

1 **Measurement, correlation and modelling of high-pressure** 2 **phase equilibrium of PLGA solutions in CO₂**

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13 **Abstract**

14 Poly (lactic-co-glycolic acid) (PLGA) is a copolymer used as drug carrier in controlled
15 release systems as microparticles or scaffolds. Foamed structures are industrially obtained
16 by injecting gas at temperatures above the melting point of the polymer that may promote
17 PLGA degradation. High temperatures are avoidable in this foaming process if a polymer
18 dissolution is used. Ethyl acetate and ethyl lactate are suitable solvents for the PLGA
19 since the polymer is easily solubilised, is environmentally friendly and highly
20 recommendable for medical purposes. CO₂ is proposed as antisolvent because is
21 environmentally benign, non-flammable and non-toxic. The knowledge of the solubility
22 of these solvents in CO₂ is essential to find the most appropriate working conditions for
23 the foaming process. In this work, the solubility of ethyl acetate and ethyl lactate in CO₂
24 in the presence of different initial concentrations of PLGA has been studied at 298.15 K
25 and at pressures up to 150 bar using a high-pressure variable volume view cell.

26 **Keywords:** Poly(lactic-co-glycolic) acid, Ethyl acetate, Ethyl lactate, Supercritical
27 carbon dioxide, Equilibrium cell, Solubility.

28

29 **1. Introduction**

30 In the last years, medical industry has focused their efforts on fabricating scaffolds
31 for drug delivery systems with high porosity, specific surface area and suitable
32 characteristics for different purposes[1]. Among the great number of different polymers
33 used to fabricate scaffolds, poly(lactic-co-glycolic) acid (PLGA) is the most important
34 biodegradable polymer thanks to its good properties such as biocompatibility and
35 biodegradability[2], which is easy to modify by adjusting the ratio lactide:glycolide. The
36 most used PLA to PGA ratios in medicine are 50:50 and 75:25. It is known that
37 degradation and drug release rate will be accelerated with decreasing molecular weight
38 of PLGA and increasing the glycolic acid (PGA) ratio of PLGA copolymers [3-6].
39 Porogen leaching, phase separation and gas foaming are achieved by the formulation of
40 porous polymers with controlled micro and nanostructures [7], in which drugs can be
41 incorporated.

42 Particularly, gas and supercritical fluids (SCFs) foaming is taking relevance in the
43 field of pharmaceutical industry because new alternatives of processing polymers are
44 being developed in order to avoid the use of harmful solvents. The knowledge about high-
45 pressure phase behaviour supposes an important issue in the design of foaming and
46 encapsulation process [8, 9]. The great properties of SCFs which are between gases,
47 thanks to its low viscosity, and liquids because of its high density, can be used to produce
48 polymeric devices employed in the biomedical industry in a green way [10-12]. In
49 particular, supercritical carbon dioxide (scCO₂) has been widely studied for the

50 processing since the mentioned advantages are further supplemented by the non-
51 flammable, non-toxic nature of the fluid, and the relative ease of solvent recovery.

52 Traditionally, PLGA foaming has been carried out at temperatures above the
53 polymer melting point in order to increase the mobility of chains, which leads to polymer
54 degradation [7, 13]. Other studies have proved the production of foams by using polymer
55 in solution, since using the correct solvent, the polymer coil is expanded behaving like a
56 polymer melt [14].

57 The employment of supercritical fluids in PLGA foaming has been studied in
58 literature because it avoids the necessity of using organic solvents [15] and even this
59 foaming technique leads to total solvent removal. PLGA polymer can be dissolved in
60 solvents such as ethyl acetate (EA) and ethyl lactate (EL) because of their similar
61 structures. Ethyl acetate is an acceptable solvent for food and nutraceutical applications
62 [16]. Ethyl lactate was accepted as GRAS (generally recognized as safe) and approved
63 by de Food and Drug Administration (FDA) as a pharmaceutical and food additive. EL is
64 produced by fermentation from corn feedstock and it is biodegradable, non-corrosive,
65 non-carcinogenic and non-ozone depleting [17]. This solvent can also be used as a
66 dissolving excipient in the pharmaceutical industry because it does not affect the
67 pharmacological activity of the active ingredient. It is a very powerful agent for
68 solubilising biologically active compounds that are difficult to solubilise in usual
69 excipients [18, 19].

70 Experimental data of phase behaviour at high pressure for the binary mixture
71 carbon dioxide-ethyl acetate were reported by Wagner et al. [20] isothermally at 303.15
72 K, 313.15 K, and 323.15 K at pressures ranging from 20 bar to 90 bar by using a modified
73 equilibrium cell [21]. Tian et al studied the equilibrium at pressure from 29.6 bar to 117.9
74 bar and temperatures from 313 K to 393 K [22]. Byun et al. [8] performed the high-

75 pressure phase behaviour for alkyl acetate in supercritical carbon dioxide. The phase
76 behaviour of the polymer/solvent/CO₂ supposes a key part during foaming process as well
77 as the knowledge of solvent solubility in the gas phase from a polymer solution.

78 In case of ethyl lactate, high pressure phase-behaviour was measured from 323.2
79 K to 363.2 K by Cho et al. [23]. Paninho et al. [24] reported the phase behaviour of the
80 binary system in the pressure range 4–170 bar and at temperatures of 313.2, 333.2, 353.2,
81 373.2 and 393.2 K. This study confirms an enhancement of mutual solubility when
82 pressure increases and temperature decreases. Moreover, it confirms that solubility of
83 CO₂ in ethyl acetate is higher than in ethyl lactate.

84 In order to avoid the degradation of polymer chains due to high temperatures, as
85 well as a possible decrease in drug activity, it is interesting to study the feasibility of the
86 separation of ethyl acetate and ethyl lactate from PLGA and further foaming when these
87 solutions are exposed to CO₂ at high pressures at 298.15 K. The influence of pressure,
88 ratio between lactide and glycolide monomers and the concentration of PLGA on the
89 solubility was measured and correlated using semi-empirical equations in order to select
90 the appropriate conditions to process PLGA foams and its impregnation.

91

92 **2. Materials and Methods**

93 **2.1 Materials**

94 Two different polymers have been studied. Both of them were Poly (lactic-co-
95 glycolic) acid (PLGA) with different ratio lactide:glycolide. PLGA5050 (PURASORB
96 PDLG 5002A, 50:50 DL-lactide/glycolide copolymer, molecular weight of 17,000 Da,
97 inherent viscosity 0.2 dl/g, PDI = 1.05, purity 99.3%) and PLGA7525 (PURASORB
98 PDLG 7502A, 75:25 DL-lactide/glycolide copolymer, molecular weight of 17,000 Da,
99 inherent viscosity 0.2 dl/g, PDI = 1.05, purity 99.3%) which were supplied by Corbion

100 Purac (Netherlands) and used as received. Ethyl acetate (purity 99.8%) and ethyl lactate
101 (purity 98%) were purchased from Sigma-Aldrich. Polymer and solvents were used as
102 received and solutions were not purified nor deaerated. Carbon dioxide with a purity of
103 99.8% was supplied by Carbueros Metálicos S.A. (Spain).

104

105 **2.2. Experimental setup and procedure.**

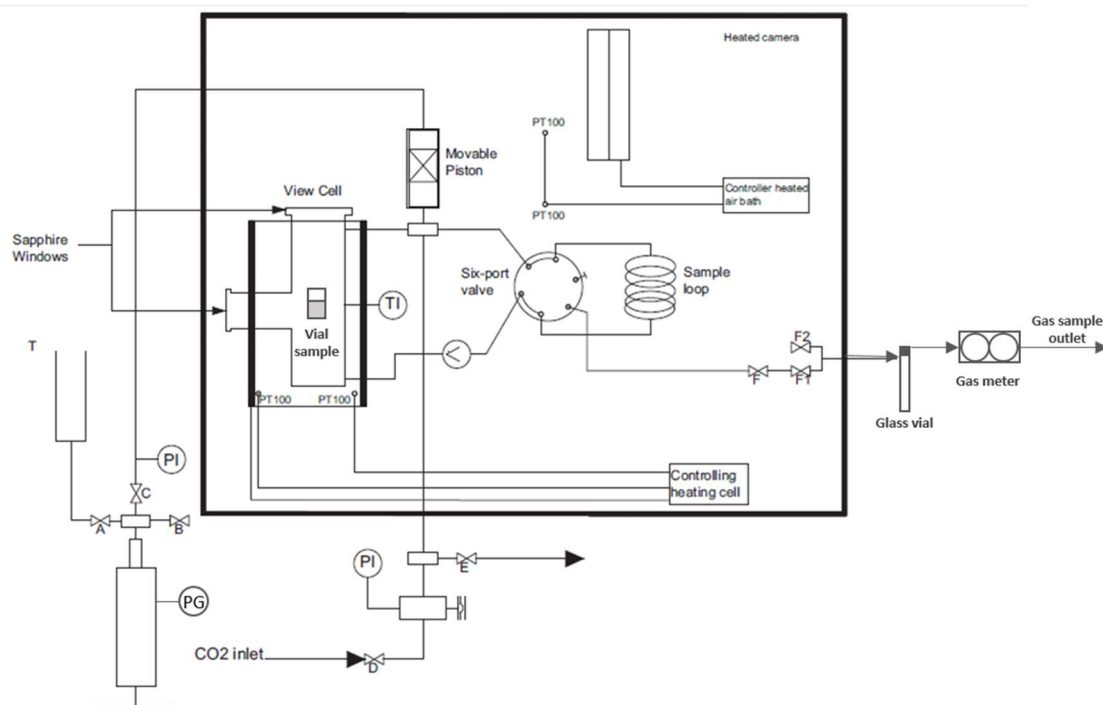
106 High-pressure variable volume cell was used to carry out experimental
107 measurements. Cell model was ProVis 500 from Eurotechnica as it is represented in
108 Figure 1 and was described elsewhere [25]. The equipment consists of a variable-volume
109 cell, supplied with a front and upper sapphire windows and light for visual observation of
110 phase separation. The cell has a maximum capacity of 50 cm³ and contains a piston
111 system consisting in a manual pressure generator, a cylinder and a movable piston made
112 of Teflon to avoid pressure drops (Valves A and C) only when samples are taken. The
113 movable piston separates the equilibrium chamber from the pressurizing circuit. To allow
114 a smooth displacement of the piston inside the cylinder, the piston was driven by a manual
115 pressure generator and water was used as the pressurizing fluid. All the system is heated
116 externally by an air bath made of Poly (methyl methacrylate) capable to resist
117 temperatures up to 353 K being the temperature inside the equilibrium chamber measured
118 by a PRT sensor (PT100) coupled to a digital led model Testo 925 (Lenzkirch, Germany).

119 PLGA/solvent solutions were prepared in vials and introduced into the cell that
120 was purged with CO₂ at low pressure to remove the residual air. After that, valve D was
121 opened, allowing CO₂ to flow into the cell to promote homogenization. Once the
122 temperature was stabilized, the experimental pressure was achieved. Then, stirring was
123 stopped, and the mixture was allowed to repose so as to phase segregation took place.

124 Samples from the top of the equilibrium cell were withdrawn isobarically through
125 a six-port valve connected to a 20 cm³ loop using capillary lines and needle valves and
126 decompressed to atmospheric pressure (by Valves F and F1). Valves were thermostated
127 at the same temperature of the equilibrium cell. The manual pressure generator was
128 employed to keep pressure constant during sampling (± 1 bar) by turning a lever in a
129 clockwise direction. For the determination of the amount of solvent solubilized in CO₂,
130 two samples were withdrawn from the equilibrium cell and expanded into a glass vial,
131 which was weighted before and after sampling in a precision analytical balance with
132 0.0001 g accuracy. Ethyl acetate and ethyl lactate were collected in cooled glass vials at
133 278 K to avoid evaporation and separated from the CO₂ by using a trap. It was assumed
134 that no PLGA polymer was dissolved in gas phase. The amount of CO₂ was measured
135 through a gas meter model RITTER TG-05 (± 0.005 L). The CO₂ density was calculated
136 as a function of pressure and temperature with the equation of Bender [26].

137 Ex situ gravimetric method was used to determine the solubility of CO₂ into
138 PLGA solutions. This method is the easiest way to obtain measurements from sorption
139 experiments. It consists of carrying out the saturation of the sample with supercritical CO₂
140 inside the variable volume equilibrium cell. After equilibrium was reached, the sample
141 was quickly depressurized to ambient pressure and the variation of the vials sample
142 weight over time was measured. In order to know the amount of solubilized CO₂ in the
143 PLGA solutions, these values were extrapolated to the first measurement time. All the
144 experiments were carried out at room temperature, 298.15 K, and in a range of pressure
145 from 20 to 150 bar.

146



147

148

149 Figure 1. Experimental set-up employed to high-pressure phase equilibrium

150 measurements. PG: pressure generator; PI-1: manometer; PI-2: pressure digital indicator;

151 T: liquid supply tank for pressurized the system; TI: temperature digital controller.

152

153 3. Results and discussion

154 In this work, the phase behaviour of the ternary systems PLGA + solvent + CO₂

155 has been studied. The influence of pressure and concentration of PLGA in solutions was

156 studied on the solubility of ethyl acetate and ethyl lactate in CO₂-rich phase, as well as on

157 the solubility of CO₂ in the solutions. The phase behaviour of the polymer/solvent/CO₂

158 system supposes a key part during foaming process. The initial concentration of the

159 polymer in the solvent varied from 0.05 g PLGA/ml solvent to 0.80 g PLGA/ml solvent.

160 All the experiments were carried out in duplicate with an error lower than 1.56% respect

161 to mean value of the duplicate experiments.

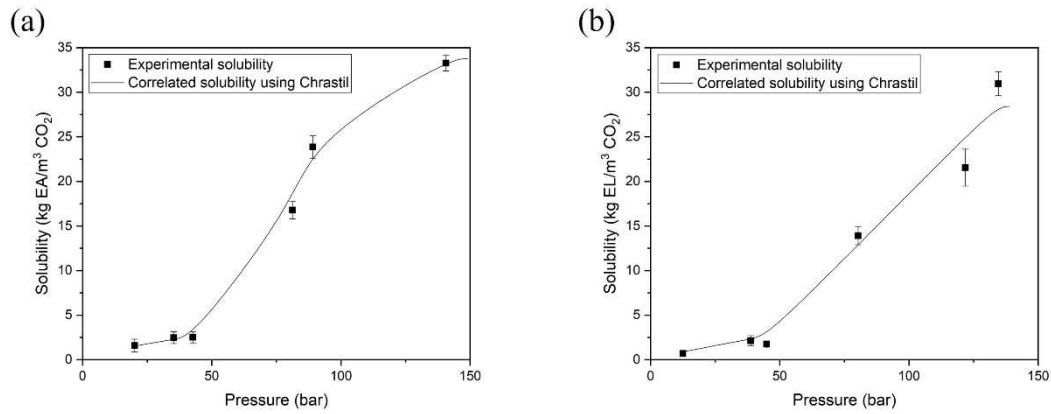
162 **3.1. Binary diagrams**

163 In order to know the equilibrium data of the ternary systems, initially, it is essential
164 to determine the relationships that exist between the pairs of compounds. The limits of
165 the ternary system can be established based on the measurement of the binary equilibrium:
166 CO₂/solvent, CO₂/PLGA and solvent/PLGA. This research has been focused on the study
167 of the pressure on the solubility of both solvents, ethyl acetate and ethyl lactate, in CO₂
168 and the sorption of CO₂ in the solutions which contain PLGA5050 and PLGA7525.

169

170 **3.1.1. Solubility of ethyl acetate and ethyl lactate in CO₂-rich phase**

171 Figure 2 shows the experimental data of the solubility of EA (a) and EL (b)
172 solvents in CO₂. All the measurements given correspond to mean values of the duplicate
173 experiments. The amount of ethyl acetate and ethyl lactate solubilized in the CO₂-rich
174 phase was calculated based on the solvent mass fraction collected in the glass vials and
175 the density of CO₂ at pressure and temperature conditions when the thermodynamic
176 equilibrium was reached. As expected, the solubility of both solvents increases with
177 increasing pressure. From 60 bar onwards, the amount of ethyl acetate and ethyl lactate
178 in the upper phase increases considerably due to the increase in CO₂ density. It can also
179 be seen that the solubility of ethyl acetate is slightly higher than ethyl lactate because its
180 lower polarity [24]. These data show agreement with previous results found in the
181 literature [24].



182

183

Figure 2. Solubility of (a) ethyl acetate and (b) ethyl lactate in CO₂.

184

185

The CO₂-rich phase was correlated using the semiempirical model of Chrastil (1).

186

It is based on the proposition that the association between solvent and solute molecules

187

produces a solvate-complex and gives a linear relationship between the logarithmic

188

solubility and logarithmic density of pure CO₂

189

$$S = \exp\left(C_1 + \frac{C_2}{T} + k \cdot \ln \rho_{CO_2}\right) \quad (1)$$

190

where S is the solubility in [kg/m³], C₁ is a constant dependent on the molecular weights

191

of the solute and solvent on the association constant, C₂ is a constant dependent on the

192

total heat of vaporization, T is the temperature in [K], k is the association number of

193

molecules in the solvate-complex, ρ is the CO₂ density in [kg/m³]. Figure 2 also represents

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the correlation between solubility and pressure using Chrastil's equation. Table 1 shows

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the results of the fitting for these solvents. The results of the adjustment are in a narrow

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range of values as both solvents have similar molecular structures. In any case, according

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to the graphs, the fit shows exactitude to the experimental solubility data obtained in the

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experiments carried out. The mean deviation between the fitting using Chrastil's equation

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and experimental data showed an average error of 2.57% for ethyl acetate and 2.91% for

200

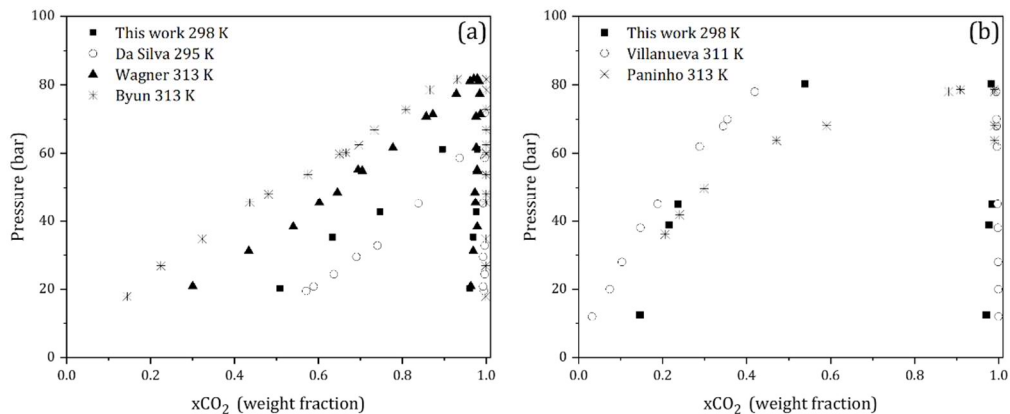
ethyl lactate.

201 Table 1. Fitted values obtained for Chrastil's equation for the solubility of ethyl acetate
202 and ethyl lactate in CO₂-rich phase.

Solvent	C ₁	C ₂	k
Ethyl acetate	-32.782 ± 1.717	0.931 ± 0.032	5.364 ± 0.257
Ethyl lactate	-48.780 ± 8.814	0.893 ± 0.063	7.711 ± 1.314

203

204 Figure 3 compares the results obtained for the phase behaviour in this work with
205 the ones reported in the literature. For ethyl acetate (Figure 3.a), the results obtained by
206 Da Silva et al. [27] at 295 K and those obtained by Wagner [20] and Byun [8] at 313 K
207 are compared. Da Silva used an equilibrium cell with two six-port valves where the
208 samples are collected by depressurization in small glass traps and analyzed in a Hewlett
209 Packard gas-liquid chromatograph. Wagner employed an equilibrium cell where the
210 sample was mixed with a carrier gas and flowed through the chromatographic six-way
211 valve. Byun stated that when the equilibrium was reached, the mixture in the cell is
212 compressed to a single phase and the pressure was then slowly decreased until a second
213 phase appeared at a fixed temperature. A bubble point was obtained if a small bubble
214 appears in the cell, and a dew point was obtained if a fine mist appeared. It can be seen a
215 good agreement between those data and the experimental data found in this work,
216 specially with Da Silva and Wagner because of the similar experimental procedures. The
217 solubility of ethyl acetate in CO₂ is favoured by an increase in pressure and a decrease in
218 temperature reaching the lowest solubility at 313 K. Byun considers that the difference
219 between the experimental data a 313 K and literature values are due to the experiment
220 technique employed [8].



221

222 Figure 3. Comparison of the experimental data for the ethyl acetate (a) and ethyl lactate
 223 (b) solubility in CO₂. (a) Ethyl acetate-CO₂ system, data from this work at 298 K (■), da
 224 Silva et al. [27] at 295 K (○), Wagner et al. [20] at 313 K (▲) and Byun et al.[8] at 313
 225 K (*); (b) Ethyl lactate-CO₂ system, data from this work at 298 K (■), Villanueva
 226 Bermejo et al. [17] at 311 K (○) and Paninho et al. [24] at 313 K (*).

227 Comparing the results obtained for ethyl lactate (Figure 3.b), certain deviations
 228 can be observed between the experimental data of this work and those found in the
 229 literature. In our case, by performing the experiments at a lower temperature, a higher
 230 solubility of the ethyl lactate in the CO₂-rich phase should be achieved. These deviations
 231 may be caused by two reasons. The first is the experimental method for the measurement
 232 of phase behaviour and the second reason could be due to the pretreatment method used
 233 for the solvent. Regarding the experimental method, the one used by Villanueva Bermejo
 234 was similar to the experimental method used in this research but Paninho used visual
 235 observation of the formation of a new phase by increasing cell pressure. On the other
 236 hand, in the case of Paninho et al. [24], the samples were dried to reduce the water content,
 237 while Villanueva Bermejo et al. [17] uses an ethyl lactate with a purity of 99%, being its
 238 water content lower than the ethyl lactate used in this work. The combination of these
 239 two facts could be the reason why these experimental data are more akin to those obtained

240 by Villanueva Bermejo. In general, in experiments carried out at the same temperature, it
241 is possible to verify a higher solubility of ethyl acetate than ethyl lactate in CO₂.

242

243 **3.1.2. Solubility of CO₂ in PLGA**

244 In the study of interactions between gases and polymers, a crucial variable is the
245 molecular weight. It has been reported in literature that an increase in the molecular
246 weight of the polymer promotes a reduction of its solubility in the gas, then high MW
247 polymers are generally insoluble in CO₂ [28]. The only polymers shown to have good
248 solubility in pure CO₂ under mild conditions are certain amorphous fluoropolymers and
249 silicones [29]. The solubility of commercial poly (L-lactic acid) (Mw 5500 g/mol) in
250 supercritical CO₂ at 250 bar and 328 K is less than 0.1 wt% [30] and higher molecular
251 weight PLGA is practically insoluble. Polymers employed in this work has a molecular
252 weight of 17000 g/mol, so it can be assumed that in the experimental conditions of
253 pressure and temperature of this research, both PLGA5050 and PLGA7525, were
254 completely insoluble in CO₂.

255 The study of CO₂ sorption in the polymeric matrix is a key factor in the synthesis
256 and production of scaffolds for its use as carrier system of bioactive compounds. For
257 polymers, depending upon the pressure, temperature and the nature of the fluid, exposure
258 to supercritical fluids at high pressures leads to either dissolution of the polymer in the
259 fluid, or more frequently, dissolution of the fluid in the polymer which leads to
260 plasticization and swelling and morphological modifications such as recrystallization
261 [31]. Porous matrices are then formed by inducing phase separation in the swollen
262 polymers which is achieved by either a pressure, temperature or compositional quench.
263 Formation of smaller pore sizes in foams are correlated with conditions that promote

264 greater amount of carbon dioxide dissolution in the polymer, such as higher pressures and
265 higher carbon dioxide to polymer mass loadings [32].

266 Two other key parameters in polymer foaming are interfacial tension and viscosity
267 because they determine the droplet break up and coalescence in blending, and thus the
268 final resulting morphology of foams. Although the study of these parameters has not been
269 carried out in this work, it is important to take them into consideration in order to carry
270 out foaming experiments. Temperature, pressure and CO₂ concentration determine the
271 changes in viscosity, solubility, surface tension, diffusivity and other properties, as well
272 as play important roles in mechanisms of cell nucleation and cell growth. The
273 combination of these parameters into models of cell nucleation would help to fully
274 understand the foaming process [33]. Hongbo [34] studied the effect of CO₂ on the
275 interfacial tension between PLGA and CO₂ at 40 °C, and pressures up to 60 atm.
276 Interfacial tension was depressed dramatically in the pressure range studied from around
277 43 to 17 dyn/cm following a linear relationship. Regarding polymer's viscosity, it was
278 demonstrate that the interactions of CO₂ with PLGA polymers decrease with increasing
279 glycolide content in the copolymers. As a result, the viscosity decreases more in the case
280 of PLGA7525 than in the case of PLGA5050. The presence of CO₂ causes the viscosity
281 of PLGA to be reduced at 35 °C compared to the 140 °C required to obtain a liquid
282 polymer with a viscosity that is easily processible at atmospheric pressure [35].
283 Furthermore, by using CO₂ to reduce the viscosity of polymers at near ambient
284 temperatures, it is possible to incorporate heat sensitive materials such as proteins [36] or
285 even drugs.

286 The sorption and swelling of CO₂ in PLA and PLGA has been widely studied. Liu
287 and Tomasko [37] reported CO₂ sorption and dilation isotherms of PLGA5050,
288 PLGA7525 and PLA100DL over a useful range of processing conditions temperatures

289 from 303 to 333 K, and pressures up to 100 bar. Pini et al. [38] studied CO₂ sorption and
290 swelling isotherms at 308 K and up to 200 bar on a variety of homo- and copolymers of
291 lactic acid and glycolic acids. In this work, solubility of CO₂ in PLGA5050 and PLGA
292 7525 has been obtained at 298.15 K and pressures from 20 bar to 150 bar. A comparison
293 of the experimental data from this research and those obtained by Liu and Tomasko and
294 Pini et al. is shown in Figure 4.a for PLGA5050 and Figure 4.b for PLGA7525.

295 Experimental data were also correlated using three different models: Henry's law,
296 the Dual-Mode sorption model and Sanchez-Lacombe Equation of State (SLEoS).
297 Henry's law (2) is only valid on the ideal solution state and in the case of diluted solutions
298 because it does not consider the interactions between the gas and the polymer.

$$299 \qquad c = H \cdot P \qquad (2)$$

300 In this equation, c is the concentration of the gas in the polymer, H is Henry's law constant
301 and P is the equilibrium gas pressure. This model predicts better gas sorption at lower
302 pressures and its use is not recommended at high pressures. Dual Mode Sorption model
303 (3) is formed of Henry's law dissolution at low pressures and Langmuir-type sorption in
304 a non-equilibrium region. This region is related to the free volume in a glassy polymer
305 resulting from the presence of microcavities capable of retaining solute molecules [39,
306 40].

$$307 \qquad S = k_H \cdot P + \frac{C'_H \cdot b \cdot P}{1 + b \cdot P} \qquad (3)$$

308 In this equation, S is the sorption of CO₂ in the polymer, k_H is analogous to Henry's law
309 constant, P is the pressure, C'_H is the saturation of the cavities and b represents the affinity
310 between the solute molecules and the Langmuir sites present in the polymeric matrix.
311 Finally, the Sanchez-Lacombe Equation of State (SLEoS) (4) has been also used to
312 correlate the experimental data. It is based on lattice-fluid theory. This model is derived

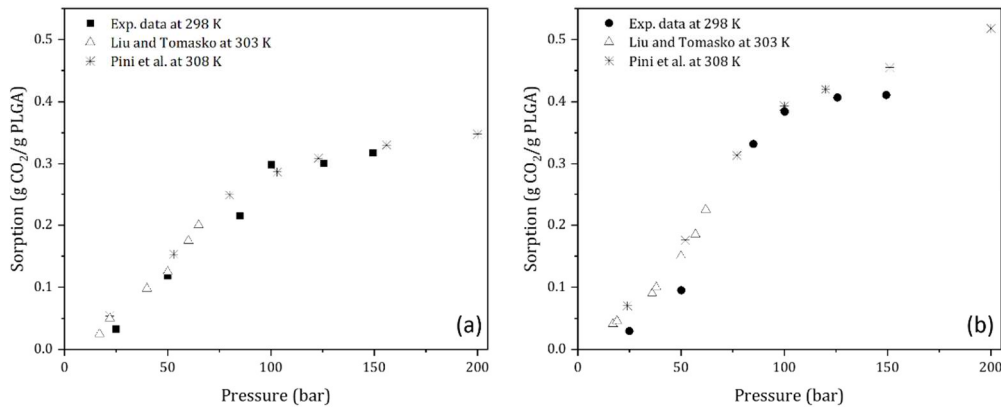
313 for polymers above their glass transition temperature (T_g). The basic form of the SLEoS
 314 is given by

$$315 \quad \tilde{\rho} + \tilde{P} + \tilde{T} \left[\ln (1 - \tilde{\rho}) + \tilde{\rho} \left(1 - \frac{1}{r_0} \right) \right] = 0 \quad (4)$$

316 Where $\tilde{\rho}$, \tilde{P} and \tilde{T} and are the reduced density, pressure and temperature, respectively.
 317 These variables are reduced by the so-called characteristic quantities:

$$318 \quad \tilde{\rho} = \rho / \rho^* = \frac{\rho r_0 v^*}{M_w}; \quad \tilde{P} = P / P^* = \frac{P v^*}{\epsilon^*}; \quad \tilde{T} = T / T^* = \frac{TR}{\epsilon^*} \quad (5)$$

319 where ρ^* , P^* , and T^* are the characteristic density, pressure and temperature which, are
 320 functions of v^* the closed packed volume of a molecule segment, r_0 is the number of sites
 321 occupied by a molecule in the lattice and ϵ^* , the interaction energy per mer. R and M_w
 322 are the ideal gas constant and the molecular weight which, in the case of polymers,
 323 corresponds to the number-average molecular weight.



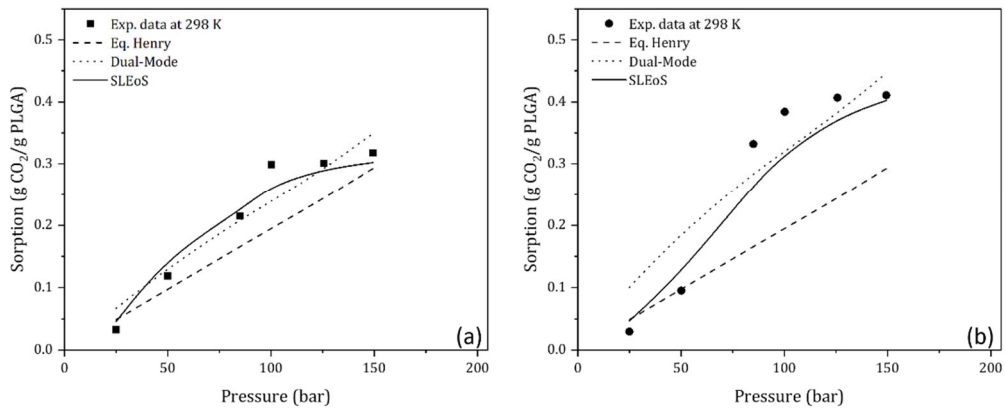
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325 Figure 4. Experimental data of CO₂ sorption in (a) PLGA5050: this research at 298 K
 326 (■), Liu and Tomasko at 303 K (△), and Pini et al. at 308 K (*); (b) PLGA7525: this
 327 research at 298 K (●), Liu and Tomasko at 303 K (△), and Pini et al. at 308 K (*).

328

329 Attending to Figure 4, it can be observed how the sorption of CO₂ in the polymeric
330 matrix is similar for both polymers at low pressures. However, as the working pressure
331 increases, there is a significant change at about 70 bar. PLGA7525 presents a higher
332 content of lactide, which leads to a better diffusion of CO₂ promoted by its affinity with
333 the monomer. The steric hindrance close to the carbonyl group and accessible free volume
334 caused by methyl pendant groups suppose a higher sorption of CO₂ at higher pressures.
335 This fact was also observed by Pini et al. [38] obtaining higher CO₂ sorption in PLA
336 homopolymers than in copolymers formed by PLA and PGA. Regarding the effect of
337 temperature, according literature, sorption of CO₂ in PLGA is higher when pressure
338 increases and temperature decreases, achieving the best results of sorption at lower
339 temperatures [37, 38, 41, 42]. In this research, the sorption values obtained ad 298 K are
340 similar to those obtained by Pini et al. at 308 K probably to the differences in the method
341 used for its measurement. Pini et al. performed sorption experiments in a magnetic
342 suspension balance provided with a calibrated sinker for *in situ* measurements while Liu
343 and Tomasko used a pressure decay apparatus where the samples were monitored *in situ*
344 and the signal was transmitted to a data-acquisition system to record the entire sorption
345 process.

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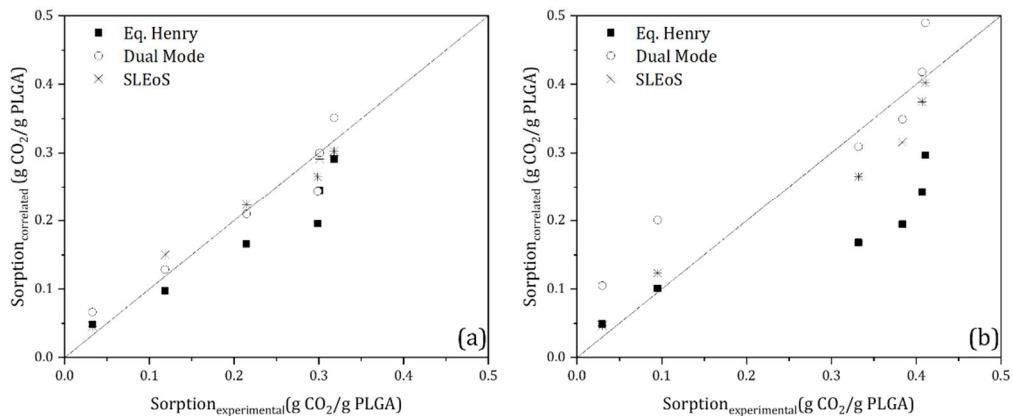


347

348 Figure 5. Experimental and correlated data of CO₂ sorption in: (a) PLGA5050 correlation
 349 of experimental data (■) using Henry's law (---), Dual-Mode model (···) and Sanchez-
 350 Lacombe EoS (—); (b) PLGA7525 correlation of experimental data (●) using Henry's
 351 law (---), Dual-Mode model (···) and Sanchez-Lacombe EoS (—).

352

353 Figure 5 shows the comparison between the experimental data obtained in this
 354 research for both ratios PLA to PGA and those data correlated with the three models
 355 previously proposed. Figure 6 illustrates the deviation of sorption measurements obtained
 356 experimentally and the correlated data.



357

358 Figure 6. Comparison between experimental and correlated data for the sorption of CO₂
 359 in the polymeric matrix with the three proposed models: (a)PLGA5050 correlated data

360 using Henry's equation (■), the Dual-Mode model (○), and Sanchez-Lacombe EoS (*);
361 (b)PLGA7525 correlated data using Henry's equation (■), the Dual-Mode model (○), and
362 Sanchez-Lacombe EoS (*).

363

364 Regarding Figures 5 and 6, the SLEoS model predicts more accurately the
365 sorption of CO₂ in the polymer matrix than the other two models, especially at high
366 pressures for PLGA5050. The total quadratic error considering the deviations for both
367 ratios PLA to PGA using the SLEoS model is 0.70%. This is the lowest error value, so it
368 can be concluded that this model predicts more accurately the CO₂ sorption in the matrix.
369 It can be seen how Henry's equation estimates well the behaviour of the system at low
370 pressures, but large deviations appear at high pressures, especially in the case of
371 PLGA7525. In this case, the maximum error is found reaching a value of 6.03%. When
372 using the Dual-Mode model a better fit is observed in the case of the PLGA5050 probably
373 due to the lower sorption values that are obtained. In the case of PLGA7525, there is an
374 overestimation of the correlated values at low pressures, adjusting better to pressures
375 above 70 bar resulting in an error compared to experimental data of 1.52%.

376

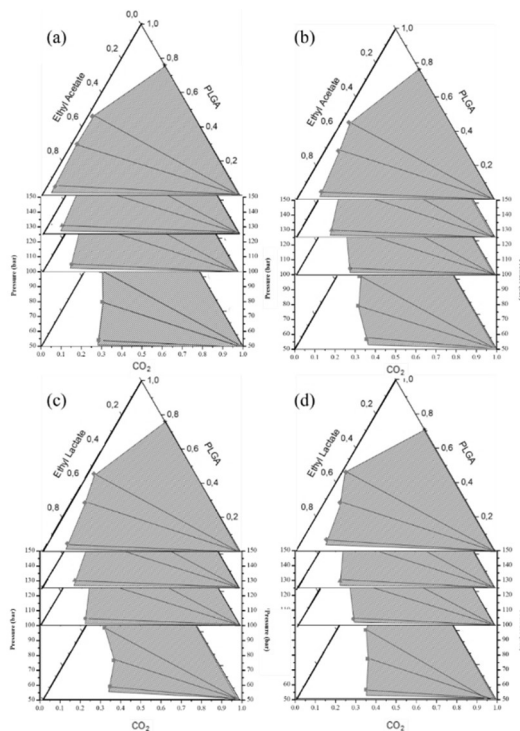
377 **3.2. Ternary diagrams**

378 Although the previously described binary systems were extensively studied in the
379 literature, it is important to consider that these ternary systems could have completely
380 different behaviours when a solute, a solvent or an antisolvent is introduced in the mixture
381 and particularly, neither the ternary CO₂/EA/PLGA nor CO₂/EL/PLGA systems have
382 been studied. It is therefore necessary to study the interactions happening when the three
383 components are in contact, especially if the solute is a polymer. The behaviour of this

384 system could be generalised in order to select experimental conditions to obtain polymeric
385 matrices used as drug carrier. In addition, operating conditions are critical during the
386 synthesis and processing of microcellular foams because the final internal structure
387 depends on them.

388 The knowledge about the homogeneous and heterogeneous regions of the mixture
389 is fundamental to carry out the separation of the polymer from its solution in ethyl acetate
390 or ethyl lactate using high pressure CO₂. A temperature isotherm was set at 298.15 K.
391 This value of temperature was not a variable of study because any degradation of the
392 polymer, or even the drug, was intended. In the triangular prism (Figure 7), that
393 constitutes the diagrams, the behaviours of the system in a range of pressures from 50 to
394 150 bar are shown. These results are expressed in wt. %.

395 As a general rule in all CO₂/solvent/polymer systems represented in Figure 7,
396 shaded areas of the ternary diagram correspond to the heterogeneous region where the
397 two liquid-liquid phases are generated in equilibrium. The existence of these two phases
398 is fundamental to be able to perform the separation of the components during the system
399 depressurization. As the amount of CO₂ increases, the homogeneous zone becomes
400 narrower. This means that an increase in the working pressure favours the mutual
401 solubility of the three components as same as it does in the binary diagrams studied
402 previously. In addition, it is observed that working with lower initial concentration of the
403 polymer, the solubility of solvents in CO₂ is enhanced. The two liquid-liquid phase
404 separation is produced when the depressurization takes place and PLGA rich and lean
405 phases are stood out. Tie lines in the diagrams are also represented in the two-phases
406 region, connecting the compositions of bottom phase rich in polymer and top phase rich
407 in CO₂. The negative slope of the tie lines indicates a greater affinity and higher
408 interaction of the PLGA for the solvents than for the CO₂.



409

410 Figure 7. Phase behaviour of the system (a) CO₂/Ethyl Acetate/PLGA5050, (b) CO₂/Ethyl
 411 Acetate/PLGA7525, (c) CO₂/Ethyl Lactate/PLGA5050 and (d) CO₂/Ethyl
 412 Lactate/PLGA7525 at 298.15K and constant pressure: 50, 100, 125 and 150 bar.
 413 Concentrations are given in mass fraction (wt. %).

414

415 Regarding the type of polymer used, it can be seen for both solvents how the use
 416 of PLGA5050 makes the heterogeneous zone slightly larger than in the case of
 417 PLGA7525 but it is not significantly influenced by shifts in the polymer type. Although
 418 PLGA7525 showed a higher CO₂ sorption in the polymeric matrix, the presence of three
 419 components improves the sorption in PLGA5050 solutions. Moreover, attending to the
 420 solvents, when ethyl acetate is employed the mutual solubility is slightly higher, as
 421 revealed the binary systems in which greater solubility was achieved. This fact is
 422 explained due to the lower polarity and molecular weight of the solvent, resulting in a
 423 more advantageous separation.

424 Despite of ternary diagrams, it is difficult to observe a clear influence of the
425 pressure and the initial concentration of the polymer on the solubility of both solvents in
426 the CO₂- rich phase, as well as the sorption of CO₂ in the PLGA solutions. These variables
427 have been analysed individually for a better understanding of the results obtained. The
428 purpose of this work is to extract and recovery the solvent to achieve a solvent-free
429 scaffold that can be directly used in the biomedical industry.

430

431 **3.2.1. Influence of PLGA concentration and pressure on ethyl acetate solubility in** 432 **CO₂-rich phase.**

433 The effect of CO₂ pressure and density on the solubility of ethyl acetate in the
434 CO₂-rich phase was studied in a range of pressure from 20 to 150 bar and in the presence
435 of PLGA. According with Figure 8, an increase in the initial concentration of the polymer
436 in the solution decreases the amount of ethyl acetate solubilized in CO₂, independently of
437 the monomer ratio lactide:glycolide. Solubility of ethyl acetate in CO₂ is higher in
438 PLGA5050 solutions, which could be attributed to the affinity of this solvent and lactide
439 as a consequence of the carbonyl group [43].

440 The maximum solubility rate is observed at a pressures about the critical point of
441 CO₂. Experiments carried out at pressures next to the critical point are refused because
442 no reproducibility is obtained. The highest solubility achieved is 19.44 kg EA/m³ CO₂,
443 which is obtained for PLGA5050 at a initial concentration of 0.05 g PLGA/ml EA and a
444 pressure of 132 bar. Conversely, the lowest value of solubility at high pressure is reached
445 using PLGA7525 and a initial concentration of 0.8 g PLGA/ml EA. This fact could be
446 due to the greater interaction between ethyl acetate and the polymer chains being less
447 accesible to solubilize the ethyl acetate.

448 An adjustment of the experimental results obtained for the upper phase in presence
 449 of the polymer is also correlated using Chrastil's equation. Figure 8 represents the fitting
 450 for solubility and pressure using equation (1).

451

452 Table 2. Fitted values obtained for Chrastil's equations for the solubility of ethyl acetate
 453 in CO₂ -rich phase: (a) PLGA5050, (b) PLGA7525.

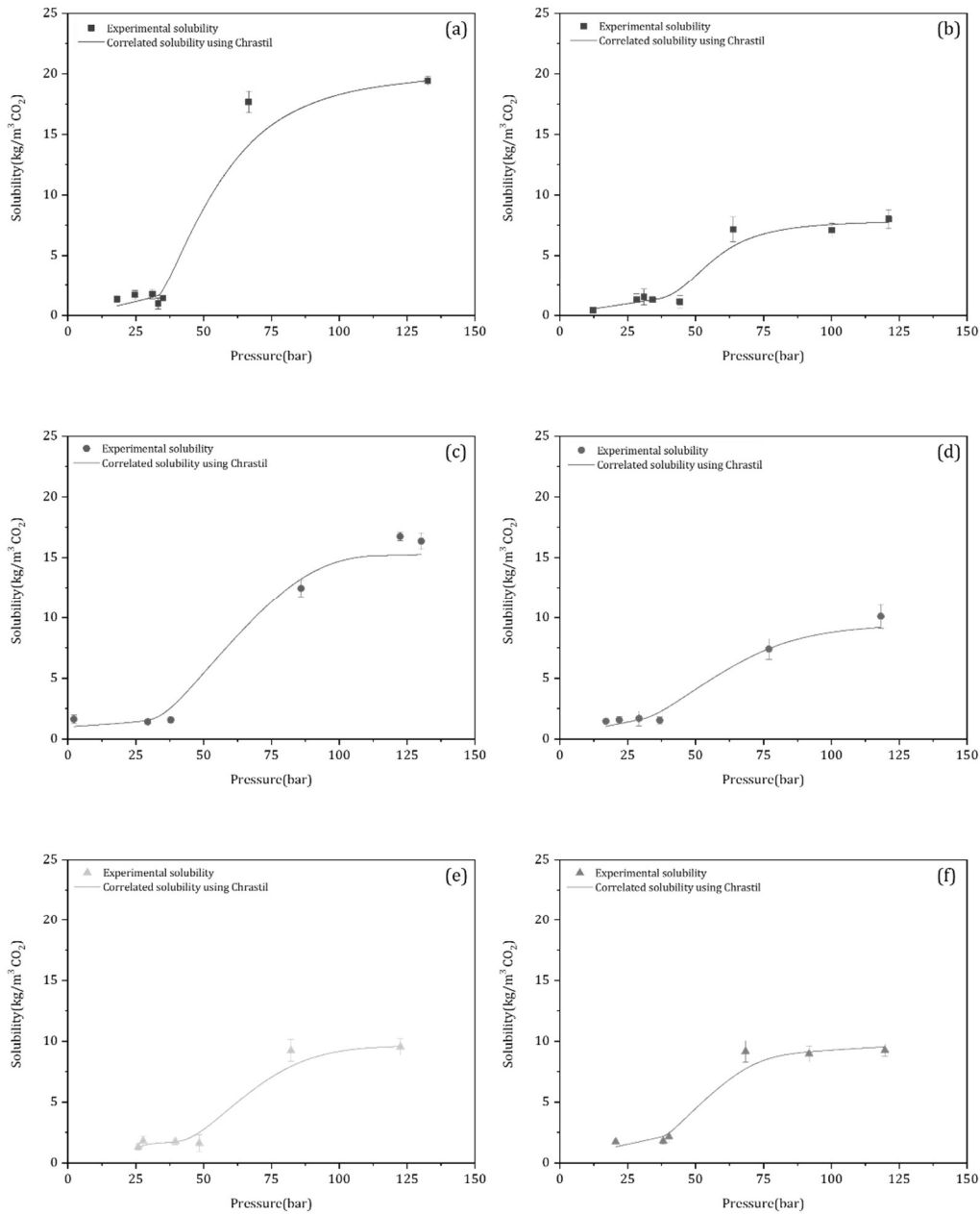
(a)

Concentration g PLGA/ml solvent	PLGA5050		
	C ₁	C ₂	k
0.05	-3.864 ± 0.548	-0.013 ± 0.002	1.013 ± 0.078
0.4	-3.399 ± 0.365	-0.073 ± 0.025	0.908 ± 0.057
0.8	-3.093 ± 0.299	-0.010 ± 0.005	0.797 ± 0.051

454

(b)

Concentration g PLGA/ml solvent	PLGA7525		
	C ₁	C ₂	k
0.05	-3.007 ± 0.871	-0.010 ± 0.002	0.750 ± 0.019
0.4	-2.311 ± 0.654	-0.010 ± 0.004	0.671 ± 0.035
0.8	-2.134 ± 0.661	-0.009 ± 0.004	0.651 ± 0.073



455

456 Figure 8. Solubility of ethyl acetate in CO₂ and in presence of PLGA. (a) PLGA5050, Ci
 457 = 0.05 g PLGA/ml EA. (b) PLGA7525, Ci = 0.05 g PLGA/ml EA. (c) PLGA5050, Ci =
 458 0.4 g PLGA/ml EA. (d) PLGA7525, Ci = 0.4 g PLGA/ml EA. (e) PLGA5050, Ci = 0.8 g
 459 PLGA/ml EA. (f) PLGA7525, Ci = 0.8 g PLGA/ml EA.

460

461 In general, a good fit of the experimental data to Chrastil's equation is observed
 462 in Figure 8. From the results obtained for the adjustment, it is established that the

463 separation of the components of the ternary system is favoured in the case of using
464 PLGA5050. For this PLA to PGA ratio the values obtained for C_1 are higher than those
465 obtained for PLGA7525. A greater affinity of the solvent for CO_2 is corroborated by k
466 values. Concerning the initial amount of the polymer in the solution, it is observed how
467 an increase resulted in a lower value of the adjustment constants, thus corroborating the
468 better solubility obtained at lower concentrations. C_2 is practically zero since this study
469 was carried out at a constant temperature and this term depends on it. In addition, these
470 values are considerably lower compared to those obtained for the binary systems shown
471 in Table 1. The presence of the polymer in the solutions decreases the solubility of ethyl
472 acetate in CO_2 since a decrease in the values of the adjustment variable, which represents
473 the PLGA-EA interaction, is observed.

474

475 **3.2.2. Influence of PLGA concentration and pressure on ethyl lactate solubility in** 476 **CO_2 -rich phase.**

477 Figure 9 shows the experimental values obtained for the solubility of ethyl lactate
478 in CO_2 -rich phase. The results obtained in these experiments are similar to those obtained
479 in the case of the system PLGA/EA/ CO_2 . As the operating pressure and CO_2 density
480 increase, so does the amount of solvent in the CO_2 -rich phase. Maximum solubility is
481 achieved for PLGA5050 at the lowest initial polymer concentration and a pressure of 152
482 bar. This value is 22.90 kg EL/ m^3 CO_2 . This result is significantly lower than the
483 maximum solubility obtained for ethyl acetate, but we must consider that ethyl lactate has
484 more adequate properties for its use in the pharmaceutical industry. In addition, it is
485 observed that as the amount of polymer in the initial solution increases, the quantity of
486 solvent in the CO_2 -rich phase is reduced. Because of that, the lowest solubility values for
487 PLGA7525 at a concentration of 0.8 g PLGA/ml EL.

488 In the same way, a correlation of the experimental data was carried out using
 489 Chrastil's equation in which the term of the initial polymer concentration is given. The
 490 fitted results are shown in Table 3.

491

492 Table 3. Fitted values obtained for Chrastil's equations for the solubility of ethyl lactate
 493 in CO₂ -rich phase: (a) PLGA5050, (b) PLGA7525.

(a)

Concentration g PLGA/ml solvent	PLGA5050		
	C ₁	C ₂	k
0.05	-5.572 ± 2.024	-0.010 ± 0.002	1.178 ± 0.024
0.4	-4.999 ± 1.547	-0.073 ± 0.001	1.103 ± 0.069
0.8	-1.195 ± 0.571	-0.810 ± 0.031	0.611 ± 0.017

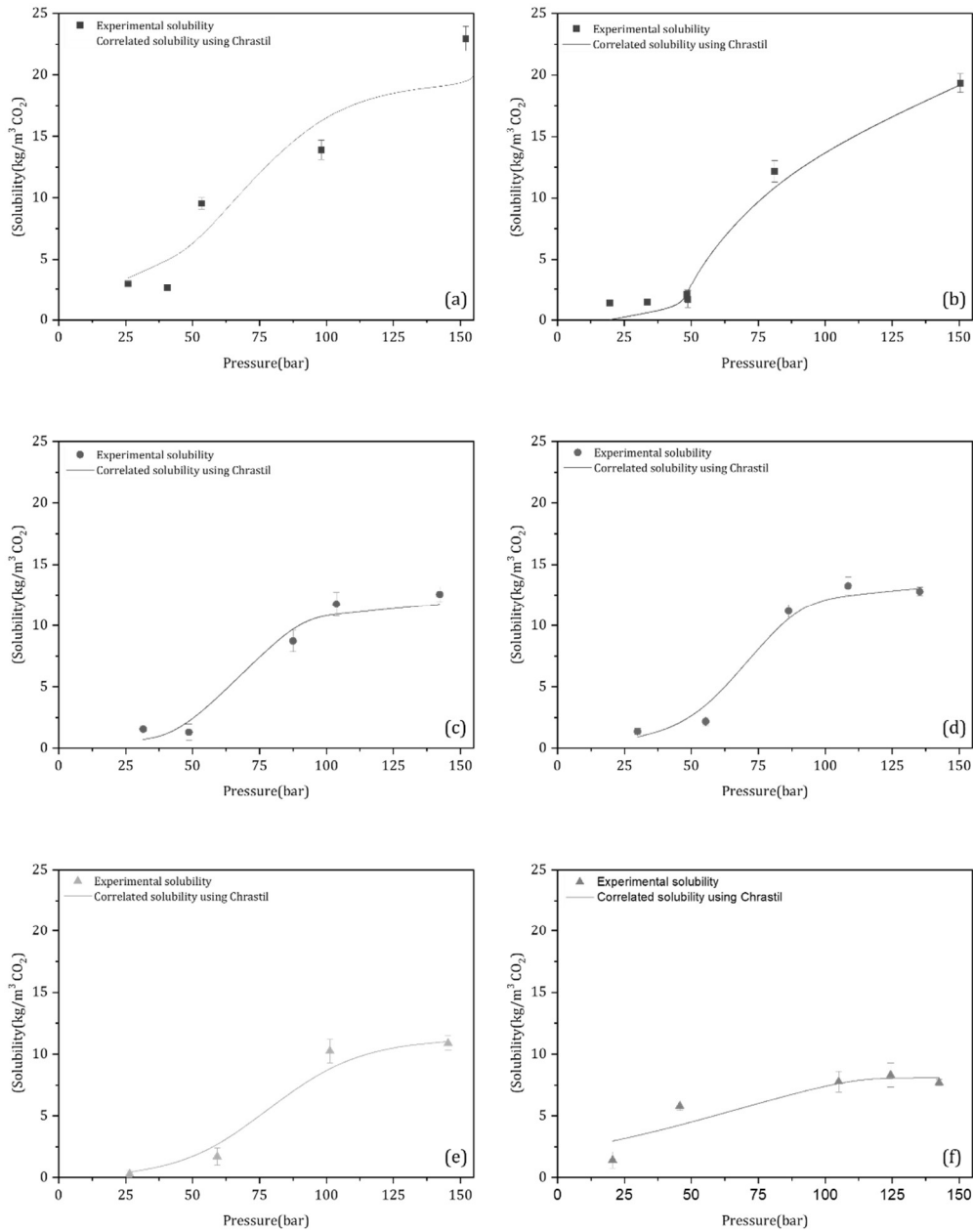
494

495

(b)

Concentration g PLGA/ml solvent	PLGA7525		
	C ₁	C ₂	k
0.05	-5.902 ± 1.021	-0.141 ± 0.003	1.297 ± 0.040
0.4	-4.326 ± 1.365	-0.010 ± 0.001	1.020 ± 0.098
0.8	-0.151 ± 0.047	-0.009 ± 0.001	0.332 ± 0.004

496



498

499 Figure 9. Solubility of ethyl lactate in CO₂ and in presence of PLGA. (a) PLGA5050, Ci
 500 = 0.05 g PLGA/ml EL. (b) PLGA7525, Ci = 0.05 g PLGA/ml EL. (c) PLGA5050, Ci =
 501 0.4 g PLGA/ml EL. (d) PLGA7525, Ci = 0.4 g PLGA/ml EL. (e) PLGA5050 Ci = 0.8 g
 502 PLGA/ml EL. (f) PLGA7525, Ci = 0.8 g PLGA/ml EL.

503

504 Regarding Figure 9, the correlation fitted quite well with the experimental data in
505 a pressure range of 25 to 150 bar, temperature of 298.15 K and especially at high initial
506 concentrations of the polymer. The positive influence of density because of higher
507 pressure is observed through the positive sign of k . The values of C_1 and C_2 are within
508 the same range as those obtained in the case of using ethyl acetate as a solvent. In this
509 case, the value of C_1 is slightly higher allowing for a good separation of the components
510 to be achieved at low initial polymer concentrations. As in the previous case, an increase
511 in the initial concentration of the polymer results in a lower solubility which is reflected
512 in the decrease of both the C_1 and k values.

513

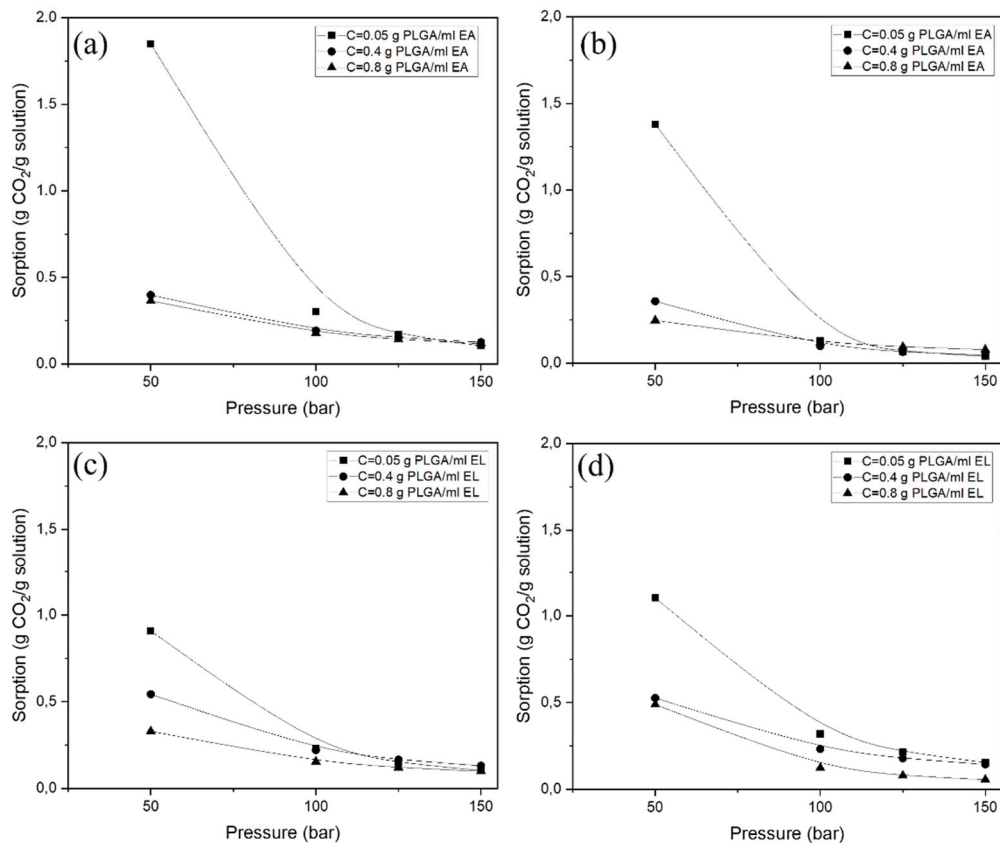
514

515 **3.2.3. Influence of solvent, PLGA concentration and pressure on CO₂ solubility in**
516 **PLGA solutions.**

517 Figure 10 shows the CO₂ sorption in polymer solutions in an initial polymer
518 concentration range of 0.05 g PLGA/mL solvent to 0.8 g PLGA/mL solvent and for
519 pressures between 50 and 150 bar.

520 It is appreciated how sorption lowers as pressure increases. The higher decrease
521 has its maximum around the critical CO₂ pressure. As previously mentioned, this
522 phenomenon can be attributed to the fact that at pressures below 70 bar, the largest
523 amount of CO₂ is found in the solvent. As pressure increases, the solvent is completely
524 solubilized in the CO₂-rich phase, causing the CO₂ to be retained only in the polymeric
525 matrix. In this way, at high pressures the sorption values are similar to those obtained for
526 the PLGA/CO₂ system.

527 When ethyl acetate is the solvent used, the highest sorption is obtained at 50 bar
 528 when the polymer employed is PLGA5050 reaching a value of 1.84 g CO₂/g solution. On
 529 the contrary, the lowest sorption is quite similar for all the experiments around 0.1 g
 530 CO₂/g solution.



531
 532 Figure 10. Sorption of CO₂ in PLGA solutions (a)Ethyl Acetate-PLGA5050, (b)Ethyl
 533 Acetate-PLGA7525, (c)Ethyl Lactate-PLGA5050, (d)Ethyl Lactate-PLGA7525 at
 534 298.15K and concentrations of (■) C= 0.05 g PLGA/mL solvent, (●) 0.4 g PLGA/mL
 535 solvent, (▲) 0.8 g PLGA/mL solvent.

536
 537 Taking into account these results and in order to obtain dry foams without solvent
 538 traces and with homogeneous structure, the best conditions would be reached at high
 539 initial concentrations of PLGA. This is explained by the reason that at pressures above

540 the critical point the CO₂ is only retained in the polymer matrix. However, the solubility
541 of the solvents was reduced at high initial concentrations of PLGA in the solvents and
542 traces of them could remain in foams making them unsuitable for use as controlled release
543 systems.

544

545 **4. Conclusions.**

546 High-pressure phase equilibrium of the ternary systems CO₂/solvent/PLGA has
547 been reported for the first time. Two different solvents, ethyl acetate and ethyl lactate,
548 and two PLA:PGA polymer ratios, PLGA5050 and PLGA7525, were employed in order
549 to obtain dry scaffolds for its use as drug carriers in medical devices.

550 Binary system CO₂/solvent demonstrated that ethyl acetate is solubilised easily at
551 higher pressures than ethyl lactate thanks to its low polarity and low molecular weight. In
552 addition, the PLGA/CO₂ system showed a greater affinity of CO₂ for PLGA7525 due to
553 its higher lactide content. Ternary diagrams confirmed the formation of heterogeneous
554 and homogeneous phases when all three compounds are present. The existence of the
555 two-phase liquid-liquid region is crucial in order to carry out the separation of the
556 components and to obtain the precipitation of PLGA. It was confirmed that an increase
557 in the amount of solvent lead to an increase in the mutual miscibility of the components.
558 Solubility of solvents in CO₂ -rich phase is enhanced when pressure increases and initial
559 concentration of the polymer in the solution decreases. Contrary to this, sorption of CO₂
560 into PLGA solutions is greater at lower pressures under the critical pressure of CO₂ but
561 also at lower initial concentration.

562 Taking into account the results obtained in this work, the best conditions to
563 produce dry scaffolds for its use in the pharmaceutical industry were PLGA5050 at a
564 concentration of 0.05 g PLGA/ml EA and at pressures above 100 bar.

565

566 **5. References.**

- 567 [1] Z.L. Mou, L.J. Zhao, Q.A. Zhang, J. Zhang, Z.Q. Zhang, Preparation of porous
568 PLGA/HA/collagen scaffolds with supercritical CO₂ and application in osteoblast cell
569 culture, *Journal of Supercritical Fluids*, 58 (2011) 398-406.
- 570 [2] Z. Pan, J. Ding, Poly(lactide-co-glycolide) porous scaffolds for tissue engineering
571 and regenerative medicine, *Interface Focus*, 2 (2012) 366-377.
- 572 [3] Y. Xu, D. Koo, E.A. Gerstein, C.-S. Kim, Multi-scale modeling of polymer–drug
573 interactions and their impact on the structural evolutions in PLGA-tetracycline films,
574 *Polymer*, 84 (2016) 121-131.
- 575 [4] F. Alexis, Factors affecting the degradation and drug-release mechanism of
576 poly(lactic acid) and poly[(lactic acid)-co-(glycolic acid)], *Polymer International*, 54
577 (2005) 36-46.
- 578 [5] H.K. Makadia, S.J. Siegel, Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable
579 Controlled Drug Delivery Carrier, *Polymers*, 3 (2011) 1377-1397.
- 580 [6] S. Sonam, H. Chaudhary, V. Arora, K. Kholi, V. Kumar, Effect of physicochemical
581 properties of biodegradable polymers on nano drug delivery, *Polymer Reviews*, 53
582 (2013) 546-567.
- 583 [7] X. Xin, Q.Q. Liu, C.X. Chen, Y.X. Guan, S.J. Yao, Fabrication of bimodal porous
584 PLGA scaffolds by supercritical CO₂ foaming/particle leaching technique, *Journal of*
585 *Applied Polymer Science*, 133 (2016).
- 586 [8] H.S. Byun, M.Y. Choi, J.S. Lim, High-pressure phase behavior and modeling of
587 binary mixtures for alkyl acetate in supercritical carbon dioxide, *Journal of Supercritical*
588 *Fluids*, 37 (2006) 323-332.
- 589 [9] F. Cansell, C. Aymonier, A. Loppinet-Serani, Review on materials science and
590 supercritical fluids, *Current Opinion in Solid State and Materials Science*, 7 (2003) 331-
591 340.
- 592 [10] H.M. Woods, M.M.C.G. Silva, C. Nouvel, K.M. Shakesheff, S.M. Howdle,
593 Materials processing in supercritical carbon dioxide: surfactants, polymers and
594 biomaterials, *Journal of Materials Chemistry*, 14 (2004) 1663-1678.
- 595 [11] A. Salerno, C.D. Pascual, Bio-based polymers, supercritical fluids and tissue
596 engineering, *Process Biochemistry*, 50 (2015) 826-838.
- 597 [12] A.M. López-Periogo, A. Vega, P. Subra, A. Argemí, J. Saurina, C.A. García-
598 González, C. Domingo, Supercritical CO₂ processing of polymers for the production of
599 materials with applications in tissue engineering and drug delivery, *Journal of Materials*
600 *Science*, 43 (2008) 1939-1947.

- 601 [13] E. Markočič, T. Botić, S. Kavčič, T. Bončina, Z. Knez, In vitro degradation of
602 poly(d, l -lactide- co -glycolide) foams processed with supercritical fluids, *Industrial*
603 *and Engineering Chemistry Research*, 54 (2015) 2114-2119.
- 604 [14] C. Gutiérrez, J.F. Rodríguez, I. Gracia, A. De Lucas, M.T. García, Development of
605 a strategy for the foaming of polystyrene dissolutions in scCO₂, *Journal of Supercritical*
606 *Fluids*, 76 (2013) 126-134.
- 607 [15] R.A. Quirk, R.M. France, K.M. Shakesheff, S.M. Howdle, Supercritical fluid
608 technologies and tissue engineering scaffolds, *Current Opinion in Solid State and*
609 *Materials Science*, 8 (2004) 313-321.
- 610 [16] S. Varona, A. Braeuer, A. Leipertz, Á. Martín, M.J. Cocero, Lycopene solubility in
611 mixtures of carbon dioxide and ethyl acetate, *The Journal of Supercritical Fluids*, 75
612 (2013) 6-10.
- 613 [17] D. Villanueva Bermejo, E. Ibáñez, R.P. Stateva, T. Fornari, Solubility of CO₂ in
614 Ethyl Lactate and Modeling of the Phase Behavior of the CO₂ + Ethyl Lactate Mixture,
615 *Journal of Chemical & Engineering Data*, 58 (2013) 301-306.
- 616 [18] C.S.M. Pereira, V.M.T.M. Silva, A.E. Rodrigues, Ethyl lactate as a solvent:
617 Properties, applications and production processes - A review, *Green Chemistry*, 13
618 (2011) 2658-2671.
- 619 [19] J.T. McConville, T.C. Carvalho, S.A. Kucera, E. Garza, Ethyl lactate as a
620 pharmaceutical-grade excipient and development of a sensitive peroxide assay,
621 *Pharmaceutical Technology*, 33 (2009) 74-82.
- 622 [20] Z. Wagner, J. Pavlíček, Vapour-liquid equilibrium in the carbon dioxide-ethyl
623 acetate system at high pressure, *Fluid Phase Equilibria*, 97 (1994) 119-126.
- 624 [21] Z. Wagner, I. Wichterle, High-pressure vapour-liquid equilibrium in systems
625 containing carbon dioxide, 1-hexene, and n-hexane, *Fluid Phase Equilibria*, 33 (1987)
626 109-123.
- 627 [22] Y.L. Tian, H.G. Zhu, Y. Xue, Z.H. Liu, L. Yin, Vapor-liquid equilibria of the
628 carbon dioxide + ethyl propanoate and carbon dioxide + ethyl acetate systems at
629 pressure from 2.96 MPa to 11.79 MPa and temperature from 313 K to 393 K, *Journal of*
630 *Chemical and Engineering Data*, 49 (2004) 1554-1559.
- 631 [23] D.W. Cho, M.S. Shin, J. Shin, W. Bae, H. Kim, High-pressure phase behavior of
632 methyl lactate and ethyl lactate in supercritical carbon dioxide, *Journal of Chemical and*
633 *Engineering Data*, 56 (2011) 3561-3566.
- 634 [24] A.B. Paninho, A.V.M. Nunes, A. Paiva, V. Najdanovic-Visak, High pressure phase
635 behavior of the binary system (ethyl lactate+carbon dioxide), *Fluid Phase Equilibria*,
636 360 (2013) 129-133.
- 637 [25] C. Gutiérrez, J.F. Rodríguez, I. Gracia, A. De Lucas, M.T. García, High-pressure
638 phase equilibria of Polystyrene dissolutions in Limonene in presence of CO₂, *Journal of*
639 *Supercritical Fluids*, 84 (2013) 211-220.
- 640 [26] E. Bender, Equations of state for ethylene and propylene, *Cryogenics*, 15 (1975)
641 667-673.
- 642 [27] M.V. da Silva, D. Barbosa, P.O. Ferreira, J. Mendonça, High pressure phase
643 equilibrium data for the systems carbon dioxide/ethyl acetate and carbon

- 644 dioxide/isoamyl acetate at 295.2, 303.2 and 313.2 K, *Fluid Phase Equilibria*, 175 (2000)
645 19-33.
- 646 [28] A.I. Cooper, Polymer synthesis and processing using supercritical carbon dioxide,
647 *Journal of Materials Chemistry*, 10 (2000) 207-234.
- 648 [29] M.A. McHugh, V.J. Krukonis, *Supercritical Fluid Extraction*, 2nd ed., Stoneham,
649 MA, 1994.
- 650 [30] J.W. Tom, P.G. Debenedetti, Formation of Bioerodible Polymeric Microspheres
651 and Microparticles by Rapid Expansion of Supercritical Solutions, *Biotechnology*
652 *Progress*, 7 (1991) 403-411.
- 653 [31] E. Kiran, Polymer miscibility, phase separation, morphological modifications and
654 polymorphic transformations in dense fluids, *The Journal of Supercritical Fluids*, 47
655 (2009) 466-483.
- 656 [32] E. Kiran, Foaming strategies for bioabsorbable polymers in supercritical fluid
657 mixtures. Part I. Miscibility and foaming of poly(l-lactic acid) in carbon
658 dioxide+acetone binary fluid mixtures, *The Journal of Supercritical Fluids*, 54 (2010)
659 296-307.
- 660 [33] D.L. Tomasko, H. Li, D. Liu, X. Han, M.J. Wingert, L.J. Lee, K.W. Koelling, A
661 Review of CO₂ Applications in the Processing of Polymers, *Industrial & Engineering*
662 *Chemistry Research*, 42 (2003) 6431-6456.
- 663 [34] H. Li, L.J. Lee, D.L. Tomasko, Effect of Carbon Dioxide on the Interfacial Tension of
664 Polymer Melts, *Industrial & Engineering Chemistry Research*, 43 (2004) 509-514.
- 665 [35] H. Tai, C.E. Upton, L.J. White, R. Pini, G. Storti, M. Mazzotti, K.M. Shakesheff,
666 S.M. Howdle, Studies on the interactions of CO₂ with biodegradable poly(dl-lactic
667 acid) and poly(lactic acid-co-glycolic acid) copolymers using high pressure ATR-IR and
668 high pressure rheology, *Polymer*, 51 (2010) 1425-1431.
- 669 [36] M.S. Watson, M.J. Whitaker, S.M. Howdle, K.M. Shakesheff, Incorporation of
670 proteins into polymer materials by a novel supercritical fluid processing method,
671 *Advanced Materials*, 14 (2002) 1802-1804.
- 672 [37] D. Liu, D. Tomasko, Carbon dioxide sorption and dilation of poly(lactide-co-
673 glycolide), 2007.
- 674 [38] R. Pini, G. Storti, M. Mazzotti, H. Tai, K.M. Shakesheff, S.M. Howdle, Sorption
675 and swelling of poly(DL-lactic acid) and poly(lactic-co-glycolic acid) in supercritical
676 CO₂: An experimental and modeling study, *Journal of Polymer Science Part B:*
677 *Polymer Physics*, 46 (2008) 483-496.
- 678 [39] S. Hilic, S.A.E. Boyer, A.A.H. Pádua, J.-P.E. Grolier, Simultaneous measurement
679 of the solubility of nitrogen and carbon dioxide in polystyrene and of the associated
680 polymer swelling, *Journal of Polymer Science Part B: Polymer Physics*, 39 (2001)
681 2063-2070.
- 682 [40] D.R. Paul, *Gas Sorption and Transport in Glassy Polymers*, *Berichte der*
683 *Bunsengesellschaft für physikalische Chemie*, 83 (1979) 294-302.
- 684 [41] J. Yu, C. Tang, Y. Guan, S. Yao, Z. Zhu, Sorption and Diffusion Behavior of
685 Carbon Dioxide into Poly(l-lactic acid) Films at Elevated Pressures, *Chinese Journal of*
686 *Chemical Engineering*, 21 (2013) 1296-1302.

- 687 [42] A. Kasturirangan, C.A. Koh, A.S. Teja, Glass-Transition Temperatures in CO₂ +
688 Polymer Systems: Modeling and Experiment, Industrial & Engineering Chemistry
689 Research, 50 (2011) 158-162.
- 690 [43] L.I. Cabezas, I. Gracia, M.T. García, A. De Lucas, J.F. Rodríguez, Production of
691 biodegradable porous scaffolds impregnated with 5-fluorouracil in supercritical CO₂,
692 Journal of Supercritical Fluids, 80 (2013) 1-8.
- 693