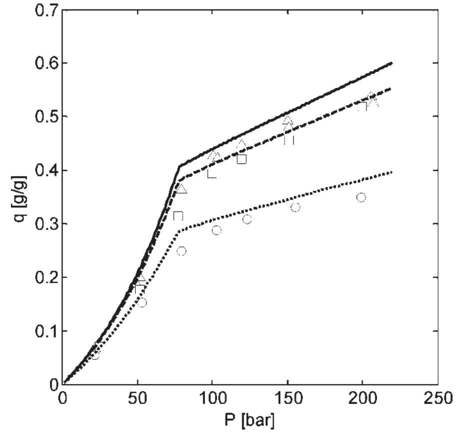

Figure 3.

Sorption of CO_2 as a function of pressure at 35°C. Points corresponds to experimental data ($P_{DL}LA$ (△), PLGA7525 (□) and PLGA5050 (○)), whereas the curves are the SL model fits: $P_{DL}LA$ (—); PLGA7525 (---); PLGA5050 (····).

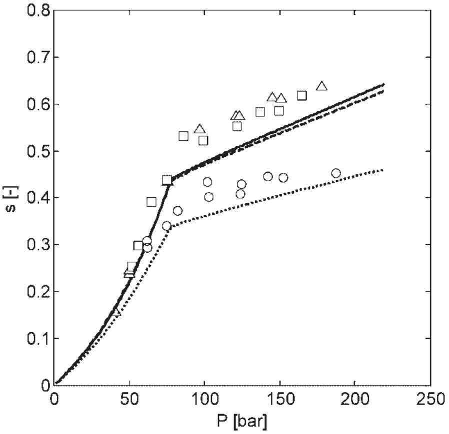

Figure 4.

Swelling of CO_2 as a function of pressure at 35°C. Points corresponds to experimental data ($P_{DL}LA$ (△), PLGA7525 (□) and PLGA5050 (○)), whereas the curves are the SL model fits: $P_{DL}LA$ (—); PLGA7525 (---); PLGA5050 (····).

Carbon dioxide has the ability to plasticize polymers, thus lowering their glass transition temperature, T_g. According to the model derived by Chow,[20] the glass transition temperature of a polymer-diluent mixture can be estimated as follows:

$$\ln\frac{T_g}{T_g^0} = \beta[(1-\theta)\ln(1-\theta) + \theta\ln(\theta)] \tag{5}$$

with the two dimensionless parameters β and θ defined as:

$$\beta = \frac{2R}{M_{w,m}\Delta C_P}, \quad \theta = \frac{M_{w,m}}{2M_{w,CO_2}}\frac{w_{CO_2}}{1-w_{CO_2}} \tag{6}$$

where T_g^0 is the pure polymer glass transition temperature (without gas), $M_{w,m}$ and M_{w,CO_2} are the molecular weight of monomer and CO_2, respectively, and w_{CO_2} is the weight fraction of CO_2 in the polymer mixture. ΔC_P is the excess transition isobaric specific heat of the polymer, and for $P_{DL}LA$ it takes a value of 0.336 J/gK as given by Ema et al.[21] Since this value has been used also for the two copolymers, the only parameter which changes with polymer composition beside the pure polymer glass transition temperature T_g^0, is the monomer molecular weight $M_{w,m}$. Moreover, θ was assumed to be small in the derivation of Equation (5)[20]: under this condition the right-hand side of Equation (5) is always negative, and T_g will then decrease at increasing θ (or w_{CO_2}). In Figure 5 the behavior of T_g as a function of the CO_2 weight fraction in polymer is shown for the three systems investigated in this study. In all cases, the T_g decreases strongly at increasing amount of CO_2 dissolved into the polymer, and it falls below 35 °C already at $w_{CO_2} = 0.013$–0.017, depending on the polymer composition. It is worth noting, that these values are well below the sorption values measured for the same systems at our minimum pressure. Therefore, it can be safely assumed that the polymers are fully amorphous in all reported experiments.

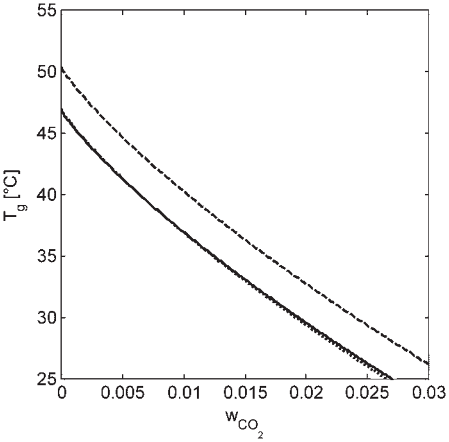

Figure 5.
Glass transition temperature T_g as a function of the CO_2 weight fraction w_{CO_2} for the three polymers $P_{DL}LA$ (—); PLGA7525 (---); PLGA5050 (····).

The polymer volume increase is directly related to the partial molar volume of the penetrant in the polymer mixture. Since the measured swelling grows linearly with sorption, such partial molar volume is constant.[15] The partial molar volume is defined as follows:

$$V_{m,CO_2} = \left.\frac{\partial V^p}{\partial n_{CO_2}}\right|_{P,T,n^p} \tag{7}$$

where V^p is the volume of the polymer mixture, n_{CO_2} and n_p are the moles of sorbed CO_2 and polymer, respectively, and P and T are the system pressure and temperature. For systems where the polymer compressibility can be neglected, which is the case under the operating conditions considered in this study, Equation (7) can be expressed as follows[16]:

$$V_{m,CO_2} = \frac{M_{w,CO_2}}{\rho_0^p}\frac{ds}{dq} \tag{8}$$

The behavior of swelling s as a function of sorption q for the three investigated polymers is shown in Figure 6. The swelling increases linearly with sorption in all cases. Straight lines passing through the origin

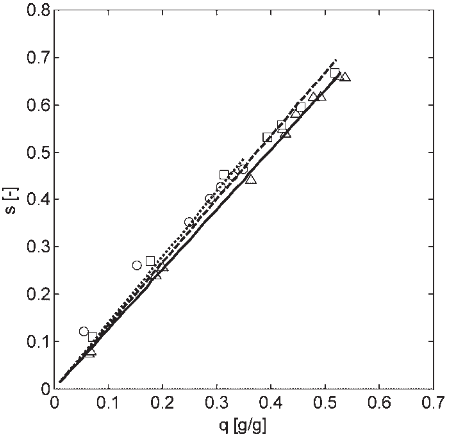

Figure 6.
Swelling as a function of the sorbed amount of CO2 at 35 °C for the three polymers investigated: $P_{DL}LA$ (△), PLGA7525 (□) and PLGA5050 (○). Curves correspond to the straight line fit of the experimental data: $P_{DL}LA$ (—); PLGA7525 (---); PLGA5050 (····).

Table 2.
Estimated partial molar volume of CO2 in the three investigated polymers.

Polymer	PDLLA	PLGA7525	PLGA5050
V_{m,CO_2} [cm^3/mol]	43.6	43.5	43.6

are in fact able to fit quite well to the experimental data. At low swelling and sorption values, the PLGA5050 data deviate slightly from the linearity. However, this copolymer melted completely only at relatively high CO_2 pressure (50–60 bar) and thus no swelling data were available in this region. Then, the sorption data were obtained using swelling values which have been linearly extrapolated and their accuracy can be affected by such procedure.

From the slope of the straight lines in Figure 6, V_{m,CO_2} can be calculated using Equation (8): the obtained values are reported in Table 2. Notably they are close to the value of partial molar volume of CO_2 typically measured in rubbery polymers, i.e. 45 cm^3/mol.[16] This observation confirms again that the polymers investigated are fully amorphous at the conditions considered in this study.

Conclusion

In this study the swelling and sorption behavior in supercritical CO_2 of poly(D,L-lactic acid) ($P_{DL}LA$) and poly(lactic-co-glycolic acid) (PLGA) have been investigated experimentally and theoretically. The $P_{DL}LA$ homopolymer shows the largest values of sorption and swelling (up to 0.5 g/g and 0.65, respectively), whereas the PLGA5050 has the lowest affinity to CO_2. The PLGA7525 sample behaves similarly to the homopolymer. The experimental data have been modeled through the Sanchez-Lacombe equation of state. Using literature values for the pure component parameters and by adjusting a single binary interaction parameter, the correlation between experiment and model was satisfactory. From the measured values of swelling and sorption it was possible to estimate the partial molar volume of CO_2 in the polymer. A linear correlation between swelling and sorption has been found, which is typical for amorphous polymers. Moreover, the obtained values for the partial molar volume are close to the values typically encountered for organic liquids and rubbery polymers.

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