l-Lactide Additive and in Vitro Degradation Performance of Poly(*l*-lactide) Films

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A B S T R A C T

Polylactide as a valuable biodegradable polymer is being widely investigated with respect to its synthesis, physical properties, biodegradation and application. The aim of this study is to evaluate hydrolytic degradation of poly(*l*-lactide) (PLLA) in the presence of added *l*-lactide dimer. High molecular weight PLLA was synthesized in presence of stannous octoate through the ring opening polymerization of *l*-lactide. PLLA films, containing 0, 1, 3 and 5% (w/w) *l*-lactide (as additive), were prepared by solution casting. In vitro degradation of the PLLA matrices were carried out in distilled water at 37°C for the definite periods. The degraded polymer matrices have been characterized by SEC, SEM and DSC techniques after periods of 3 and 6 months degradation time. It was found that during the first 3 months of degradation period, the number average molecular weight ($\overline{M}_n$) of each PLLA film containing *l*-lactide reduced slower than the control sample. Also, it is shown that the films containing *l*-lactide have higher crystallinity and melting point in comparison with non-containing *l*-lactide samples. However, after 6 months, degradation rate of PLLA matrices containing *l*-lactide increased due to penetration of water by eluting and removal of *l*-lactide from PLLA matrices.

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INTRODUCTION

Polylactide (PLA) is one of the most common commercially available aliphatic polyesters that possesses excellent biocompatibility and biodegradability, as well as mechanical properties [1-3].

The main PLA applications include surgical implant devices, drug delivery systems, fibres, and packaging. In the past three decades PLA has been intensively studied because of its significant biodegradability in the human body under natural circumstances [4-7].

The biodegradation process of PLA in an aqueous medium takes place through hydrolytic scission of the ester groups. The carboxylic acid groups, the products of hydrolytic scissions auto-catalyze the process further, thus the hydrolysis rate increases exponentially with increases in degradation time [8]. Degradation behaviour of polymers can be optimized for

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different interesting applications.

Degradation of polyesters can be categorized into two groups on the basis of their mechanisms: bulk and surface degradation. PLA usually undergoes bulk degradation. In the case of polymers that undergo bulk degradation, the rate of water penetration into the matrix is faster than the rate of polymer degradation. The bulk degradation process is considered as homogeneous, in which degradation occurs at a uniform rate throughout the polymer matrix. In contrast, in polymers that undergo surface or heterogeneous degradation, the rate of water penetration into the matrix is slower than the rate of polymer degradation [9-11]. Bulk degradation rate is enhanced by auto-catalysis due to carboxylic end groups.

The biodegradation rate of polyesters depends on several factors, such as polymer crystallinity and purity, copolymer type (composition and initial molecular weight), sample size, pH and temperature of the degradation medium, processing and sterilization methods, as well as the presence of additives [11].

Several studies have been carried out for controlling the hydrolytic degradation of polyesters. It is of major importance to understand the degradation characteristics of these polymers in order to control degradation rates according to applications and purposes. Using additives for controlling polyester degradation is performed in order to reduce microclimate pH, a result of carboxylic acid end groups during polyester hydrolysis. Typical additives commonly used to improve the degradation of PLGA and PLA from literature are as follows: magnesium hydroxide, magnesium acetate, calcium carbonate, zinc carbonate, magnesium sulphate, ammonium acetate, carbon black and sucrose [12-15]. However, it is also reported that physico-chemical properties of the drug affect the polymer degradation in drug delivery processes [16,17].

PLLA is most widely synthesized through ring-opening polymerization of *l*-lactide [18,19]. Some residual amounts of *l*-lactide remain during the synthesis process. *l*-Lactide is a cyclic dimer obtained from the dehydration of *l*-lactic acid (Scheme I). In general, residual monomers in the polymeric matrix can serve as additives with plasticization roles, which
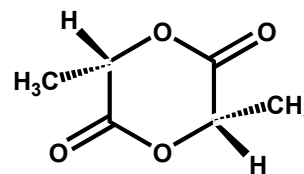
Scheme I. Chemical structure of *l*-lactide.

reduce mechanical strength and thermal stability. According to literature, the presence of *l*-lactide monomer in PLA as final product can also decrease latter's shelf life [20]. To our knowledge, there are very few reports available in the literature concerning the effect of lactide dimer (including *dl*- or *l*- configurations) on the degradation rate of PLA [21,22]. Based on analytical methods, the residual *l*-lactide concentration has been determined in PLA [23,25]. The reports included the in vitro degradation behaviour of polylactide and its copolymers, with glycolide and caprolactone. Also, PDLLA as entirely amorphous polyester and/or PLLA, and its copolymers in presence of nanoclays as additives, were studied in order to be used in packaging applications.

Many researchers have studied the degradation behaviour of these polymers in vivo as well as in vitro in order to obtain an in vivo-in vitro correlation [26-28]. For example, the changes in the mechanical properties of poly(lactide) were studied by Mainil-Varlet et al. [28]. In vitro degradation tests were carried out in static and pseudo-dynamic modes for low molecular weight poly-(lactide). It has been shown that the in vitro degradation results are in accordance with the in vivo study data.

The aim of the present work is to study the effect of *l*-lactide concentration on the degradation characteristics of poly(*l*-lactide) matrices. Samples as thin films were prepared by adding different amounts of *l*-lactide to the synthesized PLLA. *l*-Lactide polymer is selected as semi-crystalline polyester in order to receive detailed information on the in vitro degradation behaviour. The results of this study show that *l*-lactide as favoured additive can be used to control PLLA degradation due to its chemical compatibility with polymer matrix and non-toxic characteristics.

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EXPERIMENTAL

Materials

l-Lactic acid solution (85%) was supplied by Merck Company (Darmstadt, Germany). Tin (II) octoate (Sn(Oct)$_2$) was purchased from Sigma Company (St. Louis, Mo) and purified by vacuum distillation. Ethyl acetate, chloroform and hexane were obtained from Merck Company and used as received.

Polymerization

l-Lactide was prepared from *l*-lactic acid in our laboratory by the condensation polymerization method. Poly(*l*-lactide) (PLLA) was synthesized from *l*-lactide in presence of Sn(Oct)$_2$ as catalyst according to our previous article [11]. The synthesized PLLA (original) has $\overline{M}_n$ of 356 kDa with polydispersity index (PDI) of 1.88.

PLLA Matrice Preparation

PLLA Matrices were obtained by casting method. Synthesized PLLA, after recrystallization from ethyl acetate and *l*-lactide (0, 1, 3 and 5% w/w), were dissolved in chloroform, cast onto a flat glass plate, followed by the solvent evaporation at room temperature for one day, and then dried in vacuum for one week. The thickness range of the dried films was approximately 100-150 μm. The PLLA matrices containing 0, 1, 3 and 5% (w/w) *l*-lactide were labeled as control, S1, S3 and S5, in the given order.

In Vitro Polymer Degradation

The as-cast films (10 mm×30 mm×100 μm) were weighed and then placed in 10 mL distilled water at 37±0.5°C in sealed tubes.

The samples were allowed to stand in a thermostated oven for predetermined periods of time and were withdrawn from the media at each degradation time. All the samples were washed with distilled water and then dried in a vacuum oven at room temperature for one week.

Instruments and Measurements

The number average molecular weight and the polydispersity index (PDI) of the samples were determined by size exclusion chromatography (SEC) technique (Waters-150C) at 25°C. Measurements were carried out with a Waters-150C SEC system equipped with a Waters refractive index detector, serially connected in three columns, and Styragel HT columns. THF was used as an eluant at a flow rate of 1.0 mL.min^{-1} at ambient temperature for low molecular weight PLA (>50000). DMF was used for high molecular weight PLA (<50000) at 50°C.

Thermal analysis was evaluated by a Polylab 625 (UK) instrument in the temperature range of 20 to 200°C, and at scan speed of 20°C/min under nitrogen atmosphere. Crystallinity of the polymer (X_c%) was calculated from the enthalpy change using eqn (1) [29]:

$$X_c(\%) = 100 \times (\Delta H_m + \Delta H_c)/\Delta H100\% \tag{1}$$

Where $\Delta H100\%$ is the melting enthalpy of an infinitely large PLLA crystal and it is reported to be 93 J.g^{-1}.

Morphology of the films was characterized by scanning electron microscopy (SEM) using a Cambridge 360 scanning electron microscope. Dried samples were cut and sputter-coated with gold layer for 140 s (sputter coater E5200, BioRad, UK) and observed by SEM instruments.

RESULTS AND DISCUSSION

SEC Analysis

It is well known that the reduction of molecular weight of polyester takes place under hydrolysis condition due to the cleavage of ester bonds.

Table 1 presents changes in the number average molecular weight and the PDI of the PLLA matrices obtained from SEC analysis.

The results indicate that the control sample suffers 65% and 87% reduction in $\overline{M}_n$ after 3 and 6 months of degradation periods, respectively. The variety of PDI changes is large due to the decomposition of most high molecular weight polymers. However, it can be seen that, after 3 months of degradation time, the percentage of decrease in $\overline{M}_n$ for PLLA samples containing *l*-lactide is lower than the control sample. This value is reduced by *l*-lactide content so that there is only 34% reduction in $\overline{M}_n$ for S5.

The degradation process lasted for 6 months of

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Table 1. Effect of *l*-lactide on PLLA molecular weight after 3 and 6 months of immersion in aqueous media at 37°C: added with 1% (S1), 3% (S3), 5% *l*-lactide (S5), respectively.

Sample	3 months			6 months		
	$\overline{M}_n \times 10^{-3}$	Reduction percentage in $\overline{M}_n$	PDI	$\overline{M}_n \times 10^{-3}$	Reduction percentage in $\overline{M}_n$	PDI
Original	356	-	1.88	356	-	1.88
Control	126	65	3.11	47	87	1.32
S1	173	52	2.28	71	80	1.55
S3	181	49	1.65	79	79	2.00
S5	237	34	1.74	-	-	-

immersion time, as $\overline{M}_n$ was reduced by 80% for samples containing *l*-lactide. The degradation process for samples containing 5% additive (S5) was so high that they lost their integrity after 6 months and no SEC characterization could be performed.

During the first 3 months, the reduction in degradation rate of the samples containing *l*-lactide, in comparison with the control sample, could be explained as: *l*-lactide cyclic dimer molecules, which are at the surface of the film while touching aqueous medium, either adopt a dimer chain of the form HOCH(CH$_3$)C(O)OCH(CH$_3$)COOH or its monomeric form, i.e. lactic acid, hence reducing pH of the film surface. On the other hand, the pH of the internal media of the films is reduced due to degradation of esteric bonds at initial stages of hydrolysis and during the process of bulk degradation, which leads to formation of acidic climate inside the matrices. In this condition, the water diffusion basis of osmotic pressure is reduced, which reduces the hydrolysis of the esteric bonds and degradation rate of the matrices. Li et al. [30] observed similar results. They studied PDLLA degradation in acidic and neutral climates. With the changing pH of the degradation media from 7.4 to 3.7, the water diffusion into the polymeric matrices reduced 10 times. They related the additional water absorption at pH 7.4 due to osmotic pressure relevant to different pH levels of interior and exterior media of the matrices.

The results show that the rate of reduction percentage in $\overline{M}_n$ for control sample is lower than S1 and S2 (22% for control sample against 28% and
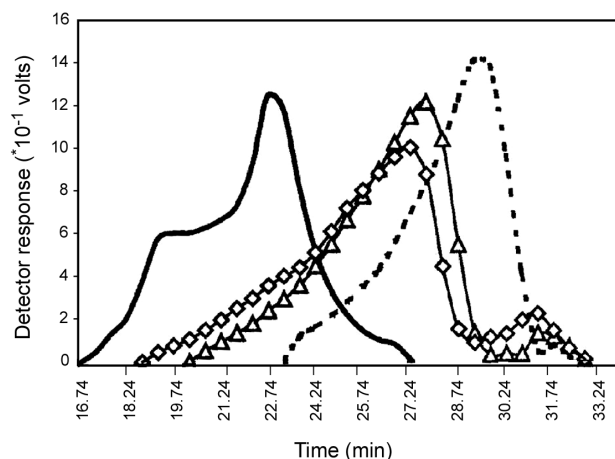
30% for S1 and S2, respectively) during the second 3 months. At this time it seems that *l*-lactide is eluted by aqueous solution from PLLA matrices. The resulting porous matrices could absorb more water. Therefore, more penetrated water molecules into matrices lead to more rapid degradation process for *l*-lactide loaded matrices.

Figure 1 shows SEC chromatograms of PLLA matrices with and without *l*-lactide after 3 months of degradation time. SEC Chromatogram of the control sample shows a bimodal distribution similar to that of the original sample. Comparison of these chromatograms proves that some of high and low molecular weight chains of PLLA have both shifted to lower molecular weight chain regions.

After 3 months of degradation time, SEC chromatograms of PLLA matrices containing *l*-lactide show normal distribution instead of the
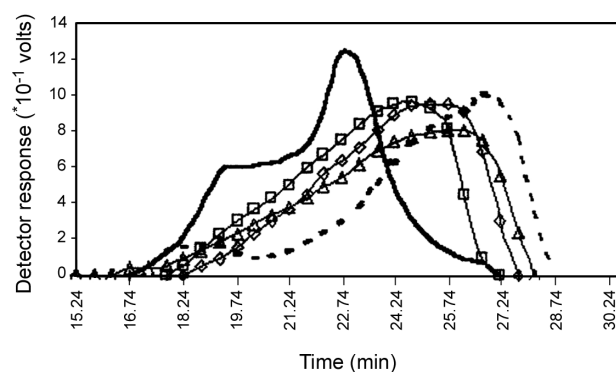
Figure 1. SEC Chromatogram of PLLA films after 3 months of immersion in aqueous media at 37°C: original (-), control (…), added with 1% *l*-lactide (Δ), 3% *l*-lactide (◇), and 5% *l*-lactide (□).

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Figure 2. SEC Chromatogram of PLLA films after 6 months of immersion in aqueous media at 37°C: original (-), control (…), added with 1% *l*-lactide (△), 3% *l*-lactide (◇).

original bimodal distribution, and their PDIs are narrow as well. The chromatograms show that higher molecular weight chains have been affected more by hydrolysis conditions than lower molecular weight chains.

After 6 months of degradation time, SEC chromatograms of PLLA matrices display a bimodal distribution (Figure 2). The degradation behaviour of

PLLA shows that the rate of degradation increases due to penetration of water by eluting and removing of *l*-lactide from PLLA matrices. Hence, the cleavage of ester bonds occurs randomly.

Morphology Study
The SEM photographs of PLLA films including control, S1, S3 and S5 samples after degradation are presented in Figures 3 and 4, which are compared with the original sample. Cross-section of the original film in SEM photograph shows a homogeneous bulky material (Figure 3a).
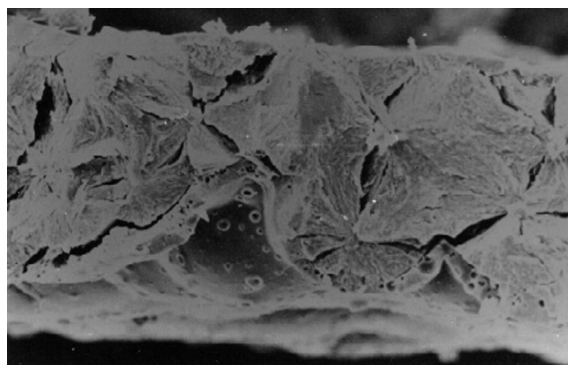
After 3 months, the cross-section of the control sample possesses some large holes due to bulk degradation (Figure 3b). The cross-sections of both S1 and S3 samples are homogeneous, which confirm the surface degradation is a predominant process (Figures 3c and 3d) and the bulk degradation is left intact. However, the SEM photograph of S5 sample shows some fine, small holes near the surface of the PLLA matrices (Figure 3e). It seems that the *l*-lactide concentration in this sample is high enough to form acidic microclimate, which causes auto-catalyzed hydrolyses of the ester bonds near the surface of the film.

(a)   (b)   (c)
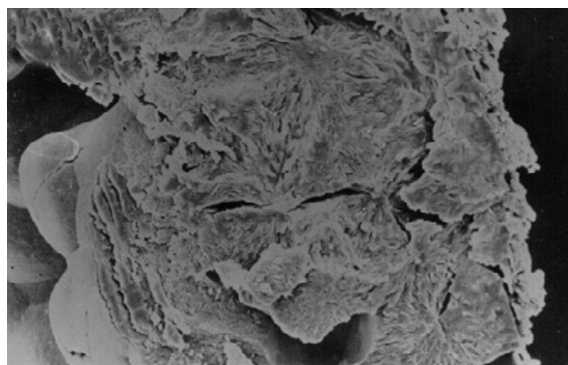

(d)   (e)
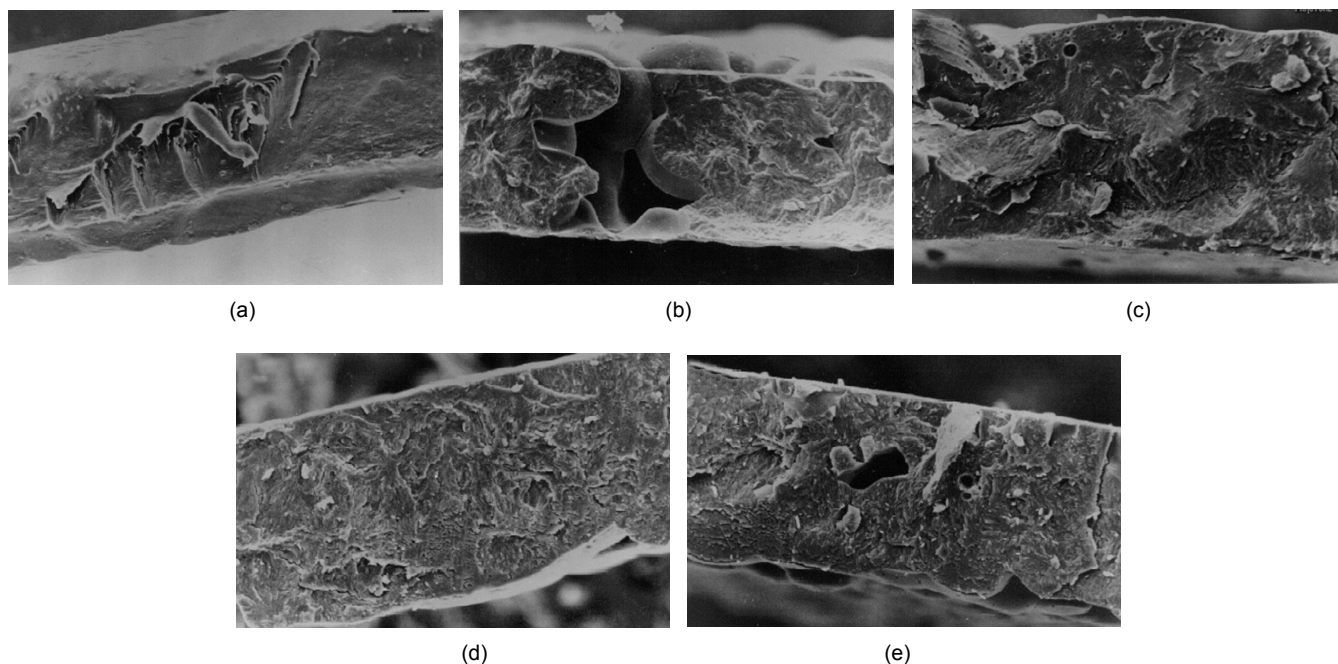
Figure 3. Cross-sections of PLLA films: original (a), control (b), 1% (c), 3% (d), 5% (e) added *l*-lactide after 3 months degradation.

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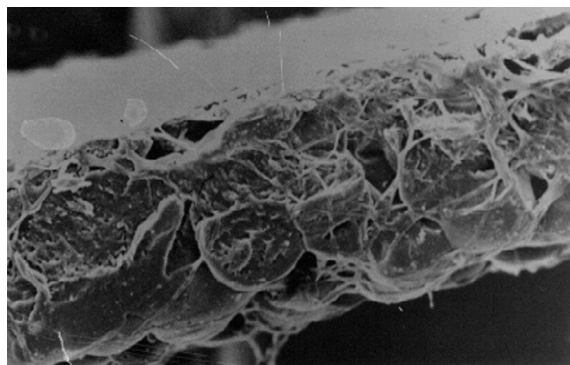
(a)

(b)

(c)

Figure 4. Cross-section of PLLA films: control (a), 1% (b), 3% (c) added *l*-lactide after 6 months degradation

Figure 4 shows SEM photographs of the cross-sections of the PLLA matrices after 6 months degradation time. The images show that the degradation of matrices has proceeded continuously. Some holes in bulk of matrix in the SEM photograph of control sample (Figure 4a) confirm that the degradation of ester bond is occurred randomly in amorphous and crystalline regions due to more diffusion of water. Some cracks are seen in photograph of S1 and S3 samples (Figures 4b and 4c)

which could be explained by the fact that initial degradation takes place in the amorphous regions of PLLA matrices, followed by a depletion of these regions that increases the overall crystallinity of the remained sample and creates some void spaces as cracks along the samples. As mentioned above, *l*-lactide can be removed from PLLA films during second 3 months due to higher exchange rate of *l*-lactides with water after lowering $\overline{M}_n$ of the matrix. Hence degradation process was occurred without *l*-lactide role in the second 3 months.

Thermal Analysis

Crystallinity ($X_c\%$) and the melting point are important properties of the polymer matrix, which affect its degradation rate. Table 2 presents thermal data obtained by DSC experiments for the original, control, S1, S3 and S5 samples after 3 and 6 months of degradation time.

These data show that the melting point (T_m) is reduced by increasing the degradation time for all samples, due to molecular weight reduction. However, samples containing *l*-lactide (S1, S3 and S5) have higher T_m than the control sample after 3 and 6 months periods. This could be related to the effect of *l*-lactide on the controlling degradation of the polymer. There is a slight incremental trend in the percentage of crystallinity ($X_c\%$) of the samples with increasing *l*-lactide contents, which could be related to depletion of amorphous chains with *l*-lactide concentration.

Finally, as a result, it can be explained that both the rate and manner of PLLA degradation is influenced by *l*-lactide presence during the first 3 months periods; the surface degradation is predominant. The existence of *l*-lactide in all PLLA films was definitely found to reduce the hydrolytic degradation. During the second 3 months periods, the bulk degradation is more distinct.

Based on our experimental results and the literature survey, presence of additives in matrices formulation is the most critical factor affecting the degradation process. The flexibility polymer chain of the sample also affects the degradation process. Chain restriction in the purified polymer has to be released before significant degradation occurs. However, chain restriction is more pronounced in the case of

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Table 2. Effect of *l*-lactide on PLLA crystallinity and melting point during 3 and 6 months of immersion in aqueous media at 37°C: added with 1% (S1), 3% (S3), 5% *l*-lactide (S5), respectively.

Sample	3 months		6 months	
	X_c (%)	T_m (°C)	X_c (%)	T_m (°C)
Original	42	179	42	179
Control	71	153	69	141
S1	63	163	74	149
S3	75	162	74	154
S5	78	162	81	154

semicrystalline polymer, e.g., poly(*l*-lactide). The researchers believe that the presence of low molecular weight substances and solvent make the polymer main chain more flexible which affect the degradation process. Zhang et al. [31] have found that due to plasticization effect of water on PDLLA, matrix degradation is much faster than pure PLLA. However, plasticization may not be significant in the case of PLLA due to the high crystallinity of this polymer. In comparison, if we consider lactide dimer as a low molecular weight substance, we also expect (like water) no profound incremental effect on the degradation rate of high crystalline PLLA due to plasticization.

Hyon et al. [22] have studied the effects of *dl*-lactide as remaining monomer on hydrolysis of poly (*dl*-lactide) films. They found that the existence of monomer in the polymer enhances hydrolytic degradation. Their results indicated that the difference in the *dl*-lactide content into the PDLLA films does not have any significant effect on a reduction of the molecular weight. They have claimed that added *dl*-lactide to the matrix is extracted under degradation condition. However, diffusion of water into matrix has enhanced the degradation rate. This difference between our observations and those of Hyon et al. may be due to their use of PDLLA as an amorphous polymer, in comparison to our PLLA with semi-crystalline characteristics.

In order to compare our results with those obtained by Zhang et al. [31] and Hyon et al. [22], it should be pointed out that there is not any plasticization effect of *l*-lactide on PLLA due to high crystallinity of this polymer. This may create a physical connection between PLLA chains and *l*-lactide. Thereby, the access of water to ester bonds is reduced, thus decreasing the degradation rate. Although it ought to be reminded that at the first 3 months periods the degradation rate is decreased, due to both reduction of osmotic pressure and water diffusion in the matrices.

CONCLUSION

The degradation of high molecular weight PLLA films containing different amounts of *l*-lactide was evaluated in aqueous medium. In vitro degradation at 37°C indicated that number average molecular weight of PLLA matrices was reduced slower than the control sample. SEM Images confirm that *l*-lactide reduces the bulk degradation. DSC Analyses showed that T_m is reduced and the percentage of crystallinity is increased slightly for PLLA matrices containing *l*-lactide, compared to control sample. The data showed that *l*-lactide as an acidic dimer does not accelerate the degradation rate, but it effectively controls the matrices degradation, especially in the earlier degradation times. As a result, *l*-lactide can be a suitable candidate for controlling PLLA degradation behaviour in medical devices or packaging technology since *l*-lactide is a non-toxic component excreted via the kreb's cycle as water and carbon dioxide.

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