Solubility and Diffusivity of Supercritical CO_2 in Bioresorbable Polymers: Measurements, Calculations and Potential Applications in Polymer Foaming

Elena Aionicesei, Mojca Škerget, Željko Knez*
University of Maribor, Faculty of Chemistry and Chemical Engineering, Laboratory for Separation Processes and Product Design, Smetanova 17, SI-2000 Maribor, Slovenia
E-mail: zeljko.knez@uni-mb.si, Fax: +386 225 27774

Supercritical carbon dioxide (SC-CO_2) found applications in polymer processing due to its potential as a plasticizer. A particular interest is shown to the use of SC-CO_2 for processing polymers destined for biomedical applications. The method offers advantages related to the absence or efficient removal of harmful organic solvents, the mild processing conditions and the control of particle and foams morphology. CO_2 – polymer phase equilibrium data, essential for process design, were obtained by using the magnetic suspension balance (MSB). Solubility and diffusivity data were measured for bioresorbable polymers which are already approved and used for biomedical applications: poly(ethylene glycol), poly(*L*-lactide), poly(*D*,*L*-lactide-co-glycolide) and poly(ε-caprolactone), at different temperatures and pressures. The results suggest that SC-CO_2 due to its good solubility and plasticizing effect in polymers can be successfully used in processing biomaterials and obtaining polymeric foams, with potential applications in tissue engineering and drug delivery systems. For obtaining polymer porous foams a solvent free approach has been employed whereby the substrate is saturated with SC-CO_2, followed by rapid depressurization at constant temperature (pressure quench). The foamed samples were analyzed by scanning electron microscopy. The porosity and pore structure depend on the amount of gas dissolved in the polymer, the rate and type of gas nucleation and the diffusion rate of gas molecules through the polymer. Therefore the foam morphology may be tailored by controlling the processing parameters. The results indicate that SC-CO_2 foaming of biodegradable polymers represents a promising technique for obtaining porous scaffolds with the desired structure.

INTRODUCTION

Polymers are the most widely used materials in biomedical applications. Their high versatility and similarity to natural compounds recommend them for applications in all domains of medicine, as implants, grafts, medical equipment, drug delivery systems or tissue engineering scaffolds.

Polymers based on glycolic and lactic acids have found a multitude of uses as biomaterials, being first approved as biodegradable sutures in the 1960s. Since then other medical devices, based on lactic and glycolic acid, as well as their copolymers with other compounds, have been accepted for use as controlled delivery systems, sutures, staples and

orthopedic fixation device [1, 2]. Such bioresorbable polymers degrade upon implantation in the organism, being replaced by host tissue while the degradation products are metabolized and eliminated. Polylactide (PLA) is a bio-based polymer with commercial importance in medicine and plastics industry [3]. Due to its biodegradability and biocompatibility, PLA has been used for biomedical applications such as sutures [1, 3], tissue engineering scaffold [4-6], and drug delivery devices [7, 8]. The copolymer of lactic and glycolic acids, poly(lactide-co-glycolide) (PLGA) is one of the most commonly used bioresorbable polymers for both medical device and drug delivery applications [9-11].

Poly(ε-caprolactone) (PCL) is a semicrystalline polymer extensively used in biomedical applications. It is a biodegradable linear aliphatic polyester, which exhibits slow degradation rate, and it is used as a long-term implant for controlled release applications [12]. Also, its mechanical properties renders PCL as an attractive candidate polymer for bone tissue engineering, where scaffolds should maintain physical and mechanical properties at least for 6 months.

Poly(ethylene glycols) (PEGs) are water soluble polymers which are widely used in the pharmaceutical and cosmetic industries because of their physiological acceptance [13]. Their hydrophilicity, antithrombogenicity and good biocompatibility recommended PEGs for biomedical applications, such as drug delivery devices [14, 15] and tissue engineering scaffolds [4].

The traditional methods for polymer processing involve either high temperatures or hazardous organic solvents. Due to the undesirable biological and environmental impact of these solvents, extensive research is focused on seeking new and cleaner methods for the processing of polymeric biomaterials. One such method is the use of supercritical fluids as processing solvents or plasticizers. Supercritical carbon dioxide (SC-CO_2) is the preferred choice due to its properties. It is non-toxic, non-flammable, chemically inert, inexpensive and it can be removed from a system by simple depressurization. Its solubility in many polymers is substantial, being influenced by temperature, pressure and, sometimes, by interactions with the groups in the polymer. Dissolved CO_2 causes a reduction in the viscosity of the polymers, by increasing their free volume. Thus the polymers are plasticized, allowing processing at lower temperatures [16]. A potential application of SC-CO_2 for polymer processing is gas foaming (GF), an alternative technique used to create porous structures. A wide range of morphologies and porosities can be obtained and sensitive bioactives can be added without the danger of degradation caused by solvents or processing heat [5].

In the present study the solubility and diffusivity of CO_2 in polymers were measured by magnetic suspension balance, while solvent free approaches have been employed for obtaining polymer porous foams. The substrate was saturated with CO_2, followed by rapid depressurization at constant temperature (pressure quench). The effect of pressure, temperature and depressurization rate on the final porous structure was investigated.

MATERIALS AND METHODS

Poly(*L*-lactide) (PLLA), Mw = 42000, and poly(*D*,*L*-lactide-co-glycolide) (50:50) (PLGA), Mw = 70000, were obtained from Boehringer Ingelheim (Germany). Poly(ε-caprolactone) (PCL), Mw = 80000, was provided by Sigma – Aldrich. Poly(ethylene glycol) (PEG) of different molecular weights (PEG 1500 and PEG 4000) was obtained from Merck, Germany. Carbon dioxide (CO_2) was obtained from Messer, Slovenia. All materials were used as received, without further purification.

For determining the solubility and diffusivity of CO_2 in polymers, for different values of temperature and pressure, a magnetic suspension balance (MSB – RUBOTHERM) was used. A detailed description of the device and of the working procedure can be found in literature [17]. The MSB allows the gravimetric measurement of the quantity of gas dissolved in the substrate, over a wide range of temperature and pressure. This is possible due to the location of the balance outside the measuring cell, in normal conditions of pressure and temperature. The measuring cell of MSB is also provided with a window, which allows observation of the sample and estimation of volume modifications during the sorption measurements.

The binary diffusion coefficient for the CO_2-polymer system can be calculated from the reduced sorption curve, recorded during the MSB measurements. Starting from Fick's second law and applying the boundary conditions for the diffusion along a cylindrical rod of length *l*, with one end and its surface sealed and the other end maintained at a constant concentration of gas, one gets an equation which can be approximated as [18-20]:

$$\frac{M_t}{M_\infty} = 2\left(\frac{Dt}{\pi l^2}\right)^{1/2} \quad (1)$$

where M_t is the total amount of diffusing substance which has entered the polymer at time *t*, M_∞ is the corresponding quantity after infinite time and *D* is the mutual or interdiffusion coefficient. The value of *D* can be deduced from the initial gradient, *S*, of the graph M_t/M_∞ as function of $t^{1/2}$ (reduced sorption curve):

$$D = \frac{\pi}{4} S^2 l^2 \quad (2)$$

RESULTS

Solubility data are important when processing polymers by using both conventional and non-conventional solvents. The scarcity of information regarding the solubility of CO_2 into polymers suggests the need of research in this direction.

The results obtained by our group for the solubility of CO_2 in different biodegradable polymers indicate that CO_2 is good soluble in all studied polymers (Figure 1). The solubility increases with increasing pressure and decreases with increasing temperature, this variation being explained by the changes in CO_2 density.

PLLA is a semicrystalline polymer, with a high melting temperature (450 K), and under the employed conditions remains solid. Additional XRD and DSC tests showed that it also maintains its degree of crystallinity. PLLA exhibits a high affinity for gas, due to interactions between the carbonyl groups of the polymeric chains and CO_2 molecules, which leads to high values of the gas solubility. The plasticizing effect of CO_2 on the polymer was studied by additional tests which showed that the melting point of PLLA decreases with an increase in gas pressure.

PLGA is totally amorphous, and under the working conditions is completely melted. It also absorbs high amounts of gas, but its affinity for CO_2 is lower than in the case of PLLA, resulting in lower solubility values.

Similar to PLLA, PCL is a semicrystalline polymer. However its melting point is much lower (333 K) than for PLLA, and this value is further decreased by the plasticizing effect of the absorbed CO_2, therefore the polymer is melted under the employed conditions. It also exhibits a high affinity for CO_2, and as a result the solubility of the gas in PCL is high.

The solubility of CO_2 in PEG was measured for both solid (298 K) and melted samples (323 K). For this polymer it was also interesting to study the influence of the molecular weight and of the physical state of the sample on gas solubility. It was noticed that a lower molecular weight and the melted state favor the solubility of CO_2 in PEG. This could be explained by a lower density of the polymer and the existence of a larger content of free volume available to the gas.

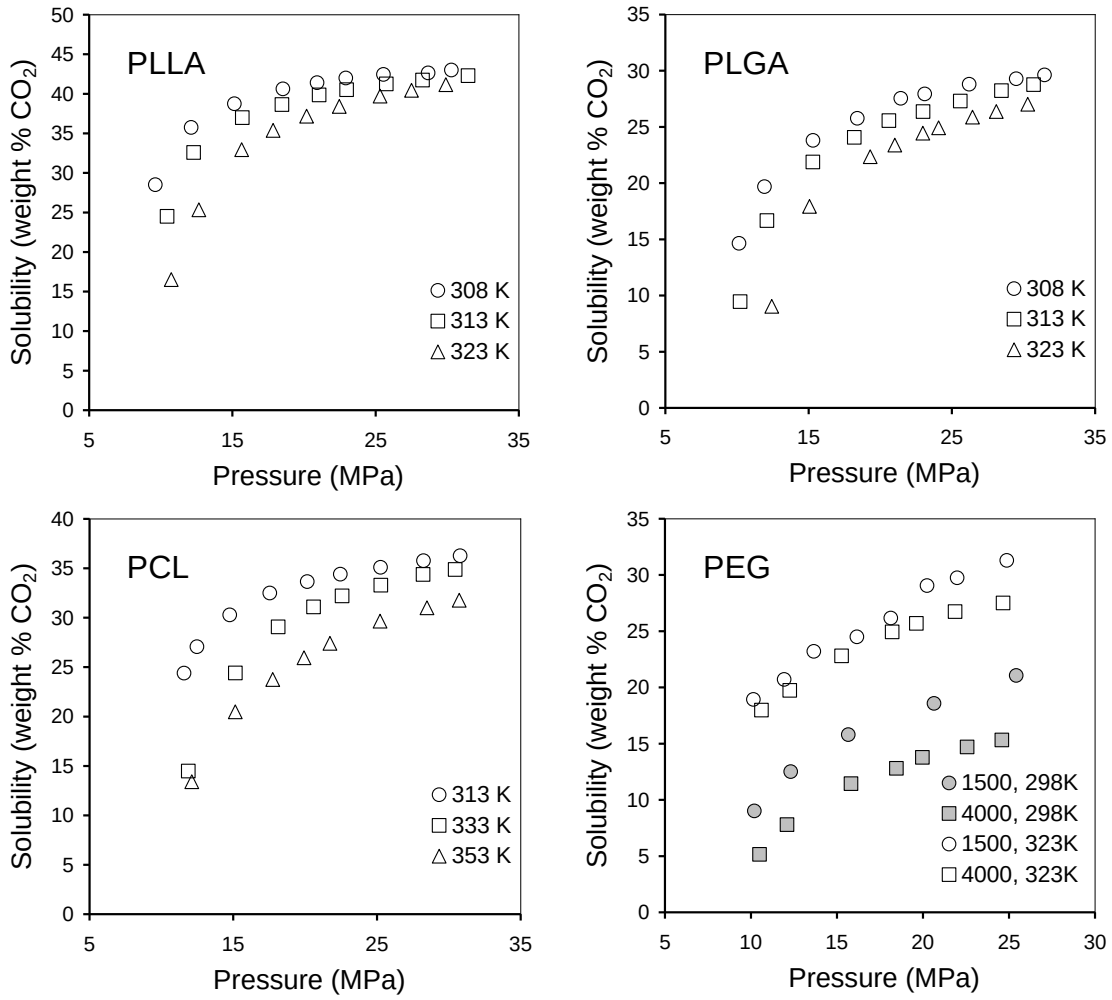

Figure 1 : Solubility of CO_2 in poly(*L*-lactide) (PLLA), poly(*D*,*L*-lactide-co-glycolide) (PLGA), poly(ε-caprolactone) (PCL) and poly(ethylene glycol) of different molecular weights (PEG 1500 and PEG 4000)

The diffusion coefficients of CO_2 in polymers were determined from the sorption curves obtained from MSB. Considering as starting point, t_0, the moment in which additional gas was introduced in the cell (the pressure was increased), the mass variation of the sample was recorded until equilibrium was reached. Using the data offered by MSB (M_t, M_∞, t), and

the thickness of the sample, *l*, the diffusion coefficient could be determined according to eq. (2). The results are presented in Figure 2.

As mentioned before, CO_2 tends to interact with polymers and causes them to swell. As a result, the diffusion coefficient becomes concentration dependent. The diffusion coefficients obtained here are the ones corresponding to the first moments of the pressure step, therefore the value of *D* will depend on the equilibrium concentration of gas corresponding to the previous pressure step.

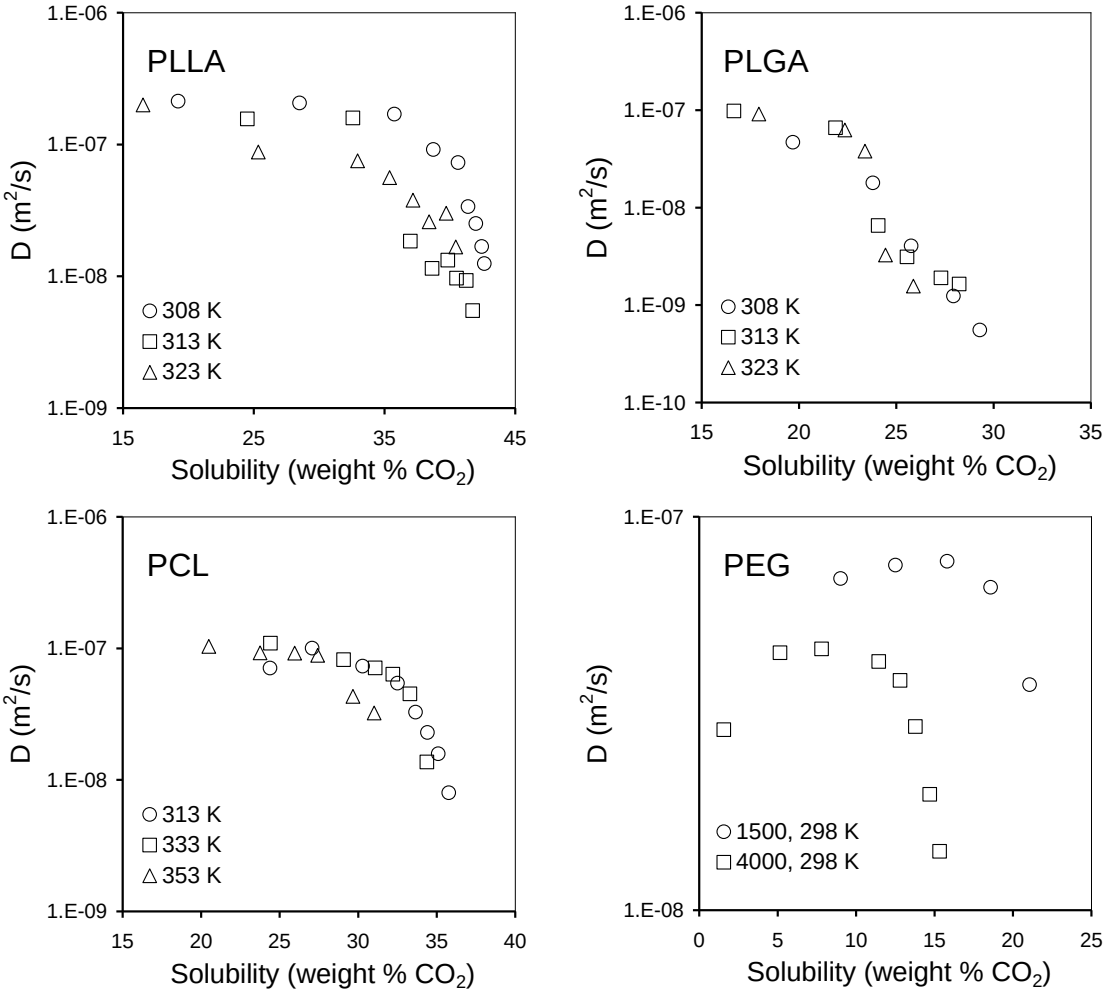

Figure 2 : Diffusion coefficient for CO_2 in polymers: poly(*L*-lactide) (PLLA), poly(*D*,*L*-lactide-co-glycolide) (PLGA), poly(ε-caprolactone) (PCL) and poly(ethylene glycol) of different molecular weights (PEG 1500 and PEG 4000)

The diffusion coefficient has high values for all studied gas-polymer systems and prove once more the combination of gas-like diffusivity and liquid-like solvating properties of SC-CO_2. As observed for all polymers, the diffusion coefficient decreased with increasing concentration. The rate of diffusion depends on the number and size distribution of existing holes and the ease of hole formation. The ease of hole formation depends on chain mobility

[19]. When the polymers absorb CO_2, the molecules rearrange themselves towards a new equilibrium conformation. For small gas concentrations, equivalent to low pressures, the plasticizing effect of CO_2 is reflected in the ease of reaching this new equilibrium and therefore in the high values of the diffusion coefficient. For high concentrations however the diffusivity decreases. The hydrostatic pressure may play a role in this decreased diffusivity through reducing the available free volume in the system [3].

The effect of temperature on the values of the diffusion coefficient could not be proved for any of the working systems. The small differences could be attributed to other factors that may influence the diffusion process: small changes in crystallinity and polymer chain orientation [20], or differences in sample morphology, molecular weight distribution and degree of branching [19].

For PEG it was observed that a lower molecular weight favors diffusivity of gas. As in the case of solubility, this may be explained by a lower density of the polymer and by the less packed configuration of the shorter chains, which offer a larger content of free volume available to CO_2.

When a polymer is submitted to high pressure of CO_2, high amounts of gas are absorbed into the substrate, which is plasticized. When the pressure is released, the sample undergoes foaming (Figure 3). For the purpose of this study, a batch foaming technique was applied for obtaining porous foams from PLGA, using CO_2 as blowing agent. The effect of pressure, temperature and depressurization rate on the final porous structure was investigated.

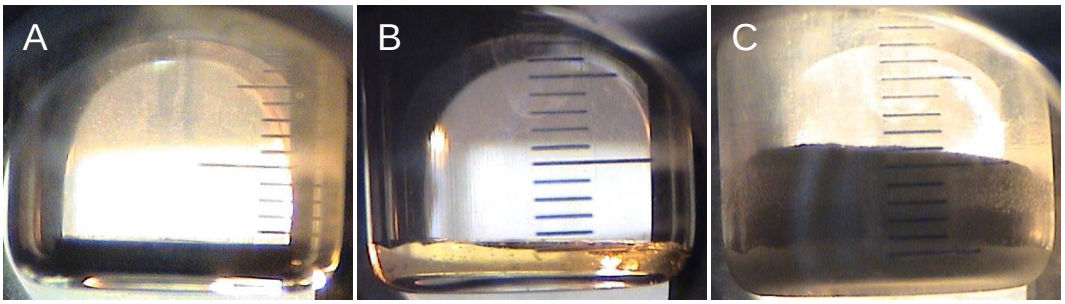

Figure 3 : Foaming of PLGA. (A), initial sample under vacuum, at room temperature; (B), sample in the presence of dense CO_2, 31.47 MPa and 308.91 K; (C), sample after depressurization.

After foaming, all PLGA samples presented a porous core surrounded by a dense, unfoamed skin. This is a typical behavior during the foaming of polymers with gases or supercritical fluids [21, 22]. The formation of this dense, nonporous skin is due to the rapid diffusion of the CO_2 that is absorbed near the surface of the sample, which thus escapes without nucleating and forming pores. After removing this unfoamed layer, the PLGA samples were studied by SEM, in order to investigate the internal structure of the foam and the effect of the processing parameters on the porosity. The results are presented in Figure 4.

The effect of temperature on the final porous structure was studied at constant pressure and depressurization rate. It was noticed that the mean pore diameter increased, while the cell population density decreased with increase of temperature. When foaming occurs at higher temperature, the viscosity of the substrate is reduced and CO_2 diffusivity is increased, therefore favoring the cell growth. Also, as the temperature increases, the CO_2 solubility in

the polymer matrix decreases. Thus, at higher temperatures there is less dissolved gas into the polymer matrix available for the nucleation and growth of pores.

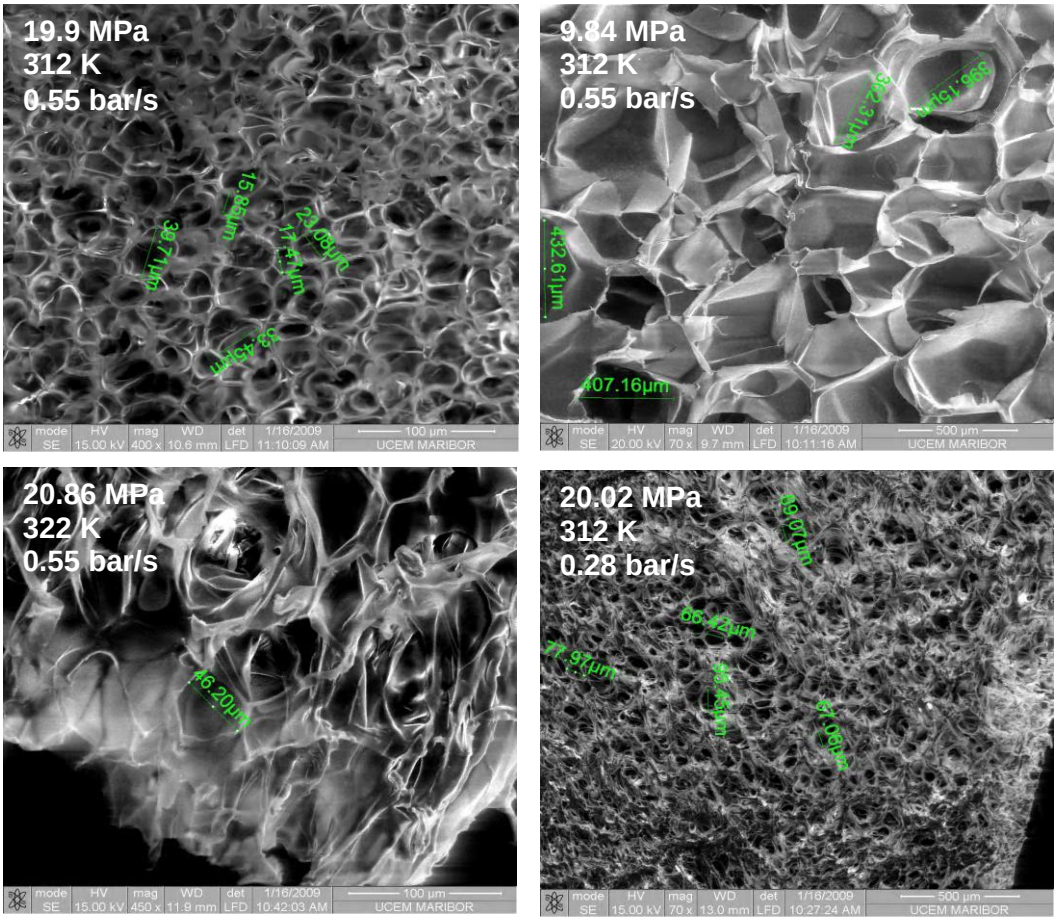

Figure 4 : SEM images for PLGA samples foamed by dense CO_2; the effect of pressure, temperature and depressurization rate

The effect of pressure on the final porous structure was studied at constant temperature and using a constant depressurization rate. It was observed that the mean pore diameter decreased, while the cell density increased with increase of pressure. As the pressure increases, more gas is dissolved into the polymer matrix, which creates more nuclei available for formation and growth of pores. Consequently, more cells with smaller size are produced.

The effect of depressurization rate on the final porous structure was studied at constant temperature and pressure. As seen in Figure 4, the mean pore diameter decreased, while the cell population density increased with increase of the depressurization rate. At lower depressurization rates the growth period of pores (the time between nucleation and ‘‘locking’’ of the porous structure due to vitrification) is larger. Consequently, the coalescence of neighboring pores is more pronounced. Also, at higher rates, more gas is used for cell nucleation instead for cell growth. Therefore, more nuclei are generated resulting in the formation of more pores with smaller size.

The effect of the amount of gas absorbed by the polymer on the pore diameter of the foams, is presented in Figure 5.

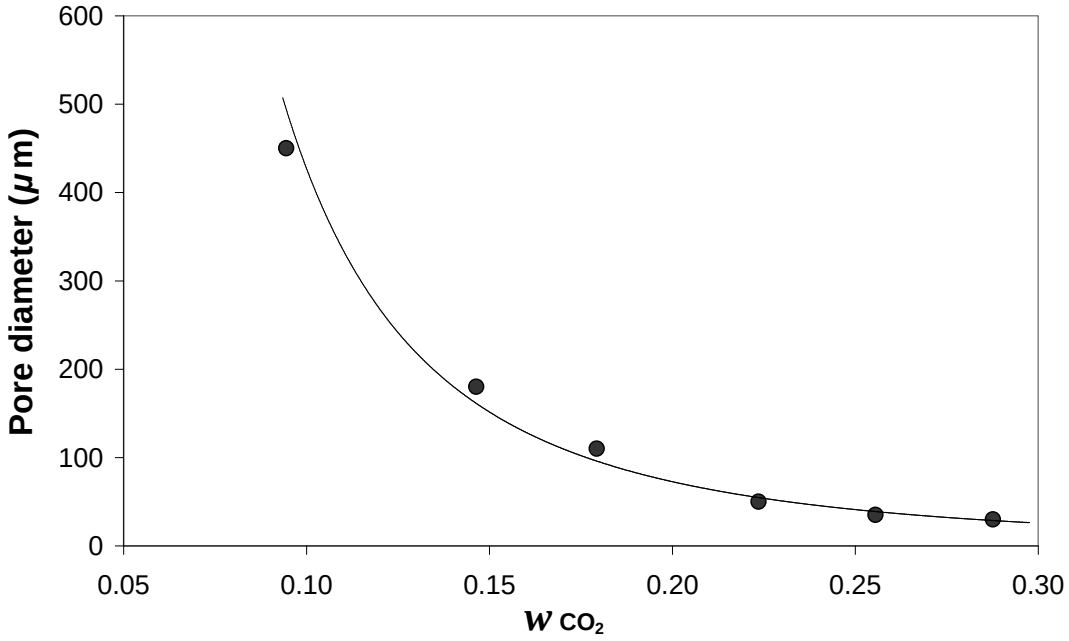

Figure 5 : The effect of the amount of CO_2 absorbed by the polymer on the pore diameter of the PLGA foams. (●), experimental values of porosity; (—), calculated values of porosity.

It was observed that the pore diameter diminishes with increase of the amount of absorbed CO_2, the decrease being more pronounced for small values of solubility. Due to the fact that the solubility itself depends strongly on the density of gas, which increases with pressure and decreases with temperature, the connection between CO_2 density and foam morphology (Figure 6), which is similar to the effect of solubility, was also noticed.

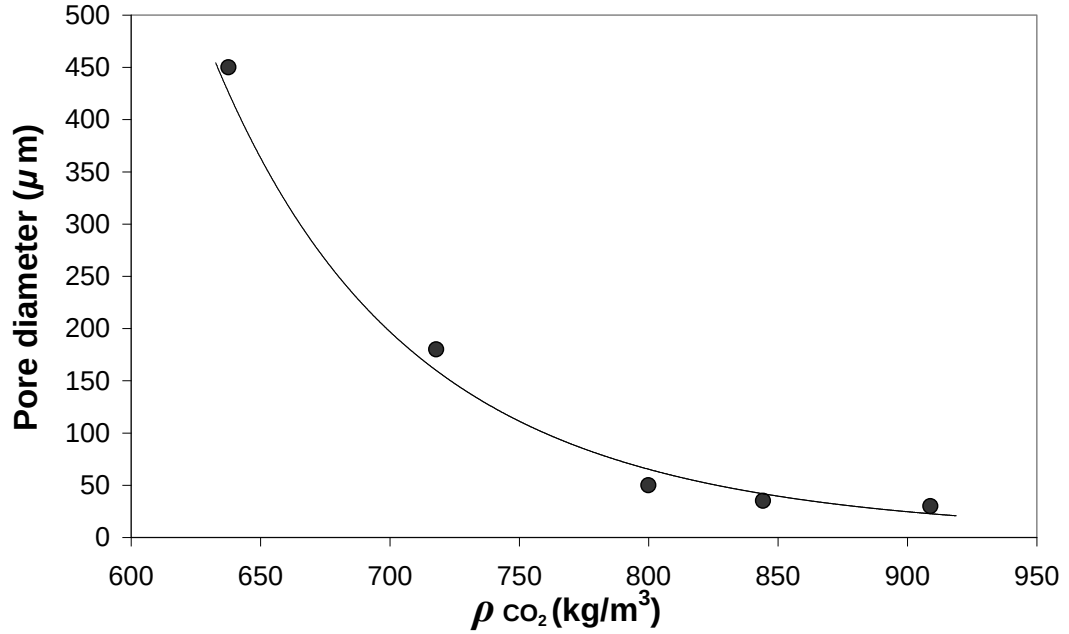

Figure 6 : The effect of CO_2 density on the pore diameter of the PLGA foams. (●), experimental values of porosity; (—), calculated values of porosity.

Using the experimental values, mathematical equations were obtained which can be used to estimate the effect of the amount of gas absorbed in the polymer and of the gas density on the pore dimensions (Figures 5 and 6). These equations may prove useful when creating foams with a certain morphology, since they offer indications about the pressure and temperature conditions that need to be employed.

CONCLUSION

The solubility and diffusivity of CO_2 in biodegradable polymers were measured by using a magnetic suspension balance. The results suggest that biodegradable polymers can be processed by using SC-CO_2, due to the high solubility of the gas in the substrate and its plasticizing effect on the polymer, even at mild temperatures. CO_2 can be used as an alternative to the classical organic solvents, offering benefits regarding the lack of environmental impact or toxicity of the final medical device. It also offers the possibility of working under mild temperature conditions, which is an essential requirement when biologically active compounds are to be introduced into the polymeric device during processing. PLLA, PLGA and PCL can be processed in the presence of SC-CO_2 for obtaining foams for tissue engineering or drug delivery. In the case of PEG, SC-CO_2 is used in the production of microparticles, with applications in medicine, drug delivery systems or cosmetic industry.

Solvent free approaches have been employed for obtaining foams from poly(*D*,*L*-lactide-co-glycolide). The influence of operating pressure, temperature and depressurization rate on the foam morphology was analyzed by scanning electron microscopy. The results indicate that gas foaming of biodegradable polymers represents a promising technique for obtaining foams with the desired structure. The porosity and pore structure is dependent on the amount of gas dissolved in the polymer, the rate and type of gas nucleation and the diffusion rate of gas molecules through the polymer, which can be regulated by the processing pressure, temperature and expansion rate.

REFERENCES:

[1] MIDDLETON, J. C., TIPTON, A. J., Biomaterials, Vol. 21, **2000**, p.2335.
[2] GUELCHER, S. A., HOLLINGER, J. O., An Introduction to Biomaterials, CRC Press, **2006**, p. 3.
[3] LI, G., LI, H., TURNG, L. S., GONG, S., ZHANG, C., Fluid Phase Equilib., Vol. 246 **2006**, p. 158.
[4] QUIRK, R. A., FRANCE, R. M., SHAKESHEFF, K. M., HOWDLE, S. M., Curr. Opin. Solid State Mater. Sci., Vol. 8, **2004**, p. 313.
[5] MATHIEU, L. M., MONTJOVENT, M. O., BOURBAN, P. E., PIOLETTI, D. P., MANSON, J. A. E., J. Biomed. Mater. Res., Part A, Vol. 75, **2005**, p. 89.
[6] MATHIEU, L. M., MUELLER, T. L., BOURBAN, P. E., PIOLETTI, D. P., MULLER, R., MANSON, J. A. E., Biomaterials, Vol. 27, **2006**, p. 905.
[7] KRANZ, H., BODMEIER, R., Int. J. Pharm., Vol. 332, **2007**, p. 107.
[8] TURK, M., UPPER, G., HILS, P., J. Supercrit. Fluids, Vol. 39, **2006**, p. 253.
[9] SINGH, L., KUMAR, V., RATNER, B. D., Biomaterials, Vol. 25, **2004**, p. 2611.

[10] GINTY, P. J., WHITAKER, M. J., SHAKESHEFF, K. M., HOWDLE, S. M., Mater. Today, Vol. 8, **2005**, p. 42.
[11] DHAWAN, S., DHAWAN, K., VARMA, M., SINHA, V. R., Pharm. Technol., **2005**, p. 82.
[12] TSIVINTZELIS, I., PAVLIDOU, E., PANAYIOTOU, C., J. Supercrit. Fluids, Vol. 42, **2007**, p. 265.
[13] WIESMET, V., WEIDNER, E., BEHME, S., SADOWSKI, G., ARLT, W., J. Supercrit. Fluids, Vol. 17, **2000**, p.1.
[14] HABRAKEN, W. J. E. M., WOLKE, J. G. C., JANSEN, J. A., Adv. Drug Delivery Rev., Vol. 59, **2007**, p. 234.
[15] LEE, S. H., SHIN, H., Adv. Drug Delivery Rev., Vol. 59, **2007**, p. 339.
[16] NALAWADE, S. P., PICCHIONI, F., JANSSEN, L. P. B. M., Prog. Polym. Sci., Vol. 31, **2006**, p. 19.
[17] SATO, Y., TAKIKAWA, T., TAKISHIMA, S., MASUOKA, H., J. Supercrit. Fluids, Vol. 19, **2001**, p. 187.
[18] CRANK, J., The Mathematics of Diffusion, Oxford University Press, **1975**, p. 69.
[19] CRANK, J., PARK, G.S., Diffusion in Polymers, CRC Press, **1968**, p. 1.
[20] KUMAR, A., GUPTA, R.K., Fundamentals of Polymers, McGraw-Hill, **1998**, p. 407.
[21] MOONEY, D. J., BALDWIN, D. F., SUH, N. P., VACANTI, J. P., LANGER, R., Biomaterials, Vol. 17, **1996**, p. 1417.
[22] BARRY, J. J. A., GIDDA, H. S., SCOTCHFORD, C. A., HOWDLE, S. M., Biomaterials, Vol. 25, **2004**, p. 3559.