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Degradation study of copolymers of PLLGA to be used as potential polymeric matrix in coronary stents

Estudio de la degradación de copolímeros de PLLGA para ser utilizado como potencial matriz polimérica en stents coronarios

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Abstract

In this work, three types of poly(L-lactic-co-glycolic acid) copolymers (PLLGA) with different lactide to glycolide ratio (70:30, 80:20 and 90:10%wt.$_{L\text{-}LA}$:%wt.$_{GA}$) were synthesized. The materials were characterized by known techniques. The degradation study of PLLGA was made in saline solution and followed by molecular weight change and mass loss percentage. The results showed that PLLGA degradation followed pseudo-first order kinetics. Prednisone (immunosuppressive drug) was incorporated into polymeric matrix. The release process was quantified by drug concentration change in the saline solution using UV spectroscopy at 240nm. The results showed that prednisone release process was governed by two phenomena: diffusion and degradation. The drug release processes were analyzed kinetically using zero order, first order, Higuchi and Korsmeyer-Peppas models. The cytotoxicity assay evidenced that PLLGA copolymers and PLLGA degradation products were not toxic in endothelial cells. Finally, a 3D printer was built and programmed to develop a procedure for the fabrication of a potential coronary stent based on polymeric matrix.

Keywords: PLLGA copolymers, degradation, desorption, prednisone, kinetic, cytotoxicity, polymeric stent.

Resumen

En este trabajo, se sintetizaron tres tipos de copolímeros de poli(ácido L-láctico-co-glicólico) con diferentes proporciones de lactida y glicólida (70:30, 80:20 and 90:10%wt.$_{L\text{-}LA}$:%wt.$_{GA}$). Los materiales se caracterizaron por técnicas conocidas. El estudio de degradación de PLLGA se realizó en solución salina y se siguió por cambios en el peso molecular y porcentaje de pérdida de masa. Los resultados mostraron que la degradación de PLLGA siguió una cinética de pseudo-primer orden. La prednisona (fármaco inmunosupresor) se incorporó en la matriz polimérica. El proceso de liberación se cuantificó por cambio en la concentración del fármaco en la solución salina usando espectroscopia UV-vis a 240 nm. Los resultados mostraron que el proceso de liberación es gobernado por dos fenómenos: difusión y degradación. Los procesos de liberación se analizaron cinéticamente utilizando los modelos de orden cero, primer orden, Higuchi y Korsmeyer-Peppas. El ensayo de citotoxicidad evidenció que el PLLGA y sus productos de degradación no son tóxicos en células endoteliales. Finalmente, se construyó y programó una impresora 3D para desarrollar un procedimiento para la fabricación de un potencial stent coronario basado en esta matriz polimérica.

Palabras clave: Copolímeros de PLLGA, degradación, desorción, cinética, citotoxicidad, prednisona, stent polimérico.

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1 Introduction

The development of biodegradable polymers as controlled drug delivery systems is one of the most promising and rapidly developing areas of chemical engineering (Dragan and Dinu, 2019). Many synthetic polymers have been used for this purpose because they have better functionality than natural polymers, being also cheaper (Dhandayuthapani *et al*. 2011). These polymers are well suited for applications such as drug delivery (which require the gradual release), 3D structure scaffolds as hydrogels (Martínez-Mejía *et al*. 2019), porous nanostructures (Esfanjani *et al*. 2016), fibers (Estrada-Villegas *et al*. 2019; Martín del Campo *et al*. 2020), or implants (Tamaddon *et al*. 2015) as prostheses pins (Vergnol *et al*. 2012) and also as stents (they have the advantage of degrading over time obviating the need for surgical removal) (McMahon *et al*. 2018; Nogic *et al*. 2019; Sevostyanov *et al*. 2020).

Since before July 2016, when the US Food and Drug Administration (FDA) approved the first fully resorbable device to treat coronary artery disease, biodegradable polymers as polylactic and polyglycolic acids and their copolymers such as poly(L-lactide-co-glycolide) (PLGA) have been used to design drug eluting devices in medical applications (Miller *et al*. 1977; Langer, 1990; Mauduit *et al*. 1993a; Mauduit *et al*. 1993b; Naghipoor *et al*. 2016; Sevostyanov *et al*. 2020). Their main advantages are that the combination of their physicochemical properties (as molecular weight, crystallinity and glass transition temperature) can be manipulated by the initial monomer ratio and the sequential arrangement of lactic and glycolic acids in the polymeric chain (Meaurio *et al*. 2006; Jadhav *et al*. 2009). As consequence, control of the degradation process and the drug desorption kinetics will be obtained (Sevim and Pan, 2018). For this reason, the simultaneous study of both processes is the key to develop new devices as biodegradable drug eluting stents (Jain *et al*. 2016; Sevostyanov *et al*. 2020).

Drug release from these devices can be also controlled by diffusion and degradation of PLGA. These processes are typically governed by a relationship between water absorption, hydrolysis and erosion and diffusion through the copolymeric matrix (Brammer *et al*. 2008). The success of these devices is the fact that they can guarantee drug delivery in each stage of recovery of the endothelium once the stent is implanted, avoiding neointimal proliferation and restenosis (Waksman and Pakala, 2010; Waksman, 2012; Sammel *et al*. 2013). For this purpose, the release of anti-inflammatory, immunosuppressive and cytostatic drugs such as tacrolimus, sirolimus, paclitaxel have been studied (Teja *et al*. 2013; Kiyukhin, 2014; Yang *et al*. 2016). In this work, poly(L-lactic-co-glycolic acid) copolymers (PLLGA) were synthesized with three different ratio 70:30, 80:20 and 90:10%wt.$_{\text{L-LA}}$:%wt.$_{\text{GA}}$. *In vitro* degradation and prednisone release (an immunosuppressive drug) studies were carried out in saline solution during 336 h at 37 °C to explore the kinetics of degradation and drug desorption process. Cytotoxicity PLLGA degradation products in endothelial cells was also investigated. In addition, a 3D printer was built from a commercial kit and was programmed to fabricate a stent from the synthesized PLLGA copolymers. The printed prototypes could be used as potential polymeric matrix in coronary devices.

2 Materials and methods

2.1 Materials

L-lactic acid ($C_3H_6O_3$) (88%) was purchased from Alquimia. Glycolic acid ($C_2H_4O_3$) (70%), tin octoate ($Sn(Oct)_2$), prednisone ($C_{21}H_{26}O_5$) and dimethyl sulfoxide DMSO (C_2H_6OS) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Saline solution (0,9%w NaCl) was purchased from Pisa Farmaceutica (CDMX, México). Methyl alcohol (CH_3OH) (99.9%), 2,5-dihydroxybenzoic acid (98%) and Dulbecco's Modified Eagle's Medium (DMEM) were purchase from Sigma-Aldrich (St. Louis, MO, USA). Ethyl alcohol (C_2H_5OH) (70%) was purchase from Fermont (Monterrey, México). All reagents were used without previous purification.

2.2 Methods

2.2.1 Synthesis of poly(acid L-lactic-co-glycolic acid), PLLGA

PLLGA copolymers with three different L-LA/GA ratio (70:30, 80:20 and 90:10%wt.$_{\text{L-LA}}$%wt.$_{\text{GA}}$) were synthesized by means of ring opening polymerization (ROP), using a method reported previously (Rueda *et al*. 2015). The reaction system consisted of a three-neck flask with a mechanical stirrer and a condenser

connected to flask. Synthesis was made in two steps. The first step was a condensation reaction of L-lactic and glycolic acids separately to produce low molecular weight pre-polymers. A cyclization reaction was followed to obtain a mixture of stereoisomers of L-lactide and glycolide. The process was made during 10 h at 145 °C and the condensation water was removed from the three-neck flask. Obtained mixture of L-lactide and glycolide was weighed. In the second step, ROP began by L-lactide and glycolide mixture and the initiator addition ($Sn(Oct)_2$ 0.5 $wt._{L\text{-}LA:GA}\%$). The process was carried out during 14 h at 165 °C. Stirring and temperature were maintained constant to increase the average molecular weight of PLLGA.

2.2.2 *Maldi-Tof Mass Spectrometry*

The molecular weight distribution of three PLLGA was obtained by matrix assisted laser desorption/ionization mass spectrometry (MALDI-TOF). Bruker spectrometer, Autoflex speed model (Billerica, MA, USA) was used for the analysis. A sample of 1 mg was weighed and dissolved in 1 mL of methanol. After that, 1.5 μL of this solution was taken and mixed with 1.5 μL of a 2,5-dihydroxybenzoic acid saturated solution. Finally, the solution was placed on a plate for its analysis.

2.2.3 *X-ray diffraction*

X-ray diffraction analysis was performed in the Rigaku X-ray diffractometer AXS, Model MiniFlex 600 (Tokio, Japan). Diffraction angle 2θ was 2 to 50° at 4 °/min, an intensity of 25 mA and a voltage of 35 kV. A small sample of each PLLGA copolymer was placed on the acrylic sample holder and leveled with its surface.

2.2.4 *Differential Scanning Calorimetry*

Thermal characterization for each synthesized PLLGA was performed by differential scanning calorimetry (DSC) using the Pressure DSC Calorimeter, Model Instrument Specialist Incorporated (WI, USA). Samples of 5-10 mg of each PLLGA copolymer were weighted into aluminum pan and hermetically sealed. The samples were heated from room temperature to 150 °C, at heating rate of 2 °C/min under argon atmosphere. Experimental glass transition temperatures were found by calculating the first derivative of the inflection point in the plots. Theoretical glass transition temperatures of copolymers were calculated by Fox eq. (1).

$$\frac{1}{T_g} = \frac{X_{L-LA}}{T_{gL-LA}} + \frac{X_{GA}}{T_{gGA}} \tag{1}$$

where X_{L-LA} and X_{GA} are the mass fractions of each monomer and T_{gL-LA} and T_{gGA} are the theoretical glass transition temperatures of each hompolymer. They were obtained from bibliography data (Middelton *et al*., 200; Miller *et al*. 1977; Tiainen *et al*., 2002).

2.2.5 *Attenuated Total Reflectance-Fourier Transformed Infrared Spectroscopy (ATR-FTIR)*

ATR-FTIR spectra of monomers and PLLGA copolymers were analyzed by infrared spectrophotometer with attenuated ATR reflectance Ge accessory Perkin Elmer, model Frontier with energy of 176 U.E (Waltham MA, USA). Spectra of the samples were recorded in transmission mode over the near infrared spectroscopy region between of 400-4000 cm^{-1}. Samples were weighed (0.05g ± 0.005) and scanned 4 times at 30 °C.

2.2.6 *Optical microscopy*

Copolymer surface change during degradation process was observed by optical microscopy. The samples were removed from saline medium and were dried and analyzed by Premier 5X-50X Optical Microscope (Tokio, Japan). Images were obtained at 5X, 10X, 20X and 50X.

2.2.7 *PLLGA degradation*

For degradation study, glass plates of 10 × 10 mm were prepared. The plates were coated with each PLLGA copolymers by dip-coating technique (v = 2 mm/min) and dried under vacuum by 5 h. The coating thickness of plates was 500 μm. Then, they were placed in 10 mL of saline solution, pH 7.4 and incubated at 37 °C for two weeks (t = 336 h). Saline solution was not refreshed during the analysis. Two repetitions were made for each copolymer.

The degradation profiles of PLLGA were obtained when the coated plates were removed from the saline solution and dried at 0.25, 0.5, 1, 2, 5, 24, 48, 168 and 336 h time intervals. Measurements of average molecular weight change were obtained from Maldi-Tof mass spectrometry data. The mass loss percentage was calculated using eq. (2).

$$M = \left[\frac{M_1 - M_2}{M_1}\right] \times 100 \quad (2)$$

where M is the mass loss percentage, M_1 the initial mass and M_2 the mass at time interval.

2.2.8 *Drug release*

The concentration of released prednisone was measured by UV spectroscopy using a Perkin Elmer LAMBDA 25/35/45 UV/Vis spectrophotometer (Waltham MA. USA) with 3 mm quartz cuvettes. For the study, glass plates of 10×10 mm were prepared. They were coated with each synthesized copolymer and 0.04 g of prednisone was added. Prednisone was previously dissolved in dimethyl sulfoxide (DMSO) 1:1 wt.drug%:wt.excipient% ratio. PLLGA-coated plates were heated over their glass transition temperature and drug was added. After that, samples were vacuum dried by 5 h. Two repetitions were made for each copolymer. Then, samples were placed in vials with 10 mL of saline solution, pH 7.4 and incubated at 37 °C by 2 weeks. Saline solution was not refreshed during the experiment. A sample of 3 mL of saline solution was taken from the vials for analysis at 0.25, 0.5, 1, 2, 5, 24, 48, 168 and 336 h time intervals, and returned to the vials. The vials were shaken before each measurement to remove any concentration gradient. A reference solution of 0.04 g/10 mL of DMSO was used and the absorbance of prednisone was measured at 240 nm.

Drug released concentration in the medium was calculated with a calibration curve of twelve solutions. The concentration range of the solutions was between 1.1 x 10^{-4} to 0.11 g/mL. The curve was adjusted to an exponential model with a correlation coefficient of 0.9933.

2.2.9 *Cytotoxicity test*

The cytotoxicity of the PLGA copolymers and their degradation products were tested by triplicate using blue alamar assays and a SpectraMaxM3, Molecular devices (CA, USA). For these experiments, a sample of 10 mg of each PLGA copolymer was placed in a separate microwell and sterilized with 100 μL of ethanol during 2 h and ultraviolet light during 30 min.

Two types of assays were performed. In the first one, the culture medium was not refreshed during 24 h to analyze if the degradation products would affect the cell viability. In the second one, the culture medium was refreshed every 3 h during a 24 h period with the aim of minimizing any toxic effect due to medium acidification (pH < 6.8), and to evaluate the toxicity of the copolymer upon the cells. The pH change in the culture medium was measured in both sets of experiments. Both assays were performed with endothelial cells EA.hy926 (CRL-2922). The cell line was obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) and was maintained with Dulbecco Modified Eagle Medium (DMEM), supplemented with 10% fetal bovine serum (FBS) at 37 °C in an atmosphere of 5 v.% CO_2.

Endothelial cells (150,000) were dispersed in 1000 μL of DMEM and added to each microwell containing the PLGA copolymer. The samples were incubated at 37 °C with 5 v.% CO_2 atmosphere. Once the incubation time was over (t = 24 h), 100μL of blue alamar was added to each microwell and incubated for 5 h. Subsequently, the samples were analyzed by fluorimetry and the percentage of cell survival was calculated. As a reference, 150,000 endothelial cells were incubated only with 1000 μL of DMEM.

2.2.10 *Stent fabrication*

The stents were fabricated in a 3D printing system. For that, a 3D printer (Zhengzhou Chaukou Electronic Technology Co.) was built with a SLDPRT kit and a syringe pump (KD Scientific model Gemini 88) was coupled with a stainless steel cannula. The printer was programed in Arduino 1.6.1. The stent design was made in CAD 3D SolidWorks 2016.

The stent fabrication was made using a solution of 4 g copolymer and 1 mL of acetone. The solution was put in a commercial syringe of 5 mL with an internal diameter of 12.060 mm. The pump rate was programed at 0.09 mL/min while the printing rate was 0.01 mL/min at 1.3 h and 70 °C.

3 Results and discussion

3.1 *Materials characterization*

Structural features of the three PLLGA copolymers were confirmed by infrared spectroscopy. FTIR spectra of L-LA and GA monomers and PLLGA copolymer with 70:30%$wt._{L\text{-}LA}$:%$wt._{GA}$ composition are shown in Fig. 1 as example.

The carboxyl group of the acids is observed, which is mainly associated to two characteristic infrared stretching absorptions νC=O (1720 cm^{-1}) and νO-H (2250 to 3300 cm^{-1}) and significantly

change with hydrogen bonding. The O-H stretching absorption signal for such dimers is very intense and broad (Colthup *et al*. 1975). Besides, L-LA and GA acids contain two different kinds of O-H bond, the first one corresponds to acid at 2500-3300 cm^{-1} and the second one to simple alcohol type for α-carbon, absorbing at 3230-3550 cm^{-1} (Cholopek *et al*., 2009). A wide band from 2250 to 3550 cm^{-1} is presented (Fig. 1a and 1b) attributing to νO-H. This absorption overlaps the sharper C-H stretching peaks, which can be seen extending beyond the O-H. These bands correspond to C-H (2997 cm^{-1}), $C\text{-}H_3$ (2947 cm^{-1}) and $C\text{-}H_2$ (2882 cm^{-1}). Carbonyl asymmetric stretching frequency of the dimer is found at 1722 cm^{-1} for L-lactic and glycolic acid. The formation of new bands at 1280-1270 cm^{-1} and 1180-1167 cm^{-1} of the C-O-C bond confirms the copolymerization between the cyclic dimers of the acids (An *et al*., 2000; Pamula *et al*., 2000; Kister *et al*. 1998; Chabot *et al*. 1983) (see Fig. 1-d).

In addition, $C\text{-}H_3$ groups vibrations are presented in poly L-lactidesegments (1367-1386 cm^{-1}), as well as bands by vibrations of $C\text{-}H_2$ groups corresponding to polyglycolide segments (1425-1458 cm^{-1}). The attributed bands to stretching C-O groups vibrations are observed at 1088, 1185, 1215 cm^{-1} for the L-lactic and glycolic acid remain unchanged for the copolymers. The spectra of the synthesized copolymers 80:20 and 90:10%$wt._{L\text{-}LA}$:%$wt._{GA}$ present the same bands.

Average molecular weights of PLLGA copolymers were obtained from the Maldi-Tof technique data (Table 1). The results showed values 6,526 < M_W/Da < 7,187.

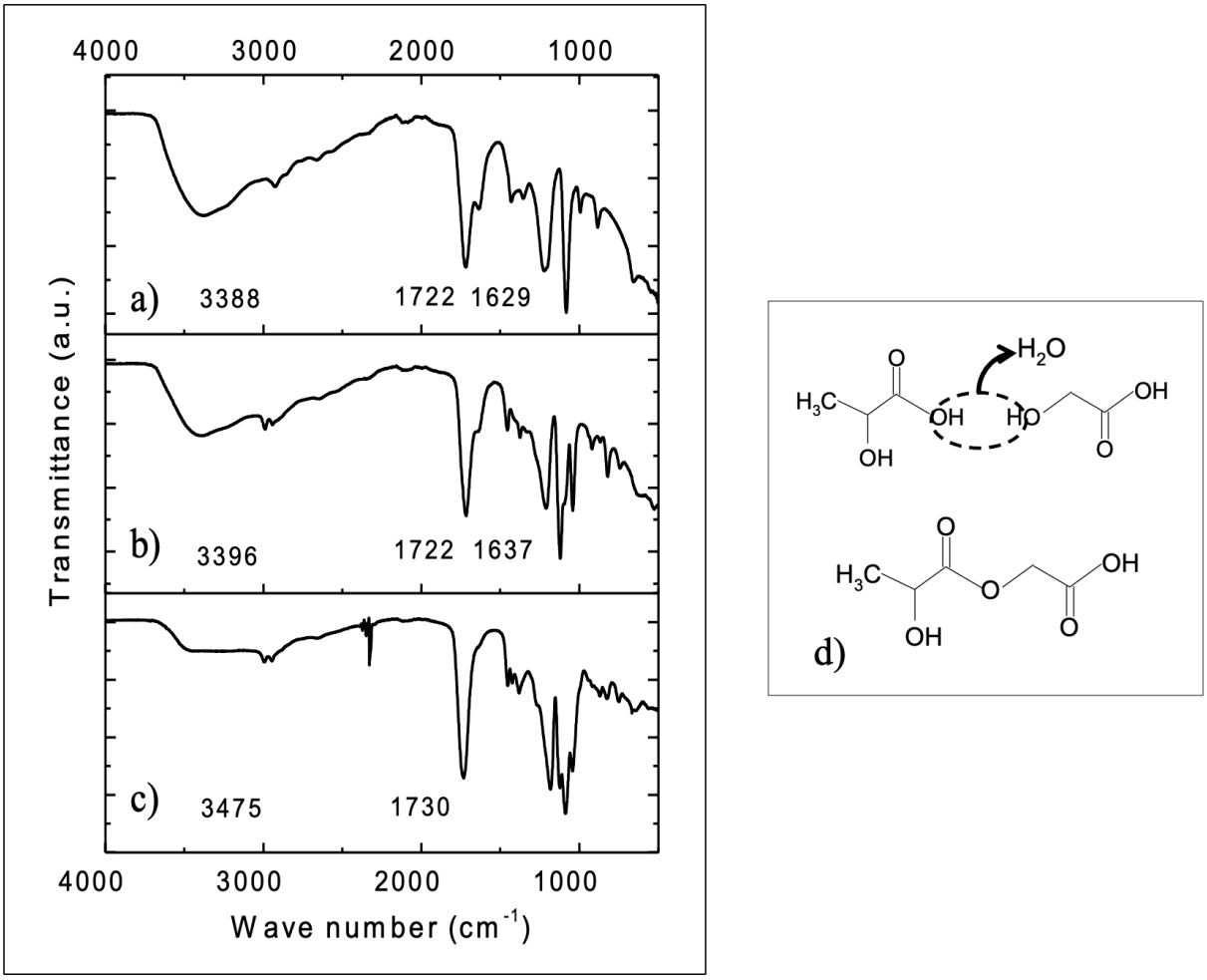

Fig. 1. IR-spectra of a) glycolic acid, b) L-lactic acid, c) 70:30%$wt_{L\text{-}LA}$:%wt_{GA}. PLLGA copolymer and d) reaction scheme of PLLGA

Table 1. Average molecular weight, polydispersity index and theoretical and experimental T_g of 70:30, 80:20 and 90:10%$wt_{L\text{-}LA}$:%wt_{GA} PLLGA copolymers.

PLLGA %$wt_{L\text{-}LA}$:%wt_{GA}	Average molecular weight (Da)	Polydispersity index (IP)	Experimental T_g (°C)	Theoretical T_g (°C)
90:10	7,187	1.2	56.84	57.22-61.69
80:20	6,921	1.2	53.45	54.33-61.42
$70:30_t$	6,526	1.2	50.56	51.69-60.78

The increment of weight average molecular weight (M_W) was obtained when L-lactic proportion increased. This is because the molecular weight of the lactide molecule is greater than the glycolide. In addition, it has been reported that besides ROP of L-lactide and glycolide proceed via pair addition of repeats units (Chabot *et al*., 1983). In other words, two repeat units of each monomer are added onto the polymer growing chains each time, which may causes an increment of molecular weight (Dobrzynski *et al*., 2005; Vert *et al*., 1981) The polydispersity index was obtained from the ratio between the weight average molecular weight (M_W) and the number average molecular weight (M_n), observing materials with high polydispersity (Table 1).

Experimental and theoretical glass transition temperatures (T_g) for each PLLGA copolymer are summarized in Table 1. It can be observed that the experimental T_g values for the three PLLGA copolymers are very close to their corresponding theoretical T_g, confirming again the obtaining of copolymers. An increment of T_g was observed when the percentage of L-lactic acid was increased. This is attributed to the presence of the methyl groups (-CH_3) of the L-lactic segments that decreases the mobility of the polymeric chains (Fisher *et al*. 1973).

The copolymers and homopolymers were also analyzed by X-ray diffraction and the results are shown in Fig. 2. The PGA diffractogram exhibited peaks of high intensity at 22.11° and 28.79°, attributed to (110) and (020) planes of an orthorhombic structure (Fig.2-e). Similar results have been reported in other works (Nishimura *et al*. 2019; Sato *et al*. 2016). These peaks were not observed for PLLA homopolymer and PLLGA copolymers (Fig. 2a-d). On the contrary, they presented a broad amorphous band with a certain structural order whose intensity increases when the glycolic acid concentration is increased (Fig. 2a-d). This was confirmed with results obtained by Singh and co-workers (Singh *et al*. 2015). In addition, it has been also reported that PLGA copolymers with content between 25-75% of glycolide units present an amorphous structure (Zhu and Braatz, 2014). This can be explained by the fact that PGA does not have the side methyl group (-CH_3) but when it is copolymerized, the copolymer matrix structure loses its symmetry due to the difficulty of coupling the chains (Makadia *et al*. 2011; Middelton *et al*. 2000; Steven *et al*. 2006). It has also been reported that an amorphous state is better for drug delivery applications, where it is necessary to have simultaneously a mass loss and molecular weight degradation as well as allows a homogeneous dispersion of the active species into the copolymer matrix (Gilding *et al*. 1979).

3.2 PLLGA degradation study

PLLGA copolymers 70:30, 80:20 and 90:10%$wt._{L\text{-}LA}$: %$wt._{GA}$ were submitted to a degradation process. Copolymers were placed on 10 × 10 mm glass plates with a thickness of 500 μm. The plates were submerged in 10 mL of buffer saline solution by a period of 2 weeks (336 h) at 37 °C. In this way, mass loss profile, average molecular weight change, and copolymer degradation profiles were determined.

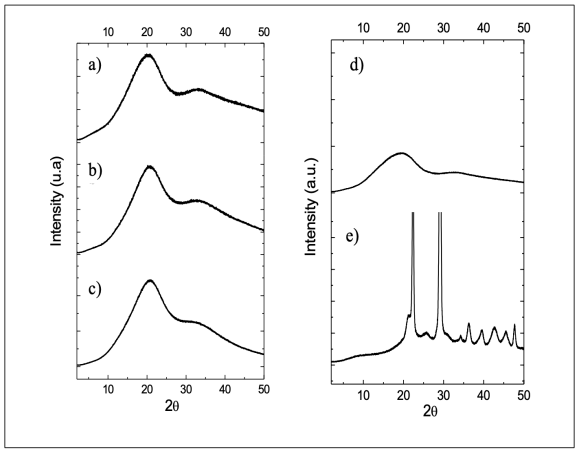

Fig. 2. X-ray diffractograms of a) 70:30, b) 80:20, c) 90:10%$wt_{L\text{-}LA}$:%wt_{GA}, d) PLLA and e) PGA.

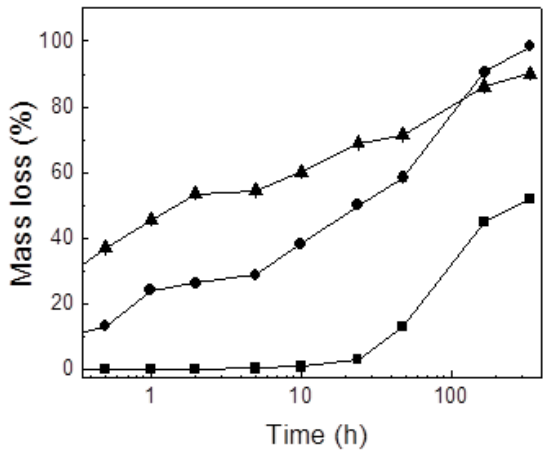

Fig. 3. Mass loss percentage as function of time: 70:30 (▲), 80:20(●) and 90:10 (■) %$wt_{L\text{-}LA}$:%wt_{GA} PLLGA copolymers.

Percentage of mass loss of the three PLLGA copolymers is shows in Fig. 3. PLLGA copolymers 70:30% and 80:20%$wt._{L\text{-}LA}$:%$wt._{GA}$ began to lose their mass during the first 15 min, and lost 50% of their mass 5 h later. Their degradation process was completed after two weeks. In the case of 90:10%$wt._{L\text{-}LA}$:%$wt._{GA}$ PLLGA copolymer, the first mass loss was observed at 5 h and lost just 50% of its mass, after 2 weeks of immersion.

Mass loss rate was calculated from the slope of mass loss curve as a function of time. It was observed that at 0.25 h, the obtained rates for 70:30 and 80:20%$wt._{L\text{-}LA}$:%$wt._{GA}$ PLLGA copolymers were 0.28 g/h and 0.26 g/h, respectively. These rates increased during the next 24 h of degradation process, presenting a parabolic-type pattern. Then, a linear behavior during next two weeks was observed. For 90:10%$wt._{L\text{-}LA}$:%$wt._{GA}$ PLLGA mass loss rate was slow (2.6 x 10^{-4} g/h) during the first 5 h, while its maximum rate was reached after 48 h (9.6 x 10^{-4} g/h). Before this point, mass loss rate had a linear behavior characteristic of S-type pattern.

Copolymers mass loss curves present two different shapes: (i) parabolic and (ii) S-type, that could be also related to the type of degradation of each material (Fig. 3). Copolymers with low molecular weight and high glycolide ratio as 70:30 and 80:20%$wt._{L\text{-}LA}$:%$wt._{GA}$ present a homogeneous degradation and a parabolic pattern. Copolymers with high average molecular weight and high lactide ratio as 90:10%$wt._{L\text{-}LA}$:%$wt._{GA}$ present a heterogeneous degradation with a S-type pattern, where the degradation process starts from the matrix surface and proceed into the matrix core. Fukuzaki and co-workers (Fukuzaki et. al 1990) studied the degradation of low molecular weight copolymer of (L-lactic-D-L-hydroxyisocaproic acid) and obtained a parabolic-type degradation pattern for copolymers with $M_n \approx 1600$ Da and it was changed into an S-type when molecular weight increased.

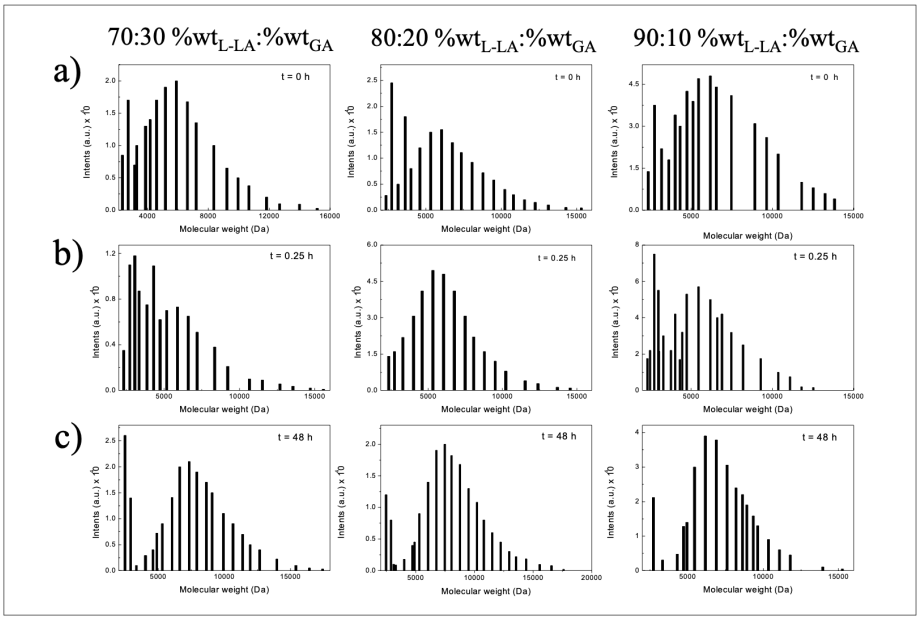

Fig. 4. Molecular weight distributions of degradation process at a) t = 0 h, b) t = 0.25 h and c) t = 48h. For the 70:30,

80:20 and 90:10%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ PLLGA copolymers.

The obtained molecular weight distribution for the three PLLGA copolymers at different degradation times: 0, 0.25 and 48 h are shown in Fig. 4. Before starting degradation process, the three copolymers had a wide molecular weight distribution (Fig. 4-a). Once the degradation process begins (0.25 h) the number of short chains in the 70:30%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ PLLGA copolymer decreased because a quick hydrolysis of material is presented, which facilitate that chains breaking in polymeric matrix and release them. However for 80:20 and 90:10%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ materials, the number of short chains increases (Fig. 4-b). When these copolymers reach 48 h of immersion, the number of short chains decreases and the molecular weight distribution become narrower than 70:30%wt.$_{L\text{-}LA}$:%wt.$_{GA}$. The chains with larger molecular weight (Mw ≈ 12,000 Da) remained at the end of the degradation process (Fig. 4-c) for all cases.

In the case of average molecular weight, a change is observed during the first minutes of sample immersion. This means that hydrolysis process starts immediately and promotes chain scissions in the copolymer matrix. This change was also observed in 90:10%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ PLLGA copolymer but was slower than 80:20 and 70:30%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ cases. These differences in the changes of average molecular weight between copolymers could be attributed to the lactide/glycolide ratio in PLLGA compositions, because the degradation process occurs first between the polyglycolic acid segments and then in those the polyL-lactic acid. Therefore, the autocatalysis process and mass loss in 70:30 and 80:20%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ copolymers were faster than 90:10 PLLGA%wt.$_{L\text{-}LA}$:%wt.$_{GA}$. This was also observed by Vasconcellos and co-workers (Vasconcellos *et al*. 2013) who found the faster hydrolysis for glycolic-glycolic bonds than glycolic-lactic and lactic-lactic bonds. They proposed that degradation products in dissolution are composed mainly of glycolic acid. Additionally, it has reported that there is a critical average molecular weight from which, the PLGA begins to lose mass (Park, 1994). This behavior is related to the increment of entrance of water molecules into the free spaces that left oligomers, when they leave the polymer matrix during autocatalysis process. This fact was also observed by Wang (Wang and Wu et.al 1997), who studied the biodegradation behavior of PLGA copolymers with several molar ratio and molecular weight. They observed that PLGA copolymers with higher content of lactic acid ratio, degraded slower. This was attributed to the hydrolysis steric hindrance of the copolymer matrix and was also observed for PLGA copolymers with same molecular weight but different lactide/glycolide ratio when they were summited to degradation process. The copolymers with higher lactic acid ratio degraded slower that those with lower ratio (Carte *et al*. 1984).

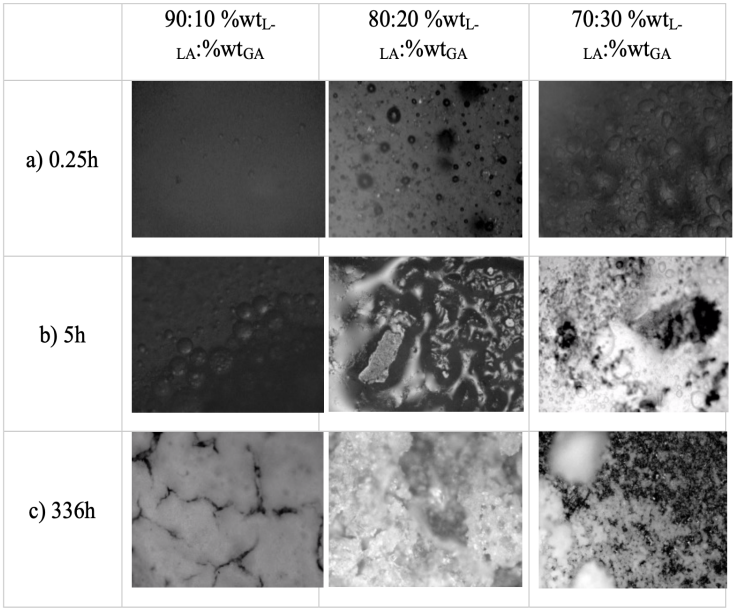

Fig. 5. Degradation process micrographs 20X a of 70:30, 80:20 and 90:10%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ PLLGA at time a) 0.25h, b) 5h and c) 336h.

Also, it is known that polyesters amorphous regions degrade preferentially over crystalline regions (Susan, 2002); however 90:10%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ PLLGA copolymer is degraded slower despite having a lower tendency to chains order than 70:30 and 80:20%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ PLLGA copolymers, so the lactide/glycolide copolymer ratio is an important parameter in the degradation process.

These results were corroborated by optical microscopy (Fig. 5). It was observed that during the first 15 min, 90:10%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ copolymer did not present a visible change on its surface, while in the case of 80:20 and 70:30%wt.$_{L\text{-}LA}$:%wt.$_{GA}$, presented some bubbles caused by hydration and swelling processes (Fig. 5-a). After 5 h, the surface of the 90:10%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ PLLGA showed few bubbles, while 80:20 and 70:30%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ PLLGA copolymers already had cracks due to the loss of material (Fig. 5-b). At the end of process (two weeks after), the 90:10%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ began to show its first failures, and the 80:20 and 70:30%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ PLLGA copolymers were completely degraded and only L-lactic acid crystals were observed on the glass surface (Fig. 5-c). This is coincident with the results of average molecular weight and X-ray diffraction in semicrystalline polymers, bonds in the amorphous region are more easily broken than those in crystalline region and a mobility increment of shorter chains is presented, causing a diffusion of them away from the polymeric matrix (Sackett and Narasimhan, 2011).

3.2.1 PLLGA degradation kinetics

The degradation process for PLGA copolymers is considered a chemical process that is resulted from chain cleavage (Sevim and Pan, 2018). Some stochastic mathematical models have been developed to explain the degradation process, and are based in phenomena of hydrolysis and erosion (Siepmann *et al*. 2002; Chen *et al*. 2011).

To obtain the degradation kinetics, the considerations of Chen and co-workers model were taken into account (Chen *et al*. 2011). They establish that the degradation process begins when water molecules penetrate into the polymeric matrix, leading to hydrolytic scissions of their ester bonds. If the matrix is reduced at micrometers size, a large number of pores inside the matrix are formed. This causes an increment in acid catalysis near these pores, which can accelerate the local hydrolysis degradation rate.

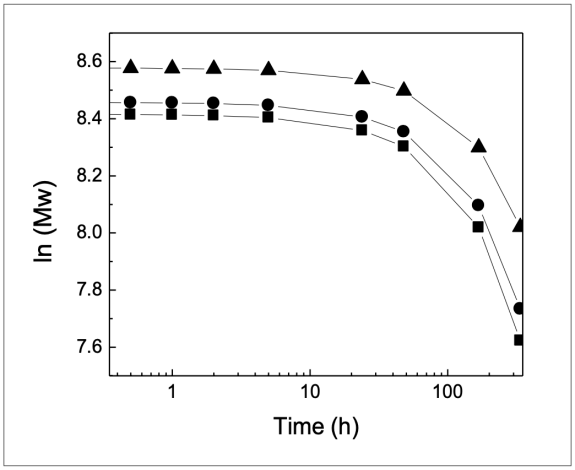

Fig. 6. Natural logarithm of the average molecular weight as function of time: 70:30 (▲), 80:20 (●) and 90:10 (■)%wt.$_{L\text{-}LA}$:%wt.$_{GA}$ PLLGA copolymers.

In this way, the degradation by autocatalytic effect can be neglected. They also report that this phenomenon can be observed when holes appear in the surface of polymeric matrix. This is coincident with what was observed in obtained optical microphotographs (Fig. 5). For these reasons, the data of average molecular weight were adjusted to pseudo-first order kinetics (eq. (3)) and then, the degradation rate constant was calculated.

$$\ln[M_W]_t = -kt + \ln[M_W]_0 \tag{3}$$

where $[M_W]_t$ is of average molecular weight during degradation process, k is degradation reaction rate constant, and $[M_W]_0$ is the initial average molecular weight. The degradation rate constant (k) for each material was obtained from the slope of the straight lines of plot in Fig. 6.

The obtain degradation rate constant values were 2.36 x 10^{-3}, 2.15 x 10^{-3} and 1.54 x 10^{-3} h^{-1} for 70:30, 80:20 and 90:10 wt.$_{L\text{-}LA}$:%wt.$_{GA}$ PLLGA, respectively. The results were corroborated with those obtained of mass loss and molecular weight change. It is observed, that when the copolymer had the lower lactide concentration, rate constant values are increased.

3.3 Drug release

For the drug release study, a mixture of PLLGA and prednisone was made. The mixture was put on glass plates of 10 × 10 mm, and they were immersed in vials of 10 mL of saline solution at 37 °C.

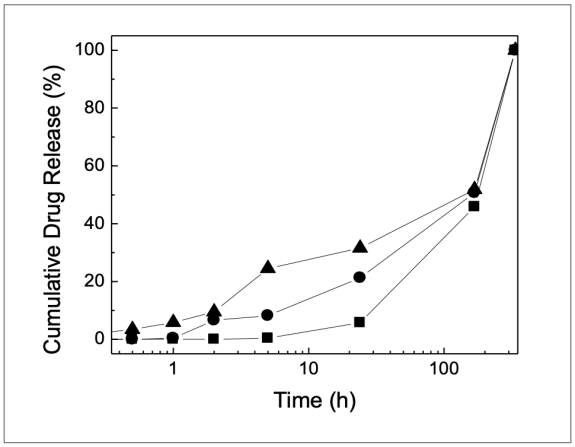

Fig. 7. Cumulative drug released as function of time of 70:30 (▲), 80:20(●) and 90:10 (■) %wt.$_{\text{L-LA}}$:%wt.$_{\text{GA}}$ PLLGA copolymers.

Samples of 3 mL of medium were taken of each vial at several time intervals for two weeks (360 h). The drug concentration change into saline solution was analyzed by Uv-vis spectroscopy at 240 nm.

From the obtained results of cumulative prednisone release percentage (Fig. 7), a bi-phasic profile for 70:30 and 80:20%wt$_{\text{LA}}$:% wt$_{\text{GA}}$ PLGA copolymers was observed. The first stage $0 < t/\text{h} < 48$, a faster drug desorption (burst effect) around 40% of drug release was observed. This fact could be explained by rapid water penetration into the PLGA matrix, which pushes a significant amount of prednisone out the surface, coincident with the obtained results of degradation where the 70:30%wt$_{\text{LA}}$:% wt$_{\text{GA}}$ presented a faster mass loss and change in the appearance of its surface (see Fig. 5). In addition, the prednisone hydrophobicity could contribute to the rapid diffusion of the molecules located into the spaces left from copolymer chains scission and, the liquid-filled pores (Versypt *et al*. 2013; Zhu and Braatz, 2015). A second stage $48 < t/\text{h} < 336$ with a slow and constant desorption rate can be observed, where the half of the pharmaceutical load is released as consequence of the continuous degradation process into the copolymer matrix. That is, short chains population increases and the matrix become dense, making the drug molecules diffusion more complicated (Sharma *et al*. 2016).

For 90:10 wt$_{\text{LA}}$:% wt$_{\text{GA}}$ PLGA copolymer, a lineal profile was observed during the whole release process. About 50% of drug desorption was appreciated during the first week and 100% download was reached until final process. This behavior is similar with other works where drug release in PLGA matrix is governed by polymer degradation process (Ma *et al*. 2011). This could also explain why the three copolymers reached 100% of the pharmaceutical loading desorption after two weeks, since the 90:10 wt$_{\text{LA}}$:% wt$_{\text{GA}}$ PLGA copolymer does not completely degrade but the breakdown of its chains leaves enough pores for prednisone diffusion. The drug release profiles were fitted to four very common models, chosen because their simplicity and applicability (Estrada-Villegas *et al*. 2019; Tamaddon *et al*. 2015).

Zero order kinetics:

$$F = K_0 t \tag{4}$$

First-order kinetics:

$$\ln(1 - F_t) = K_1 t \tag{5}$$

Higuchi model:

$$F = K_2 t^{1/2} \tag{6}$$

Korsmeyer-Peppas model

$$F = K_3 t^n \tag{7}$$

Here is defined as released fraction at any time t, K_0, K_1, K_2 y K_3 are release rate constants while n is the diffusional exponent that is dependent on the system geometry and release mechanism. When $n = 0.5$ a Fickian diffusion mechanism is presented. If $n = 1$ the mechanism responds to a case II transport (zero order), while $0.5 < n < 1$ corresponds to an anomalous (non-Fickian) diffusion mechanism. Finally, when $n > 1.0$ the mechanism is considered a super case II transport (Korsmeyer *et al*. 1983).

The results are summarized in Table 2 and showed that drug release data fit well to a zero-order model. That means that release rate can be attributed to changes on the matrix surface produced by erosion and diffusional path length; this fact ensures a sustained drug release (Dash *et al*. 2010). This suggests that prednisone release is at constant rate and at the same degradation rate of copolymer (Yadav *et al*. 2013; Thombre and Himmelstein, 1985). In addition, this is synonymous that the scale and geometry of device do

not interfere with the degradation kinetics (Giovagnoli *et al*. 2008).

The prednisone desorption data also had well-adjusted to Korsmeyer-Peppas model. This model takes into account the degradation process (hydration, expansion and dissolution of copolymer chains) (Versypt *et al*. 2013). It can be observed that 90:10 wt_{LA}:% wt_{GA} copolymer presents a super case II, characterized by $n > 1$. This mechanism is an extreme case II diffusion ($n = 1$) where the diffusion of the medium is faster than the relaxation of the polymeric chains when it penetrates the polymer (Sevostyanov *et al*. 2020); while 80:20 wt_{LA}:% wt_{GA} and 70:30 90:10 wt_{LA}:% wt_{GA} showed an anomalous (non-Fickian) diffusion behavior, which is the combination of drug diffusion and polymer relaxation as drug release mechanisms (Tammaddon *et al*. 2015).

3.4 Cytotoxicity of PLGA

PLLGA cytotoxicity in cells was determined by blue alamar assays. Two tests were performed. In the first assay, the culture medium was not refreshed during 24 h while in the second, the culture medium was refreshed every 3 h during 24 h. Both assays were made in adherent endothelial cells dispersed in 1000 μL of DMEM and analyzed by fluorimetry.

When culture medium (DMEM) was not refreshed during the 24 h, it began to acidify due to the presence of the PLLGA degradation products of L-lactic acid and glycolic acid. In spite of this, a percentage of cell viability greater than 50% was observed in the 80:20 and 90:10% $wt._{L\text{-}LA}$:% $wt._{GA}$ copolymers, not being the case of 70:30% $wt_{L\text{-}LA}$:% wt_{GA} that presented a cellular viability percentage of 30%. The cytotoxicity assays revealed that PLLGA copolymers that presented a faster degradation rate and therefore an accelerated decrease of medium pH, became toxic for the endothelial cells. However, it should be mentioned that in an *in vivo* system, blood circulation could avoid this effect and, PLLGA degradation products could not be considered as cytotoxic. This was verified by the second test, where the medium was refreshed every 3 h and where the three PLLGA copolymers reached a percentage of cellular viability greater than 50%, therefore it was concluded that the synthesized copolymers and their degradation products were not cytotoxic for the cells.

3.5 Stent fabrication

The obtained materials were used to fabricate a polymeric stent to be applied as possible coronary device. The stent was designed with CAD 3D SolidWorks 2016. According to some authors (Schiavone *et al*., 2015; Kumar *et al*., 2019) the stent geometry was decided to be a cylindrical mesh of 37.35 mm of length, inner diameter of 9 mm, outer diameter of 15 mm and thickness of 3 mm. The design was obtained in STL format to be manipulated with REPERTIER HOST Software. The polymeric stent was fabricated in a 3D printer. It was built according to the operation manual and equipment assembly and programmed in Arduino 1.6.1. The stent printing parameters were set as: printing rate 0.08 mL/min, printing time 1.19 h and temperature 70 °C.

The printer was tested first with commercial PLLA and then with the synthesized copolymers during this work. In this way, the stents were fabricated from a polymeric solution prepared with 4 g of polymer and 1 mL of acetone. The solution was put in the syringe and injected to the printer at 0.09 mL/min. The results showed the best material to fabricate the device was 90:10% $wt._{L\text{-}LA}$:% $wt._{GA}$ copolymer, because it has the highest average molecular weight.

Table 2. Kinetic parameters for zero order, first order, Higuchi and Korsmeyer-Peppas models in 90:10, 80:20 and 70:30%wt_{LA}:%wt_{GA} PLGA copolymers.

Copolymer %wt_{LA}: %wt_{GA})	Zero order		First order		Higuchi		Korsmeyer-Peppas		
	K_0	R^2	K_1	R^2	K_2	R^2	K_3	R^2	n
90:10	0.643	0.99	0.014	0.76	11.19	0.94	1.99	0.98	1.29
80:20	0.287	0.98	0.014	0.44	5.14	0.94	1.39	0.98	0.53
70:30	0.269	0.92	0.009	0.57	4.90	0.95	1.73	0.94	0.51

R^2 = Correlation coefficient
n = Diffusion exponent

Conclusions

PLLGA copolymers degradation holds a pseudo-first order kinetics which depends on the average molecular weight, the structure and the glass transition temperature, but the lactide/glycolide ratio is one of the most important factors in PLLGA degradation process and control prednisone released. Prednisone release kinetics was governed by two phenomena: diffusion and degradation for 80:20 and 70:30 $wt_{L\text{-}LA}$:% wt_{GA} copolymers while 90:10% $wt_{L\text{-}LA}$:% wt_{GA} a super case II (transport) was presented. The effect that PLGA copolymers had on endothelial cells was attributed to acidification of the medium caused by their acidic degradation products.

Finally, the synthesized copolymers were used to fabricate polymeric stents of PLLA by means of a 3D printer. The parameters of printing were set as: printing rate 0.08 mL/min, printing time 1.19 h and temperature 70 °C. The synthesized 90:10%$wt._{L\text{-}LA}$:%$wt._{GA}$ PLLGA showed the best physicochemical properties to be used in the stent fabrication.

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