Improvement of PLGA loading and release of curcumin by supercritical technology

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Abstract.

This work studies the viability of supercritical technology for the improvement of the loading and release of curcumin in PLGA. We firstly synthetized the PLGA support, determining the effect of PLGA molar composition in the range (20:80 to 80:20). A curcumin solubility study selected acetone, methanol and ethanol like more convenient solvents. Curcumin impregnation process was studied at atmospheric pressure and high pressure using $scCO_2$. High-pressure impregnation performances practically doubled bulk results, leading to values up to 84.3% and practically free of solvent. These samples could be commercialized without any further purification step. The release kinetics of the samples constantly delivered more than 90% of curcumin between 9 and 12 days according to a Type I process. Compared to other technologies our samples improved significatively the combined loading and release characteristics, indicating that supercritical technology can be an interesting alternative for curcumin loading and controlled delivery in medical applications.

Keywords: Curcumin; PLGA impregnation; supercritical CO2; delivery kinetics

1. Introduction

Biodegradable polymers are defined as any substance, material or combination of both, that can be used as a part of a treatment, replacement of tissues, organs or any organism function. The main use of this type of polymers is the medical application, where polyesters have an important paper because of their important properties. [1]

Between all the currently polyesters, polylactide acid (PLA) and glycolic acid (PGA) are the most interesting due to they can be used in a high interval of possible applications [2]. However, both present several limitations to be used as monomers in medical applications. These limitations are solved by copolymerization of lactide and glycolide (PLGA) due to the additional advantages achieved from the combination of both monomers. PLGA is one of the polymers with higher potential as a drug delivery carrier because of its tuneable properties as degradation, processability and mechanical strength[3]. The main advantage of this polymer is the property of varying degradation rate depending on the ratio of monomers (PLA/PGA) used to carry out the polymerization. According to previous research, a molar composition of polylactide (PLA) in PLGA between 75 and 100% provide a variation of copolymer half-life from 2 weeks to 6 months[4].

Nowadays several drugs are studied to carry out drug delivery in polymers. One of the drugs whose importance is increasing recently is curcumin[5]. It is a yellowish orange colour substance found in the rhizome of Curcuma longa. This herb is composed of three different species called curcuminoids in different proportions: curcumin (77%), demethoxycurcumin (17%) and bis-demethoxycurcumin (6%) [6].

At first, curcumin was used as colouring agent and as a food additive, but applications for this drug have changed to pharmaceutical uses due to the excellent results obtained in several studies. Properties as antioxidant, anti-inflammatory, antimicrobial

and anticarcinogenic make curcumin an excellent candidate to perform the polymer impregnations[7, 8].

There are some different alternatives to carry out polymer impregnations. In this work, low pressure and supercritical carbon dioxide ($scCO_2$) were chosen to impregnate curcumin in the PLGA previously synthesized. Supercritical fluid technology was tested for the first time in the curcumin impregnation of PLGA like an interesting alternative because of its excellent properties, like mass transfer, lack of residual solvent in the products or plasticization of polymers [9]. These properties are crucial for pharmaceutical applications, because the solvent must be removed completely from the polymer. Plasticization of polymers is another required property to increase the performance of impregnation, because $scCO_2$ swells the polymer achieving to increase its free volume, so the amount of drug loaded in the polymer is higher than if the impregnation had been carried out in bulk [10-12].

To determine the possibility of improving loading and release of curcumin, this work studies in a fist stage the polymerization of the PLGA support, to determine the influence of PLA molar composition in PLGA. Once the PLGA is synthetized, a study of curcumin impregnation was carried out varying the pressure and solvent to get to know the best conditions in which the drug is impregnated. Once the best solvent and molar composition of PLGA were determined, an in vitro drug delivery test was performed to study the kinetic release of curcumin from PLGA.

2. Experimental

2.1. Materials

Glycolide (G) (1,4-dioxane-2,5-dione; Purac Biochem bv, The Netherlands) and D,L-lactide (L) (3,6-dimethyl-1,4-dioxane-2,5-dione; Purac Biochem bv, The Netherlands) both with a purity higher than 99.5%, Tetrahydrofuran (THF) (HPLC grade; SDS S.A., Spain), carbon dioxide (Carburos metálicos, S.A., Spain) with a purity of 99,5%. Stannous octoate (tin(II) 2-ethylhexanoate (Sigma-Aldrich Química, S.A., Spain), Methanol anhydre (MeOH) (SDS S.A., Spain) with purity higher than 99.85%, Ethanol (Panreac Química S.L.U., Spain) with purity higher than 99,60%, acetic acid (Panreac Química S.L.U., Spain) with purity higher than 99,4%, ethyl Lactate, butyl lactate and curcumin (Sigma-Aldrich Química, S.A., Spain) with analytical grade.

2.2. Bulk polymerization installation

Experiments were carried out in a set-up consisting on a glass stirred-tank reactor with a volume of 500 ml and put into an inert atmosphere of nitrogen. Temperature was controlled by means of a temperature controller with a sensor inside the reaction melted mixture.

2.3.Supercritical carbon dioxide impregnation installation

Experiments were carried out in a lab scale installation divided into three modules: feed system, reactor, and depressurization line, respectively.

Feed system consisted of two heat exchangers, one positive displacement type pump for liquid CO_2, model MD140G4M500 / ND VV2 Z , refrigerator unit for cooling feed and CO_2 pump head; and back pressure regulator (GO) for controlling pressure in reactor.

Stirring tank reactor had a nominal volume of 1200 ml, and a maximum pressure of 200 bar at 230 ºC and it was equipped with a magnetically coupled mechanical stirrer.

This reactor is also equipped by a heater with temperature control by a PID, and for cooling a serpentine refrigerator inside was used.

Depressurization line was heated with an electrical heating tape and two pressure regulators with a valve to prevent freezing of CO_2 by Joule-Thompson effect during the depressurization stage.

The procedure in supercritical carbon dioxide is composed of many steps: At first, the sample is introduced in the vessel and reactor is closed to avoid CO_2 leakage, secondly the reactor is loaded with the required pressure for each experiment, and heater is connected until the pressure and temperature values are achieved. When the experiment time expires, is the beginning of depressurization stage, where the CO_2 is removed from the reactor. Finally, once reactor is depressurized, it is opened and the sample is taken. Further information about experimental set up can be found in reference[13]

2.4. Polymer characterizations

2.4.1. FTIR

IR spectra of synthetized and impregnated polymers were obtained with a spectrophotometer Varian model 640-IR in range from 4000 to 400 cm^{-1}, with a resolution of 4.0 cm^{-1} and 64 scanning, using the software Varian Resolution.

2.4.2. UV spectra

The measurements were carried out using and spectrophotometer UV with dual beam Shimadzu UV-1603 with a spectral range from 190 to 1100 nm, halogen and deuterium lamps and a silicon photo diode detector. It was provided with the software UVPC Personal Spectroscopy Software, Version 3.6.

2.4.3. GPC

Molecular weight of polymers was determined by gel permeation chromatography on GPC cromatrograph (Waters, Spain) model 717. It is equipped by one column Viscotek, whose interval of molecular weight is 500-2000 g/mol, two peristaltic pumps, electric oven and a refractive index detector. The eluent used was tetrahydrofuran (THF) at 35ºC (flow: 1 $mL \cdot min^{-1}$; injection volume of 100 µL. Samples were dissolved in THF at a concentration of 1.5 mg·mL-1 and filtered before injection.

2.4.4. TGA

PLGA and mixture PLGA-curcumin compositions were determined by thermogravimetric analysis. In this analysis is possible to determine the amount of solvent, residue and drug impregnated which is present in every sample.

2.4.5. DSC

The calorimetric analysis was determined by DSC model Q100, equipped by a refrigeration system (TA Instruments). Samples of 3-10 mg were prepared in aluminium capsules. This analysis was carried out in 3 stages according to is shown in Table 1.

Table 1. Temperature intervals in DSC analysis.

Polymer	Ramp (°C/min)	Temperature interval (°C)
First heating	10	40 to 280
Cooling	10	280 to -50

Second heating	10	-50 to 280

3. Results and discussion

The main objective of this work is to determine the viability of supercritical technology for improvement for the loading and release of curcumin in PLGA samples. For that purpose, we firstly studied the synthesis of the PLGA support, determining the effect of PLGA molar composition. Once PLGA polymers were synthetized, bulk and supercritical impregnation alternatives were studied for the second impregnation step. Finally, we performed a study of drug delivery in vitro corresponding to the samples impregnated previously in supercritical CO_2. Samples showing better results were compared to other bibliography studies in terms of efficiency and time of release.

3.1. Synthesis of PLGA

In order to determine the best PLGA composition for drug impregnation, in this study three different (D-L-lactide:Glycolide) molar ratios were synthetized according to a procedure previously described in bibliography by this research group [12, 14]. This process involved placing monomers in a bulk reactor with catalyst and initiator at high temperature to form a viscous growing prepolymer, which after a 4 hours reaction led to a solid polymer finished when cooled to room temperature. Ratios of 20:80, 50:50 and 80:20 were tested to build the polymer support in which curcumin will be impregnated in the second step. For a lower ratio of lactide (20:80), a solid unreacting block was formed in the first minutes of reaction, so that this PLGA relation monomer was excluded for the impregnation of curcumin. For this reason, only polymers with molar composition of 50:50 and 80:20 were considered in the rest of the work.

159 Operational conditions for polymerization of viable polymers in agreement with
160 previous studies [14] were: atmospheric pressure (1 atm), temperature 130 ºC, agitation
161 of 100 rpm and a total mass of 100 g of monomers in the reactor. The relations monomer-
162 catalyst (Stannous octoate) and catalyst-initiator are the same for both polymerizations,
163 90:1 and 1:2, respectively. The total time of polymerization was 4 hours and samples
164 were taken every 30 minutes to analyse the evolution of synthetized polymer during the
165 reaction.

166 **3.1.1. Characterization of PLGA synthetized at atmospheric pressure**

167 PLGA polymers were characterized according to techniques described in section
168 2. Table 2 shows the results for the molecular weight for the selected polymers using GPC
169 analysis. Bulk polymers showed a molecular weight distribution in which it was achieved
170 the theorical molecular weight Mw -weighed contribution of each monomer- for all
171 PLGA relations synthetized during reaction. This fact indicates that the synthesis of
172 PLGA support was performed as expected. Due to the polidispersity, the averaged
173 molecular weight for the polymer, Mn, was lower to Mw as previosly observed in [15].

174 Main functional groups of PLGA were analysed in IR spectra, where different
175 groups were observed : C=O (1760 cm^{-1}), CO (1000 and 1215 cm^{-1}), CH- (671 cm^{-1}), -
176 CH_3 (1520 cm^{-1}) and CH (2353 cm^{-1})[16]. Figure 1 shows the polymer IR spectra, where
177 the main PLGA functional groups are shown.

178

179 **Table 2.** Molecular weight and Tg of PLGA in bulk polymerization.

Polymer	Mw (g/mol)	Mn (g/mol)	Tg (ºC)
PLGA 80:20	14425	6875	51.90

PLGA 50:50	12811	7165	48.59

Evolution of glass transition temperature (Tg) was measured with DSC, where it was observed in Table 2 an increasing of Tg when increasing Lactide proportion from PLGA50:50 to PLGA80:20. This evidence is due to the higher Lactide molecular weigh as observed previously in GPC analysis [17].

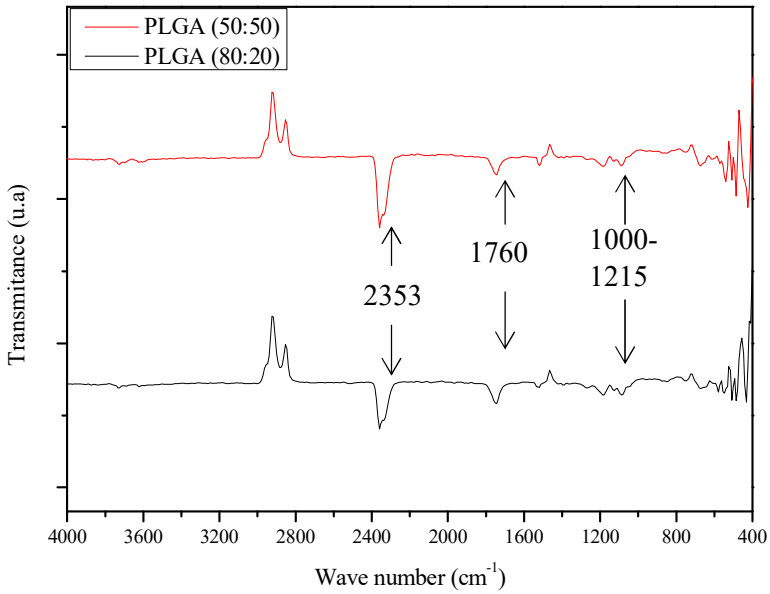


Figure 1. FTIR spectra of PLGA obtained in bulk polymerization.

3.2. PLGA curcumin Impregnation

Curcumin impregnations in PLGA were performed using bulk and supercritical carbon dioxide. A previous solubility study was performed to select solvents with both,

200 higher curcumine solubiliby and affinity to CO2. After solubility test, impregnation
201 process for both alternatives was carried out. In this last part, the effect of supercritical
202 technology in the polymer impregnation was studied to determine those conditions
203 leading to the maximum quantity of loaded drug.

204 **3.2.1. Study of curcumin solubity in different solvents**

205 Selection of a solvent with high value of curcumin solubility is one of the main
206 requests to carry out the impregnations. The solubility values were obtained
207 experimentally. Saturated solutions of curcumin were prepared to determine the
208 maximum amount of drug that is solubilized in each solvent. Table 3 shows the solubility
209 results for the different solvents chosen in this study.

210 **Table 3.** Curcumin solubility in different solvents.

Solvent	Solvent purity (%)	Solvent solubility (mg/ml)	CO_2 affinity
Acetone	99.80	78.80	High
Acetic acid	99.50	5.10	High
Water	100.00	0.60	High
Ethanol	99.70	6.20	High
Ethyl lactate	98.00	17.40	Low
Butyl lactate	98.00	15.00	Low
Methanol	99.95	8.05	High

211

212 According to Table 3 results, the three solvents chosen to carry out the
213 impregnations were acetone, ethanol and methanol. In spite of higher values of solubility
214 in ethyl lactate and butyl lactate, they present low affinity to CO_2. This fact will mean
215 higher residual content in the loaded polymer in the high pressure processing because of
216 the lower solubility in CO_2. For this reason, they were discarded.

3.2.2. Bulk impregnation of curcumin

Bulk impregnation consisted on 1500 PLGA mg mixed with a solution of saturated curcumin. Once the polymer was impregnated, the solvent was separated from the mixture PLGA-curcumin through evaporation at room temperature. Table 4 shows results obtained for the PLGA impregnations carried out at atmospheric pressure.

Table 4. Curcumine PLGA bulk impregnations results.

Sample	Polymer	Solvent	Curcumin (mg)	Impregnation efficiency (%)	Tg (ºC)
I-01	PLGA 80:20	Acetone	170	38.64	37.56 (14.38)
I-02	PLGA 80:20	Methanol	40	32.5	31.24 (20.70)
I-03	PLGA 80:20	Ethanol	31	31.93	31.03 (20.91)
I-04	PLGA 50:50	Acetone	170	35.04	35.06 (13.53)
I-05	PLGA 50:50	Methanol	40	28.86	30.85 (17.74)
I-06	PLGA 50:50	Ethanol	31	27.94	29.79 (18.80)

As can be observed in Table 4, six impregnations were made, using the three different solvents and two PLGA relations selected. Column #4 give the total amount of curcumin contained in the initial solution, of which only a part will be finally impregnated in the polymeric matrix. Impregnation performance was obtained by thermogravimetric analysis (TGA), which determined the amount of drug impregnated in the polymeric matrix.

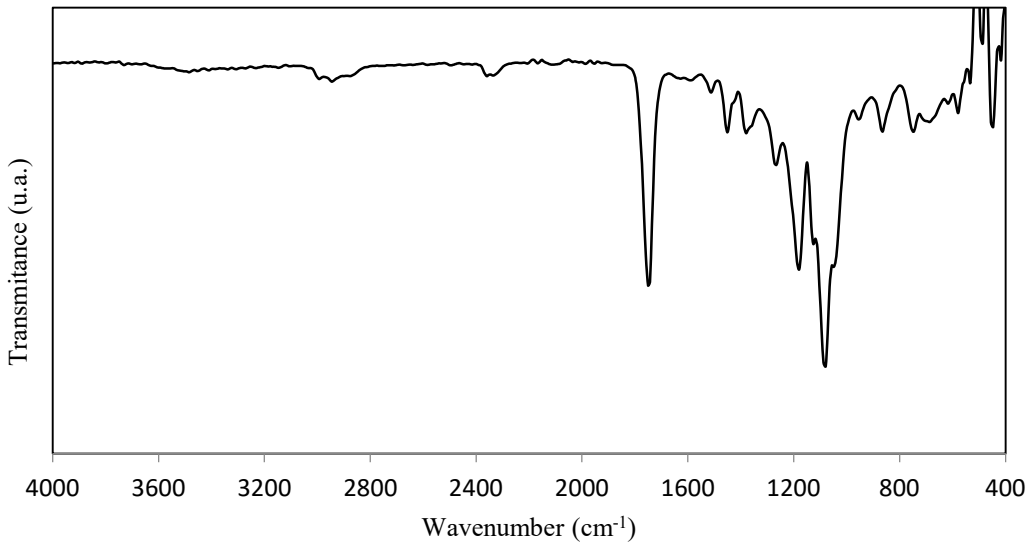
According to the results in Table 4, there is a higher impregnation efficiency for acetone due to its higher solubility (Table 3). In addition, it can be observed that molar ratio of PLGA has also influence in the performance of impregnation. A higher composition of Lactide in PLGA (80:20) always favored the impregnation of curcumin.

234 This fact is related to the molecular weight of the polymer, as it was previously described
235 [18].

236 **3.2.3. Characterization of PLGA impregnated in bulk**

237 The IR spectra exhibit characteristics bands related to curcumin and bands related
238 to PLGA. As example, Figure 2 represents IR spectra correspondent to PLGA (80:20)
239 impregnated in bulk using acetone as solvent. The most characteristic absorbance band
240 arising from the PLGA impregnated is the peak at 1760 cm^{-1} characteristic of the carbonyl
241 group (C=O), whose size is higher than the absorbance band of pure polymer (Figure 2).
242 From 3000 cm^{-1} there are observed some tiny absorbance bands that correspond to the
243 existence of solvent in the polymeric matrix which was not totally removed in the
244 evaporation process, what means an important problem in order to use samples for
245 medical applications. Similar results were obtained for the rest of impregnations carried
246 out at atmospheric pressure.

247 Table 4 also shows the glass transition temperature, Tg, of impregnated PLGA
248 samples determined by DSC analysis. According to Table 4, different Tg data were
249 obtained depending on the solvent used, being all values lower to those corresponding in
250 Table 2 for unloaded samples. The lower values indicate that a significant amount of
251 solvent is placed in the polymeric matrix. The Tg reduction with respect Table 2 (values
252 in parenthesis) is proportional to the residual solvent content in the polymer, not removed
253 in the evaporation step. From Table 4 results acetone produced the lowest amount of
254 residual solvent in the loaded sample, while us for methanol and ethanol a higher
255 percentage of solvent is kept in the polymeric matrix. This last finding makes acetone the
256 best option to carry out the impregnations due to the solvent must be completely removed
257 from the polymeric matrix for pharmacological applications.



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259 **Figure 2.** IR spectra correspondent to PLGA (80:20) impregnated in bulk using acetone
260 as solvent.

261 **3.2.4. CO_2 impregnation of PLGA**

262 Next task in this work studied the impregnation of PLGA with curcumin using
263 supercritical technology with CO_2 as a solvent, comparing these results with previous
264 bulk results and other alternatives described in the literature. This study will led us to
265 determine if supercritical technology can be an interesting alternative for curcumin
266 loading for medical applications. To determine whether the advantages of this technology
267 can improve the characteristics of these polymers, curcumin impregnation was studied at
268 high pressure. To simplify operational process, the value of pressure chosen for
269 impregnation in $scCO_2$ was the same used in a previous study about PLGA
270 polymerization using supercritical carbon dioxide [14].

271 To use all the supercritical carbon dioxide advantages a polymer temperature close
272 to glass transition (Tg) is required, because of one of the main effects of $scCO_2$ on
273 polymers is the plasticizing effect, where CO_2 acts as a lubricant in PLGA[19]. High

pressure Polymer Tg was calculated using Chow equation (1) and values of CO_2 solubility in PLGA obtained from bibliography [20, 21].

$$\ln\left(\frac{T_g}{T_{g,0}}\right) = \beta \cdot [\theta \cdot ln\theta + (1-\theta) \cdot \ln(1-\theta)]$$

where θ and β are obtained from equations (2) and (3), respectively

$$\theta = \frac{M_m}{zM_d}\frac{\omega_1}{1-\omega_1} \quad (2)$$

$$\beta = \frac{zR}{M_u \Delta C_{pp}} \quad (3)$$

In these equations Tg is the glass transition temperature of the polymer containing a weight fraction, ω_1, of the dissolved component; $T_{g,0}$ is the glass transition temperature of the pure polymer; M_m is the molar mass of the polymer repeat unit; M_d is the molar mass of the dissolved component; R is the gas constant; ΔC_{pp} is the excess transition isobaric specific heat of the pure polymer, and z is the lattice coordination number. In this study z=1; ΔC_{pp}=0.336 J/(g K); and $T_{g,0}$= 331.15 K.

For comparison purposes, the same number of impregnations were carried out in $scCO_2$ as in previous bulk tests. The quantity of polymer used was 1500 mg as in impregnations carried out at atmospheric pressure. The procedure for high pressure impregnations was the same that those described for bulk impregnation in the preparation of the saturated solution. Once the solution was prepared, the solution was placed in the supercritical reactor and the CO_2 was charged until the desired values of pressure and temperature were reached. Results are shown in Table 5.

Table 5. High pressure CO_2 impregnations of PLGA.

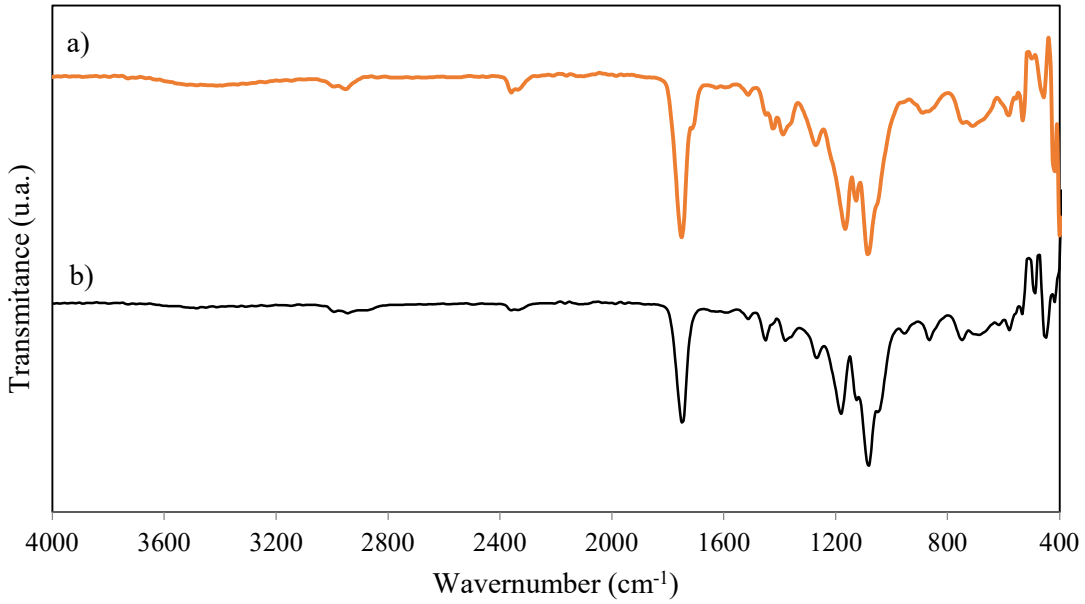
Sample	Polymer	Solvent	Loading time (h)	Impregnation yield (%)	Tg (ºC)
I-07	PLGA 80:20	Acetone	8	84.3	50.78 (1.16)
I-08	PLGA 80:20	Methanol	16	66.5	40.57 (11.37)
I-09	PLGA 80:20	Ethanol	16	65.8	40.32 (11.62)
I-10	PLGA 50:50	Acetone	8	58.2	47.01 (1.58)
I-11	PLGA 50:50	Methanol	16	50.1	39.86 (8.73)
I-12	PLGA 50:50	Ethanol	16	51.3	38.79 (9.80)

Table 5 shows that impregnations were accomplished in a maximum time of 16 hours when ethanol and methanol were used as solvents, being reduced to 8 hours for acetone. This fact supposes an operational advantage with respect to impregnations carried out at low pressure, for which impregnation time was 24 hours.

Glass transition and amount of curcumin impregnated in the polymer were analysed with TGA and DSC. As it can be observed in Table 5, the samples loaded with supercritical CO2 obtained an impregnation yield almost two times than those obtained in bulk conditions. PLGA 80:20 presented again a higher value of impregnation efficiency independently of solvent used, being the best results obtained for acetone. DSC analysis showed low residual solvent content of samples. Impregnations were acetone was used as solvent presented similar Tg to bulk PLGA, what means practically the complete elimination of solvent from the polymeric matrix. As obtained, these loaded samples could be used for prevention and treatment of cancer in market medical formulations without additional processing, avoiding any further concentration or solvent elimination step [19].

3.2.5. Characterization of PLGA impregnated in $scCO_2$

312 The IR spectra analysis of PLGA impregnated at high pressure presents the same
313 functional groups which were observed in PLGA impregnated at atmospheric pressure
314 previously. This evidence indicates that impregnation was carried out satisfactorily again.
315 This finding is shown in Figure 3, which compares the IR spectra correspondent to PLGA
316 (80:20) impregnated at high pressure using acetone (a) to PLGA obtained in bulk
317 conditions (b). Similar results were obtained for the rest of impregnations.



318

319 **Figure 3.** Comparison of IR spectra in transmittance correspondent to a) PLGA (80:20)
320 impregnated in $scCO_2$ using acetone as solvent; b) PLGA (80:20) impregnated in bulk
321 using acetone as solvent.

322

323 **3.3. In vitro release study.**

324 Once the best ratio of lactide:glicolide, solvent and procedure were chosen, the
325 following task studied the curcumin release profile from the polymer. Two experiments
326 were performed for this study varying the quantity of curcumin impregnated in the
327 polymer as it can be seen in Table 6.

328 **Table 6.** Drug delivery study.

Impregnation	Polymer (mg)	Initial curcumin (mg)	Impregnation yield (%)	k_{degr} (cm^{-1})
I-07	1500	170	84.3	0.114
I-13	1500	270	86.1	0.151

329

330 To quantify the amount of impregnated curcumin it was determined by UV spectra
331 at 421. A calibration line was used to get to know the concentration of curcumin in the
332 sample impregnated according to the value of absorbance registered. Polymer
333 impregnated with curcumin were suspended in a phosphate saline solution (PBS) 0.1 M
334 (pH 7.4, 1 M), placed in the middle of a 100 mL flask hermetically closed and preserved
335 from light, stirred at 100 rpm, and incubated in a shaking water bath at 37 °C. 5 ml
336 solution was periodically removed from the flask in order to measure by UV
337 spectrophotometry the quantity of curcumin released. Release profiles were calculated in
338 terms of the cumulative release percentage of curcumin.

339 According to bibliography there are described several theoretical mechanisms for
340 controlled release of drug from biocompatible polymers [22]. These mechanisms are
341 composed up to 3 steps, where the first one corresponds to the initial burst of drug release
342 of the most accessible drug, generally located in the surface of the particles and controlled
343 by the diffusion in the film. The second step is controlled by the internal diffusion into
344 the most tortuous or narrow pores. The last step is the step controlled by the degradation
345 of the polymer. Due to the homogeneous distribution of the drug into the polymer matrix
346 consequence of the easy access using CO2 in addition to the tailored biodegradability of
347 the PLGA, this study showed only one long constant-high release stage (Figure 4). This

stage corresponds to a degradation of the complex polymer-drug in the PBS. Compared to a classical 3 step profile, Figure 4 (c), associated to an heterogeneous distribution of the drug mainly located in the particles surface, supercritical loaded samples showed a more interesting release profile for medical applications. According to the results obtained in this work, a minimum of 9 and 12 days are necessary to constant release more than 90% of drug impregnated in the polymer. Release time depended on the quantity of curcumin impregnated in the polymer, being necessary a higher number of days in the experiment where 270 mg of curcumin was used.

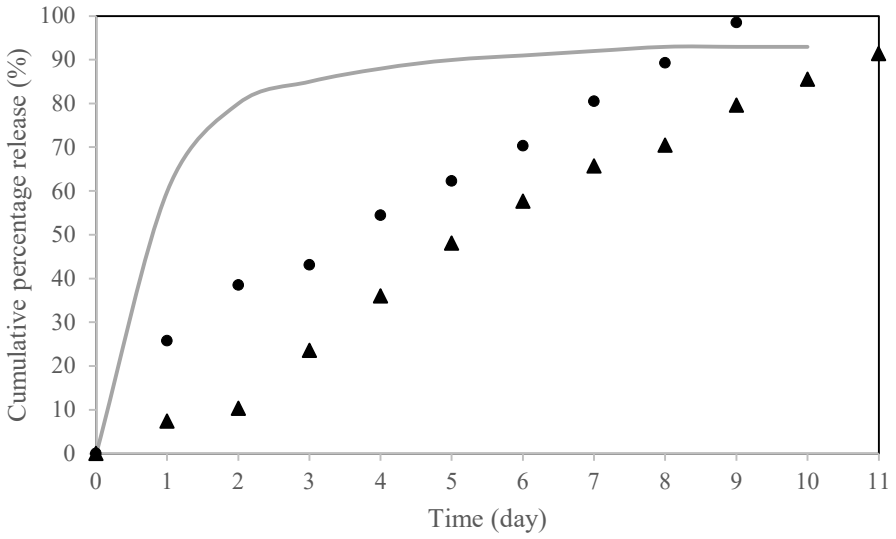


Figure 4. Drug release profile of curcumin in PLGA at 37º C of a) (●) I-07 using 170 mg of curcumin; b) (▲) I-13 using 270 mg of curcumin; c) (—) Typical profile correspondent to 3 steps release.

Release kinetics can be modelled using equation (4), where M_0 and M_f represent the total mass at the beginning of the release and at the end of the experiment respectively, R_0 is the initial radius of the spherical foam (0.2 cm) and k_{degr} is the pseudo-first kinetic constant of degradation for the PLGA foam.

364 $$\left(\frac{M_f}{M_0}\right)^{\frac{1}{3}} = 1 - \frac{k_{degr}}{R_0} \quad (4)$$

365 Using the equation 4 the constants correspondent to degradation stage for both
366 experiments can be determined, as indicated Table 6. There were obtained a value of
367 0.114 cm for I-07 and 0.151 cm for I-13, respectively, in a drug release profile
368 correspondent to Type I, which corresponds to the monophasic release from a single
369 homogeneous phase [23]. This trend is expected to be the desirable behaviour for
370 pharmacological applications of constant, durable and high dosage release.

371 Finally, our results were compared in Table 7 to other works where different
372 techniques are used to improve curcumine loading and release [24-26].

373 **Table 7.** Proposed methods for increased curcumin loading and release.

Method	Release time (days)	Curcumin loaded (mg)	Reference
Liposome	1	348.75	Sherbini, et al[24]
Vapor induced phase inversion	1.5	0.45	Bajpai et al[25]
Coating stent	18	0.16	Pan et al[26]
This work (I-13)	10	232.36	-

374

375 As can be observed in Table 7, supercritical technology allows the significative
376 improvement of both, drug loading and time of release. This fact suggest that supercritical
377 technology is an interesting alternative for curcumin loading and controlled delivery in
378 medical applications.

379

4. Conclusions

This work determined the viability of supercritical technology for the improvement of the loading and release of curcumin in PLGA. Compared to classical bulk atmospheric process, samples impregnated using supercritical CO_2 showed important improvements about loaded curcumin and remaining solvent in the polymer. These characteristics could make these samples able to commercialize without any further purification or concentration step. In addition, these samples showed a single long constant-high release of curcumine, the most interesting profile for medical applications. Comparison to other impregnation technologies showed that our samples improved significatively the combined loading and release characteristics, indicating that supercritical technology can be an interesting alternative for curcumin loading and controlled delivery in medical applications.

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