Homogeneous hydrolytic degradation of poly(lactic-co-glycolic acid) microspheres: Mathematical modeling

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A B S T R A C T

The homogeneous hydrolytic degradation of poly(lactic-co-glycolic acid) (PLGA) microspheres was investigated. A mathematical model was developed that estimates the evolutions of ester bonds concentrations and average molecular weights along the degradation process. The model is based on a detailed kinetic mechanism that includes the hydrolysis of the different types of ester bonds by random chain scission and considers the effect of polymer chemical composition and molecular structure. Novel and published experimental data were used to adjust and validate the model. The experimental work consisted of homogeneous hydrolytic degradation of PLGA microspheres. The predictions are in very good agreement with the experimental results.

1. Introduction

Biodegradable polymer systems have received considerable attention for drug delivery in pharmaceutical and biomedical fields [1,2]. These systems allow to effectively control the drug release within the desired therapeutic range, avoiding consequences of an excess or deficit, which could compromise its effectiveness. Specially, the family of aliphatic polyesters, such as poly(lactide) (PLA), poly(glycolide) (PGA) and their copolymer, poly(lactide-co-glycolide) (PLGA) has been widely employed for these purposes due to their biodegradable and biocompatible properties [3–6]. These polymers are safe for the body and are hydrolyzed to metabolic products [7,8].

The degradation of aliphatic polyesters has been investigated by many authors, both *in vitro* and *in vivo* [9,10]. In particular, PLGA microspheres have been widely studied for drug delivery applications and their degradation is known to be affected by the system preparation method [11,12], by polymer properties such as initial molecular weights, devices morphology and lactide/glycolide ratio of the copolymers [8,13,14], as well as by physical and chemical parameters such as temperature and pH of the external medium [15]. Many studies have also been carried out to evaluate the effect of particle size [16,12], number of carboxylic end groups [17] or enzymes in the external medium [18] on the degradation behavior of poly(α-hydroxy acids). In an aqueous environment, PLGA degrades through bulk erosion. Water penetrates the device and reaches a saturation level very rapidly in comparison with polymer degradation [19]. Water molecules attack ester bonds in the polymer chains through hydrolysis reactions and the chain cleavage produces shorter chains with alcohol (−OH) and carboxylic (−COOH) groups. The carboxylic end groups can act as a catalyst to accelerate the hydrolysis reaction [20]. In addition, the restricted diffusion of degradation products can result in high concentration of carboxylic end groups inside the materials and produce heterogeneous degradation, in which the center of the material is degraded faster than its surface [21,22]. It was shown that large size PLGA devices degraded heterogeneously while small-sized devices such as thin films and microspheres degraded homogeneously [13]. During hydrolysis, the molecular weight of the polymer decreases due to chain scission and when it is small enough, the oligomers can dissolve in the surrounding medium causing the mass loss of the system. Antheunis et al. [23] determined that the critical molecular weight of PLGA oligomers dissolution in PBS buffer at 37 °C was 850 g mol^{-1}. This result suggests that, for this polymer and for the studied conditions, oligomers up to about thirteen monomer units are buffer-soluble. Also, this value corresponds to those reported by Schliecker et al. [24] for PLA.

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Many models have been proposed to describe PLGA degradation, erosion and drug release from the bulk polymer [20]. Typically, polymer degradation is assumed to follow a pseudo first-order kinetics where degradation rate is a function of water, ester bonds or acid catalyst concentrations. The concentrations of the other two species are either ignored or assumed constant [25,26]. In addition, second-order, autocatalytic hydrolysis kinetics for PLA and PLGA have been modeled in several reports [23,27,28,19], where the catalyst and ester bonds concentrations were allowed to vary while the water concentration was assumed constant during degradation. Nishida et al. [28] used moment analysis to predict the change in the average molecular weight of aliphatic polyesters subject to catalysis by carboxylic end groups. Han and Pan [19] developed a model for degradation of bioresorbables polyesters taking into account the autocatalytic hydrolysis reaction and oligomer production and diffusion. The model can predict the evolution of molecular weight distribution in a device as well as the weight loss as a function of time. Antheunis and coworkers [23] proposed a mathematical model based on the autocatalytic kinetics of aliphatic polyesters hydrolysis and it is able to describe the decrease of the average molecular weight and also to reasonably predict the mass loss trend of the polymer phase as a function of degradation time. This model was simplified to develop a basic model that describes the decrease of the number average molecular weight for aliphatic polyesters before mass loss occurs [27].

In the present work, a new mathematical model that simulates the homogeneous degradation of PLGA microspheres is developed. The model takes into account the autocatalytic effect of carboxylic groups and the polymer composition on the polymer degradation rate and it is based on a detailed kinetic mechanism that considers the hydrolysis of the different types of ester bonds in the copolymer by random chain scission. It allows to estimate the evolutions of the ester bonds concentrations and average molecular weights throughout the degradation process and it is also able to predict the mass loss and pH profiles of the system. The model was adjusted and validated with published [29] and new experimental data.

2. Materials and methods

2.1. Materials

PLGA 50/50, Resomer® RG 502H, weight-average molecular weight (M_w) 8650 Da (Boehringer Ingelheim Pharma KG, Ingelheim, Germany), ethyl acetate, tetrahydrofurane (THF), dichloromethane, polyvinyl alcohol (PVA), sodium hydroxide and sodium azide (NaN_3) were provided by Sigma–Aldrich (Argentina) at reagent grade and they were used without further purification. Distilled and deionized water was used to prepare all the solutions.

2.2. Microsphere preparation

Emulsions and PLGA microspheres were prepared based on a method propossed by Sah et al. [30]. The emulsion (O/W) was obtained by dissolving 1 g of PLGA in 4.5 mL of ethyl acetate, this solution was called phase 1. Phase 2 was composed of 15 mL of a PVA aqueous solution (2% w/v). Phase 1 was added dropwise into the mechanically stirred phase 2 using an Ultra-Turrax T25D homogenizer (dispersing element S25N-18G, IKA, Germany) at 3400 rpm. Stirring was increased to 4000 rpm for 15 min to finally obtain the O/W emulsions. Then, water was added to the emulsion and it was magnetically stirred for 50 min until complete evaporation of ethyl acetate from microspheres. Finally, the solid spheres were collected by centrifugation at 2750 rpm for 5 min, lyophilized and stored at −20 °C until further assays.

2.3. Degradation studies

Approximately 65 mg of dry microspheres were placed into a glass vial with sodium azide in d-water (0.02% w/w) as the degradation medium. The vials were orbitally shaken at 50 rpm in an oven with digital temperature control at 37 °C. The degradation medium was removed at different times and the polymer sample was dehydrated under vacuum at room temperature.

During degradation, pH evolution was monitored with an Orion potentiometer. At each time point, four randomly selected samples were centrifuged for 5 min at 3500 rpm to determine the pH of the medium. Then, samples were resuspended with vortexing for 2 min and placed again to continue the degradation test.

2.4. Characterization

2.4.1. Microsphere size distribution

The microsphere suspensions were observed in an optical microscope coupled with a Leica DM 2500M DFC 290HD camera. The particle size distributions were determined by analyzing the images with the Image Pro Plus software.

2.4.2. Mass loss determination

Samples were collected by centrifugation at 3500 rpm for 5 min and then washed with d-water. This step was repeated three times. Then, the remaining mass was dried under vacuum up to constant weight and examined for weight loss. Polymer mass loss was determined gravimetrically using Eq. (1).

$$\%\ Mass\ loss = \frac{w_t}{w_0} \times 100 \quad (1)$$

where w_0 is the initial weight of microspheres and w_t is the weight of the dried microspheres after the incubation period.

2.4.3. Molecular weight of polymer

The average molecular weights of polymer were determined by size exclusion chromatography (SEC). A Waters 1525 pump with four Ultrastyragel® columns (HR 0.5, HR 1, HR 2, HR 3, 7.8 mm × 300 mm, 5 μm) and a Waters 2412 refractive index detector were used with tetrahydrofuran as eluent, with a flow rate of 1.0 mL min^{-1}, at 25 °C. Polystyrene (PS) standards (Shodex SM-105, Showa Denko) were used for calibration.

2.4.4. Morphology studies

The morphology of microparticles was studied by scanning electron microscopy (SEM). Samples were put over an aluminum stub and were then sputter coated with gold under argon atmosphere (SPI Supplies, 12157-AX) and examined using an acceleration voltage of 20 kV, in a JEOL JSM-35C equipped with the image acquisition program JEOL SemAfore.

2.5. Degradation experiments of Blanco et al. [29]

For model adjustment and validation, experiments performed by Blanco et al. [29] were also considered. The experimental work consisted of *in vitro* degradation of PLA, PLGA 50/50 and PLGA 75/25 microspheres (Exps. 1, 2 and 3, respectively) prepared by the spray drying method. For each polymer sample, test tubes of polyethylene containing 40 mg of microspheres and 3 mL of phosphate buffer (1 mM, pH 7.4) were prepared and incubated in darkness at 37 °C. Test tubes were stirred once a day for 1 min in a vortex. At appropriate time intervals, the phosphate buffer was removed and the polymer sample was dried under vacuum. The maximum incubation time was 5 months. The average molecular weights and

mass loss measured along the degradation process are presented in Table 1 and Figs. 1 and 2. From the average molecular weights of Table 1 and the copolymer composition, the evolution of ester bonds concentration was calculated considering random bond distribution. These results are also shown in Fig. 1c.

Experimental data taken from Blanco et al. [29] only refers to microspheres that have an average diameter smaller than 2 μm, for which the diffusion phenomenon can be considered negligible [13].

For all experiments, the polymers molecular weight profiles decrease with time. The degradation products trapped within the microsphere have the potential to catalyze the degradation of the remaining polymer material. When the molecular weight is sufficiently low, the polymers begin to lose mass because of oligomers dissolution [8]. In Exp. 1, microspheres mass loss was not observed due to the slow degradation rate of PLA. Degradation patterns observed in Exps. 2 and 3 indicate that it occurs through bulk erosion. There is an initial period without mass loss during which molecular weight decreases, i.e., cleavage of the polymer chains occurs throughout the sample. The polymer molecular weight profile shows a typical S-shaped curve which can be divided into three stages (Fig. 1). In the first stage, the molecular weight decrease is slow due to the low concentration of carboxylic groups. In the second stage, the number of carboxylic groups increases and accelerates the hydrolysis reaction. Therefore, the molecular weight decrease is faster. In the last stage, the low concentration of ester bonds delays degradation.

3. Results and discussions

3.1. Experimental study

Fig. 3 shows a SEM micrography of PLGA microparticles synthesized. As observed, they were spherical and not aggregated, and their surface was smooth. The obtained average diameter was 3.4 ± 0.79 μm.

Experimental data of degradation studies are presented in Table 2 and Figs. 4–5. From averages molecular weights of Table 2, the evolutions of ester bonds concentrations were determined considering random bond distribution and polymer composition (Fig. 5a). Fig. 4 presents the evolution of polymer average molecular weights. The molecular weights clearly decrease right from the beginning of the experiment due to the low molecular weights of the polymer, which causes the rapid generation of acidic degradation products, accelerating the hydrolysis reaction of the ester bonds in the copolymer.

The mass loss along degradation process is shown in Fig. 5b. The weight loss indicates that water-soluble oligomers and monomers are produced by hydrolytic degradation and then released from the microspheres into the surrounding media. The mass loss is observed from the beginning of the experiment and exhibits a similar profile to the molecular weight. The degradation products quickly reach the necessary molecular weight to dissolve in the medium.

Fig. 5c shows the evolution of medium pH with immersion time for the PLGA microspheres. The decrease in pH is due to the generation of acidic degradation products. The carboxylic end groups have a high degree of dissociation and quickly acidify the medium. The pH begins to decrease immediately after immersion in accordance to the mass loss profile.

3.2. Mathematical model

The degradation model is an autocatalytic random hydrolysis model that considers the influence of carboxylic acid end groups. The general equations for self-catalyzed ester bonds hydrolysis can be expressed as follows:

$$E + H_2O \rightarrow COOH + ROH \quad (2)$$

$$COOH \rightleftarrows COO^- + H^+ \quad (3)$$

where E is an ester bond and COOH and ROH are acid and alcohol terminal groups, respectively.

In order to consider the degradability of each ester bond type, the detailed hydrolysis mechanism of Squeme 1 is extended from

Table 1
Degradation of PLA and PLGA Microspheres (taken from Blanco et al. [29]).

N	Exp. 1 PLA			Exp. 2 PLGA 50/50			Exp. 3 PLGA 75/25		
Time (days)	M_n ($\times 10^3$ g/mol)	M_w ($\times 10^3$ g/mol)	Mass (%)	M_n ($\times 10^3$ g/mol)	M_w ($\times 10^3$ g/mol)	Mass (%)	M_n ($\times 10^3$ g/mol)	M_w ($\times 10^3$ g/mol)	Mass (%)
0	25.4	42.6	100	24.2	38.8	100	39.8	65.4	100
1	25.4	42.0	100	23.9	38.2	100	39.7	64.2	100
5	25.2	41.6	100	22.1	36.6	100	–	–	–
9	24.3	40.4	100	21.3	35.4	100	39.5	64.4	100
14	–	–	–	20.2	34.6	100	–	–	–
16	–	–	–	–	–	–	38.2	59.2	100
19	24.0	40.2	100	18.7	30.3	100	–	–	–
22	–	–	–	17.1	26.9	100	–	–	–
25	23.5	39.8	100	–	–	–	–	–	–
28	–	–	–	11.6	19.3	100	33.0	52.3	100
35	23.3	39.5	100	5.4	8.1	97	31.2	50.3	100
42	–	–	–	3.2	4.9	90	–	–	–
45	22.5	38.8	100	–	–	–	29.1	45.4	100
49	–	–	–	1.8	2.3	83	–	–	–
51	–	–	–	–	–	–	27.1	44.4	100
56	–	–	–	1.4	1.7	57	–	–	–
58	22.3	39.9	100	–	–	–	–	–	–
71	21.3	36.7	100	1.1	1.2	18	20.8	34.0	100
78	–	–	–	1.0	1.1	15	–	–	–
84	21.0	36.2	100	–	–	–	16.0	25.8	100
96	20.8	35.7	100	–	–	–	10.6	17.4	100
109	20.0	34.7	100	–	–	–	6.2	9.2	86
126	19.6	33.9	100	–	–	–	2.0	2.1	73
144	18.9	32.1	100	–	–	–	1.1	1.2	47

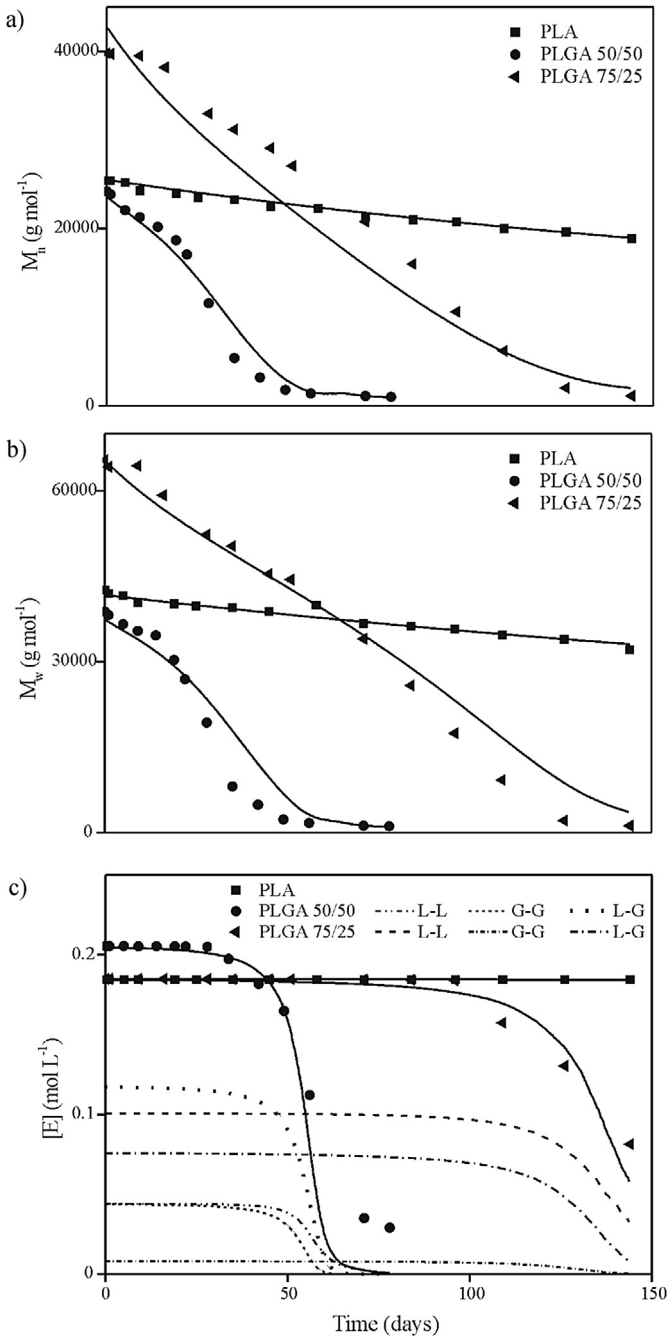

Fig. 1. a), b) Evolution of average molecular weights (M_n and M_w) for Exp. 1–3; and c) Evolution of ester bonds concentrations for Exp. 1–3. (Experimental data in dots and simulation results in solid lines).

Eq. (2). The polymer species are characterized by their chain length and by the number of each ester bond type. The following nomenclature is adopted: P_n (l, g, c) represents a polymer chain of length n with l, g and c, Lactic–Lactic (L–L), Glycolic–Glycolic (G–G) and Lactic-Glycolic (L-G) ester bonds, respectively; and $k_{L\text{-}L}$, $k_{G\text{-}G}$, $k_{L\text{-}G}$ are the hydrolysis constants corresponding to L–L, G–G and L-G ester bonds.

On the basis of the detailed hydrolysis mechanism, the mathematical model for the degradation is derived. It consists of Eqs. (1)–(17) of Appendix and predicts the evolutions of ester bonds concentrations, molecular weight distributions and average molecular weights as well as mass loss and pH profiles. The model

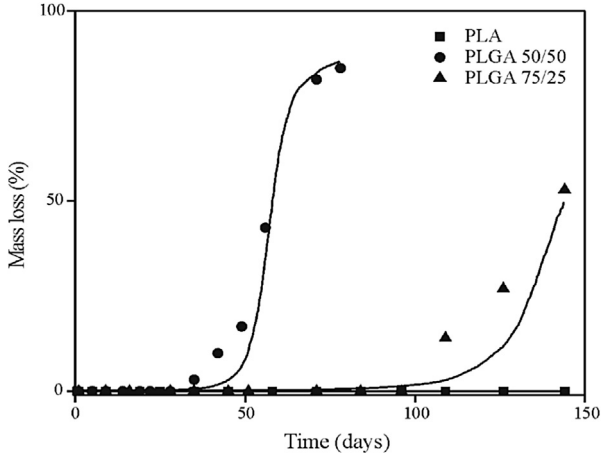

Fig. 2. Evolution of mass loss for Exps. 1–3. (Experimental data in dots and simulation results in solid lines).

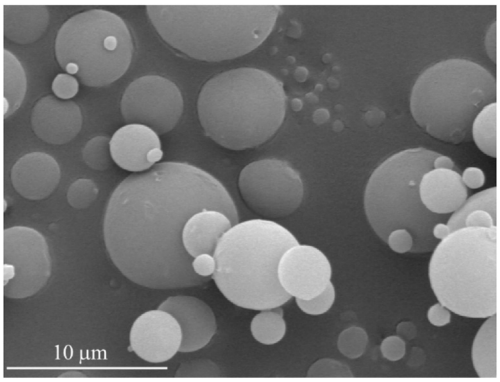

Fig. 3. Scanning electron micrography of PLGA microspheres.

Table 2
Degradation of PLGA microspheres.

Exp. 4 PLGA 50/50				
Time (days)	M_n (g/mol)	M_w (g/mol)	Mass (%)	pH
0	2355.4	6787.4	100	5.25
1	2374.8	6397	95.64	5.24
3	1943.2	5157.5	90.87	5.14
5	1648.4	3691.5	89.51	4.47
7	1725	3410.3	88.07	4.08
9	1255.1	2660.6	81.37	3.72

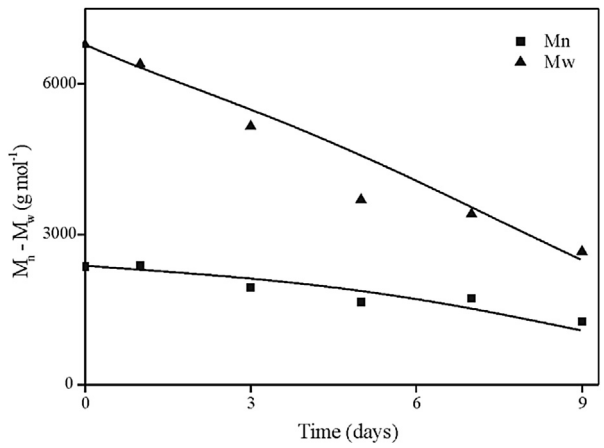

Fig. 4. Evolution of average molecular weights for Exp. 4. (Experimental data in dots and simulation results in solid lines).

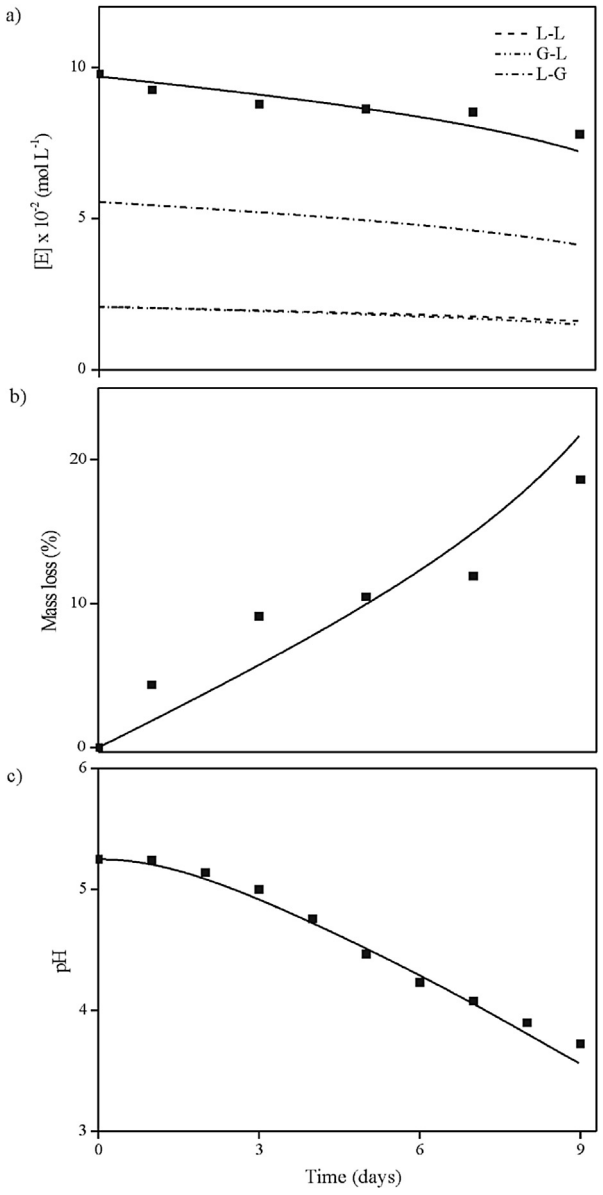

Fig. 5. a) Evolution of ester bonds concentrations for the Exp. 4; b) evolution of mass loss; and c) evolution of pH. (Experimental data in dots and simulation results in solid lines).

assumes: hydrolysis rate constants are independent of chain length; ester bonds are uniformly distributed inside the polymer chain; all particles have the same size (equal to their mean diameter); polymers are amorphous and only the dissolution of oligomers with a chain length up to n_S is taken into account. Note that for homogeneous systems, pH inside microspheres is assumed to be uniform.

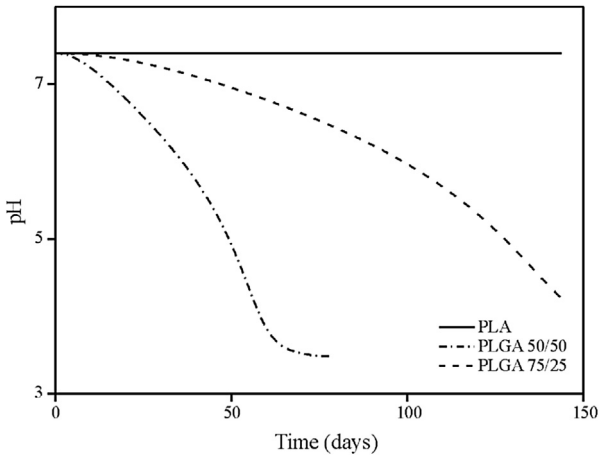

Fig. 6. Simulated evolution of pH for Exps. 1–3.

3.3. Simulation results and discussion

The computer program was written in Matlab R2012a. The mathematical system consists of a set of ordinary differential equations solved by a forward Euler method. A typical simulation required about 30 s of computing time.

In Figs. 1 and 2, experimental and theoretical results for Exps. 1–3 are compared. In general, predictions obtained are in very good agreement with the experimental results. The hydrolysis constant $k_{L\text{-}L}$ was estimated from data of Exp. 1 and $k_{G\text{-}G}$ and $k_{L\text{-}G}$ were estimated from data of Exp. 2 considering that $k_{L\text{-}G}$ is a mean value between $k_{L\text{-}L}$ and $k_{G\text{-}G}$ [23]. The direct and reverse acid dissociation constants k_{a1} and k_{a2} are related by the equilibrium dissociation constant of carboxylic groups. The estimated kinetic constants are detailed in Table 3. These results indicate that the cleavage rate of G–G bonds is faster than L–L bonds, consistent with experimental observations [31,32]. In Fig. 1, it can be observed that PLGA 50/50 molecular weight decreases faster compared to PLGA 75/25 and PLA. The estimated value of chain length at which oligomers can dissolve in the medium (n_s) was 10 repeat units, consistent with reported data for PLA and PLGA and similar experimental conditions [23,17].

In Figs. 4 and 5, experimental and theoretical results for Exp. 4 are presented. The predictions obtained are in concordance with the experimental results. The estimated kinetic constants are listed in Table 3. The results indicate that polymer degradation in aqueous medium is faster. This can be attributed to the rapid generation of an acid environment which catalyzes the hydrolysis of ester bonds of the polymer.

Other theoretical predictions are presented in Figs. 6–8. In Fig. 6, the simulated pH evolutions for Exps. 1–3 are shown. The pH remains virtually constant for PLA during the experiment due to the slow degradation rate, while for copolymers, a pronounced decrease in pH was observed. For PLGA 50/50, the pH change was higher as a consequence of faster generation rate of acidic products.

Table 3
Kinetic constants for experiments 1–4.

Exps. 1–3					
$k_{L\text{-}L}$ (L mol^{-1} s^{-1})	$k_{G\text{-}G}$ (L mol^{-1} s^{-1})	$k_{L\text{-}G}$ (L mol^{-1} s^{-1})	k_d (m^{-2} s^{-1})	k_{a1} (s^{-1})	k_{a2} (s^{-1})
7.87×10^{-4}	8.34×10^{-3}	4.57×10^{-3}	1.04×10^{-15}	2.08×10^{-12}	6.01×10^{-9}
Exp. 4					
$k_{L\text{-}L}$ (L mol^{-1} s^{-1})	$k_{G\text{-}G}$ (L mol^{-1} s^{-1})	$k_{L\text{-}G}$ (L mol^{-1} s^{-1})	k_d (m^{-2} s^{-1})	k_{a1} (s^{-1})	k_{a2} (s^{-1})
7.87×10^{-4}	6.03×10^{-3}	3.41×10^{-3}	2.31×10^{-25}	2.78×10^{-20}	8.22×10^{-17}

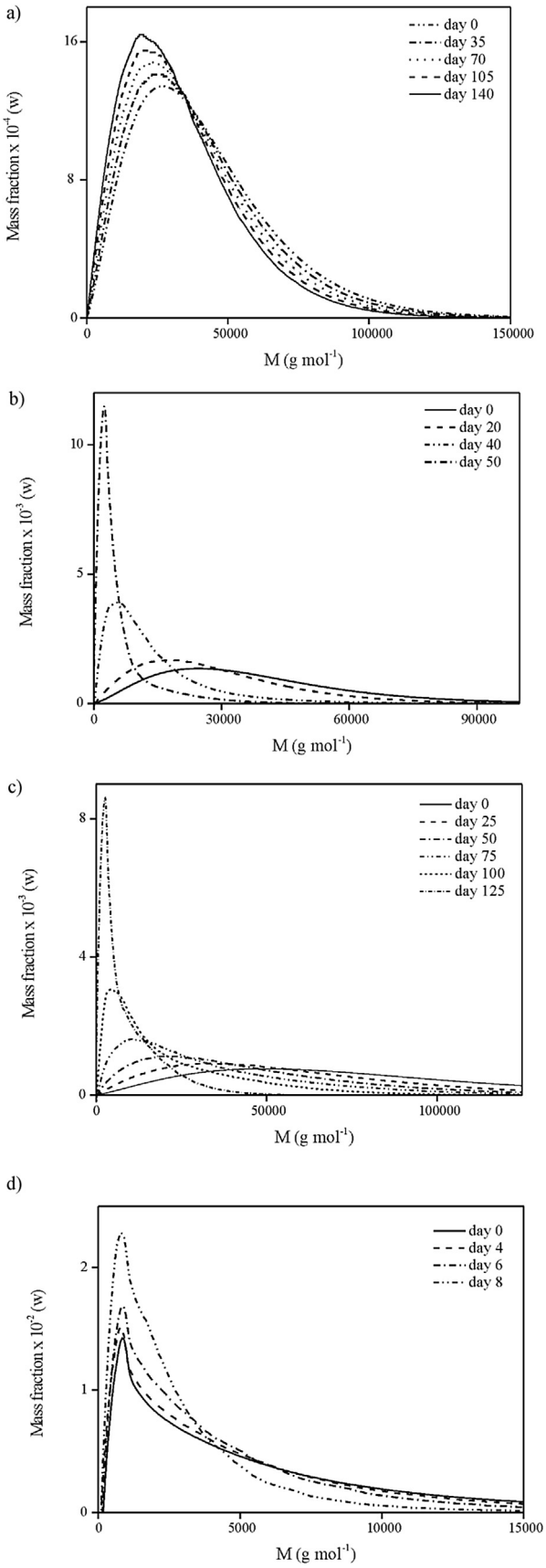

Fig. 7. Predicted molecular weight distributions: a) Exp. 1; b) Exp. 2; c) Exp. 3; and d) Exp. 4.

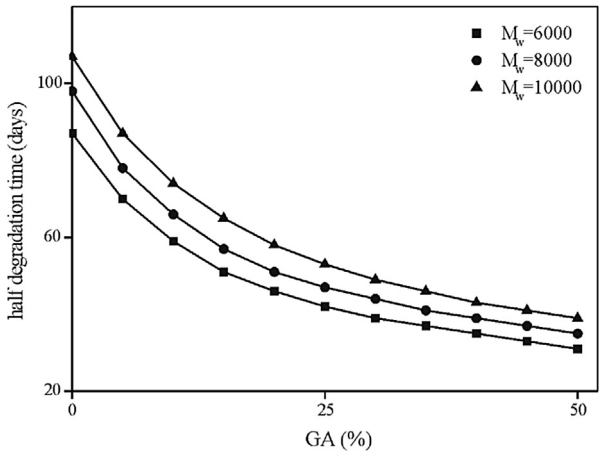

Fig. 8. Predicted half-life of PLA and PLGA as a function of the copolymer ratio for different molecular weights.

Theoretical evolutions of molecular weight distributions (MWD) for Exps. 1–4 are presented in Fig. 7. As shown in Fig. 7, the MWD shifts towards lower molecular weights along degradation time. This shift was slight for PLA and increases with the GA content for copolymers. Fig. 8 shows the predicted half degradation time of the copolymer as a function of the copolymer ratio. The half degradation time is defined as the time taken for the polymer to halve its mass. At high percentages of LA content the copolymer increases the half degradation time because the L–L bonds degrades more slowly than G–G bonds. It can be observed that this effect is accurately predicted by the model. In addition, the half degradation time rises with the increase in the average molecular weight of the copolymer.

4. Conclusions

A mathematical model to predict the homogeneous hydrolytic degradation of PLGA microspheres was developed. The model estimates the evolutions of ester bonds concentrations, average molecular weights, mass loss and pH profiles during the degradation process. The theoretical results are in very good agreement with experimental measurements. The incubating media affects the degradation of the copolymer, a buffered medium slow down the degradation in comparison with an aqueous medium. The model accurately predicts the effect of copolymer ratio and molecular weight on the degradation rate of the copolymer and can be used to select an optimal composition and/or molecular weight in order to achieve a prespecified degradation time. In further works, the model will be extended to heterogeneous systems for predicting pH profiles inside the particles and the evolution of particles morphology and molecular structure of polymer.

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Appendix. Mathematical model

From Scheme 1 and considering the catalytic effect of the acid

$$P_n(l,g,c)+H_2O \xrightarrow{k_{L-L}} P_{n-m}(l-l'-1,g-g',c-c')+P_m(l',g',c')$$
$$n=1,2,3,\ldots$$
$$l,g,c=0,1,2,3,\ldots$$
$$l'=0,1,2,3,\ldots,(l-1)$$
$$g'=0,1,2,3,\ldots,g$$
$$c'=0,1,2,3,\ldots,c$$

$$P_n(l,g,c)+H_2O \xrightarrow{k_{G-G}} P_{n-m}(l-l',g-g'-1,c-c')+P_m(l',g',c')$$
$$n=1,2,3,\ldots$$
$$l,g,c=0,1,2,3,\ldots$$
$$l'=0,1,2,3,\ldots,l$$
$$g'=0,1,2,3,\ldots,(g-1)$$
$$c'=0,1,2,3,\ldots,c$$

$$P_n(l,g,c)+H_2O \xrightarrow{k_{L-G}} P_{n-m}(l-l',g-g',c-c'-1)+P_m(l',g',c')$$
$$n=1,2,3,\ldots$$
$$l,g,c=0,1,2,3,\ldots$$
$$l'=0,1,2,3,\ldots,l$$
$$g'=0,1,2,3,\ldots,g$$
$$c'=0,1,2,3,\ldots,(c-1)$$

Scheme 1. Detailed hydrolysis mechanism of PLGA microspheres degradation.

medium, the following mass balances are derived:

where V is the particle volume, p_i is the rupture probability of a chain with i ester bonds, n_s is the critical chain length for oligomers dissolution, and k_d is the oligomers dissolution rate constant. Note that the chain length n is related to the number of ester bonds as $n = l + g + c'+1$. The generation of polymer species by chain scission is modeled assuming an uniform rupture probability distribution for each type of ester bond. The following global dissociation equilibrium can be written for the polymeric species with acid groups:

$$P \underset{k_{a2}}{\overset{k_{a1}}{\rightleftharpoons}} P^- + H^+ \tag{2A}$$

Considering $[P^-] = [H^+]$, the following mass balance for H^+ is derived:

$$\frac{d}{dt}\left\{\left[H^+\right]V\right\} = k_{a1}[P]V - k_{a2}\left[H^+\right]^2 V \tag{3A}$$

where [P] is the total concentration of polymer, defined as:

$$[\mathrm{P}] = \sum_{n=1}^{\infty}\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n(l,g,c)] \tag{4A}$$

From Eq. (1), the number chain length distribution (NCLD) of the

$$\frac{d}{dt}\{[P_n(l,g,c)]V\} = -k_{L-L}l\left[P_n(l,g,c)\right]\left[\mathrm{H}^+\right]V - k_{G-G}g\left[P_n(l,g,c)\right]\left[\mathrm{H}^+\right]V - k_{L-G}c\left[P_n(l,g,c)\right]\left[\mathrm{H}^+\right]V - fk_d\left[P_n(l,g,c)\right]4\pi R^2 + \\ + \sum_{m=n+1}^{\infty}\sum_{k=l+1}^{\infty}k_{L-L}p_k k[P_m(k,g,c)] + k_{G-G}\sum_{h=g+1}^{\infty}p_h h\left[P_m(l,h,c)\right] + \sum_{d=c+1}^{\infty}k_{L-G}p_d d[P_m(l,g,d)]\Bigg)V \tag{1A}$$
$$n=1,2,3,\ldots$$
$$f=0 \text{ if } n>n_s$$
$$f=1 \text{ if } n<n_s$$

$$\frac{d}{dt}\left(\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n]V\right) = -k_{L-L}l\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n]\left[\mathrm{H}^+\right]V - k_{G-G}g\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n]\left[\mathrm{H}^+\right]V - k_{L-G}c\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n]\left[\mathrm{H}^+\right]V \\ - f\,k_d\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n]4\pi R^2V + +\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}\Bigg\{\sum_{m=n+1}^{\infty}\sum_{k=l+1}^{\infty}k_{L-L}p_k k\left[P_m(k,g,c)\right] \\ + k_{G-G}\sum_{h=g+1}^{\infty}p_h h\left[P_m(l,h,c)\right] + \sum_{d=c+1}^{\infty}k_{L-G}p_d d[P_m(l,g,d)]\Bigg)V\Bigg\} \tag{5A}$$
$$n=1,2,3,\ldots l,g,c=0,1,2,3,\ldots f=0 \text{ if } n>n_s f=1 \text{ if } n<n_s$$

copolymer can be estimated:

Multiplying Eq. (5) by the average molecular weight of the repeating unit (M_{RU}), the weight chain length distribution (WCLD)

$$\frac{dM}{dt} = -\sum_{n=1}^{\infty}\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n(l,g,c)]\; n\; M_{RU}\; k_d f 4\pi R^2 \tag{15A}$$

where M is the total mass of the particle and R is the radius.

$$\begin{aligned}\frac{d}{dt}\left(\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n]nM_{RU}V\right) = \Bigg\{ & -k_{L-L}l\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n]\left[H^+\right]V - k_{G-G}g\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n]\left[H^+\right]V - k_{L-G}c\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n]\left[H^+\right]V \\ & - f\,k_d\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n]4\pi R^2 + + \sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}\left[\sum_{m=n+1}^{\infty}\left(\sum_{k=l+1}^{\infty}k_{L-L}p_k k\left[P_m(k,g,c)\right]\right.\right. \\ & \left.\left. + k_{G-G}\sum_{h=g+1}^{\infty}p_h h\left[P_m(l,h,c)\right] + \sum_{d=c+1}^{\infty}k_{L-G}p_d d[P_m(l,g,d)]\right)V\right]nM_{RU}\Bigg\} \\ & n = 1,2,3,\ldots l,g,c = 0,1,2,3,\ldots f = 0\ if\ n > n_s f = 1\ if\ n < n_s\end{aligned} \tag{6A}$$

can be calculated:

where $M_{RU} = x_{L\text{-}L}\,M_{L\text{-}L} + x_{G\text{-}G}\,M_{G\text{-}G} + x_{L\text{-}G}\,M_{L\text{-}G}$. In this equation, $M_{L\text{-}L}$, $M_{G\text{-}G}$ and $M_{L\text{-}G}$ are the molar masses of the corresponding ester repeating units and $x_{L\text{-}L}$, $x_{G\text{-}G}$ and $x_{L\text{-}G}$ represents the molar fraction of L–L, G–G and L-G ester bonds, given by:

$$x_{L-L} = \frac{[E_{L-L}]}{[E_{L-L}] + [E_{G-G}] + [E_{L-G}]} \tag{7A}$$

$$x_{G-G} = \frac{[E_{G-G}]}{[E_{L-L}] + [E_{G-G}] + [E_{L-G}]} \tag{8A}$$

$$x_{L-G} = \frac{[E_{G-L}]}{[E_{L-L}] + [E_{G-G}] + [E_{L-G}]} \tag{9A}$$

The ester bonds concentrations are calculated using:

$$[E_{L-L}] = \sum_{n=1}^{\infty}\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty} l\,[P_n(l,g,c)] \tag{10A}$$

$$[E_{G-G}] = \sum_{n=1}^{\infty}\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty} g\,[P_n(l,g,c)] \tag{11A}$$

$$[E_{L-G}] = \sum_{n=1}^{\infty}\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty} c\,[P_n(l,g,c)] \tag{12A}$$

The copolymer average molecular weights are estimated as follow:

$$\overline{M}_n = \frac{\sum_{n=1}^{\infty}\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n(l,g,c)]\;\; n\,M_{RU}}{\sum_{n=1}^{\infty}\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n(l,g,c)]} \tag{13A}$$

$$\overline{M}_w = \frac{\sum_{n=1}^{\infty}\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n(l,g,c)]\;\; n^2 M_{RU}}{\sum_{n=1}^{\infty}\sum_{l=0}^{\infty}\sum_{g=0}^{\infty}\sum_{c=0}^{\infty}[P_n(l,g,c)]\;\; n} \tag{14A}$$

The mass loss can be calculated from the following total mass balance that considers the dissolution of low molar mass species:

Considering the particle density ρ to be constant during degradation, the particle volume is calculated using:

$$\frac{dV}{dt} = \frac{1}{\rho}\frac{dM}{dt} \tag{16A}$$

Finally, the radius of the particle is estimated with the following equation:

$$R = \sqrt[3]{3V/4\pi} \tag{17A}$$

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