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Hydrolytic degradation of poly(lactide-co-glycolide) films: effect of oligomers on degradation rate and crystallinity

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Dedicated to Prof. Dr. Hans Junginger on the occasion of his 60th birthday.

Abstract

Oligomers are thought to accelerate the hydrolytic degradation of devices prepared from poly(lactide-co-glycolide), PLGA, due to their increased number of carboxylic end groups. To experimentally verify this hypothesis, two D,L-lactic acid oligomers having molecular weights close to their critical limit of solubility were synthesized and incorporated into PLGA films in three concentrations (0, 10, and 30% w/w). All films were translucent, rather flexible and initially amorphous. With increasing oligomer concentration the glass transition temperature (T_g) and the molecular weight of films decreased prior to erosion. The degradation studies show that initial mass loss and water absorption are increased in oligomer-containing films as a function of average molecular weight and oligomer concentration. However, the incorporation of oligomers does not accelerate the degradation of films. By contrast, oligomer-containing films show extended lag phase until onset of polymer erosion. This was shown to be related to crystallization. Moreover, it was found that crystallization occurs earlier in oligomer-containing films and that the degree of crystallization is related to the average molecular weight of the oligomer. These findings bring new insight into the role of oligomers in the degradation process and can be used to explain why erosion in massive polymer devices occurs from the center to the surface.

Keywords: D,L-lactic acid oligomers; PLGA; Blends; Degradation; Crystallinity

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1. Introduction

Poly(lactide-co-glycolide) (PLGA) is one of the most frequently studied class of biodegradable polymers, especially for controlled delivery of peptides (Blanco-Preto et al., 2000; Cleland et al., 1997) and proteins (Bittner et al., 1999; Cohen et al., 1991). The major advantage of these polymers is that they do not require surgical removal after completion of drug release (Lewis, 1990).

The degradation of aliphatic polyesters has been investigated by numerous authors. It is generally accepted that PLGA, and their homopolymers polylactic acid (PLA) and polyglycolic acid (PGA) degrade via bulk hydrolysis of ester bonds (Kenley et al., 1987; Li et al., 1990a,b). Finally, their constituent monomers lactic and glycolic acid are formed which are eliminated by metabolic pathways (Wu, 1995). It has been shown that the degradation rate is affected by several physical and chemical factors, such as initial pH, ionic

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strength and temperature of external medium, copolymer ratio, molecular weight, crystallinity, and specimen size (Grizzi et al., 1995; Makino et al., 1986; Miyajima et al., 1997).

However, until now the degradation process has not been completely understood. From a general point of view, two phenomena are discussed. Firstly, degradation causes an increase in the number of carboxylic end groups, which are known to autocatalyze ester hydrolysis (Pitt, 1992; Shah et al., 1992; Vert et al., 1994a,b). Secondly, with increasing degradation time the amount of oligomer within the polymer matrix increases and soluble oligomers can escape from the whole mass of the device. In larger specimens only soluble oligomers which are located close to the surface can diffuse from the matrix before they are totally degraded, whereas oligomers located more inside the matrix remain entrapped and increase the acidity within the matrix. The encapsulated oligomers increase the concentration of carboxyl groups, which results in an increased degradation rate and autocatalysis with respect to the outer part of the specimen. These diffusion-reaction phenomena (Therin et al., 1992; Vert et al., 1998) lead to a differentiation between surface and center in larger specimens (Grizzi et al., 1995; Li et al., 1990a; Li et al., 1990b). Recently new parameters have been identified which contribute to the bulk erosion process (deJong et al., 2001; von Burkersroda et al., 2002).

Although oligomers play an important role in the complex bulk degradation mechanism only few authors have studied their influence on degradation kinetics (Grandfils et al., 1996; Mauduit et al., 1996). However, the molecular weight of low molecular weight polymers studied was far away from their critical limit of solubility (Braud et al., 1996; Vidil et al., 1995). Due to the fact that this parameter is important with respect to their effect on polymer degradation (Vert et al., 1994a,b) only limited information can be obtained from previous studies about the role of oligomers in this process.

For this reason a series of D,L-lactic acid oligomers were synthesized and characterized with regard to solubility, degradation rate, and degradation mechanism (Schliecker et al., 2003). Two oligomers having average molecular weights close to their critical limit of solubility were selected and incorporated into PLGA films in different concentrations (0, 10, and 30% w/w).

The intention of the present study was to test the hypothesis that oligomers autocatalyze the degradation process (Pitt, 1992; Shah et al., 1992; Vert et al., 1994a,b). If oligomers increase the polymer degradation rate the lifetime of the oligomer-containing PLGA films should be shorter than the lifetime of the oligomer-free PLGA film.

In consideration of the fact that until now crystallization caused by PLGA degradation has never been investigated as a function of the oligomer, the main interest was focused on this issue.

2. Experimental

2.1. Materials

D,L-lactic acid oligomers (OLA) were synthesized by polycondensation of 90% D,L-lactic acid aqueous solution without any catalyst as described previously (Schliecker et al., 2003). Briefly, 90% D,L-lactic acid aqueous solution was allowed to concentrate by gentle distillation of water. The reaction started at normal pressure and was then changed to reduced pressure after removal of water. The temperature was slowly increased to reach 140 °C after 3 days. The polydisperse oligomers obtained had weight average molecular weights ($\bar{M}_w$) of 1700 Da (OLA-1) and 3200 Da (OLA-2).

Uncapped poly(lactide-co-glycolide), Type Resomer® RG 503H, lactide/glycolide ratio 50:50, $\bar{M}_w$ 27.4 kDa, was purchased from Boehringer Ingelheim, Ingelheim, Germany. All organic solvents were HPLC grade and provided from Merck, Darmstadt, Germany.

2.2. Preparation of films

All films were prepared by a solvent-casting method. Briefly, 0, 10, or 30% (w/w) of OLA-1 or OLA-2 were added to PLGA and dissolved in 10 ml acetone. The solution was poured into a Teflon® mould and the solvent was allowed to evaporated at 8 °C for 24 h. The films were then dried under vacuum at room temperature to remove residual solvent until a constant weight was obtained. The resulting films had a thickness of about 200–250 μm and were cut into disks of 11-mm diameter using a punch. The final weight of films was 16.4±0.96 mg ($n = 30$).

2.3. Determination of molecular weight

The average molecular weight was determined by size exclusion chromatography (SEC) using polystyrene standards (M_w 400 to 2.5×10^6 Da; Polymer Standard Service, Mainz, Germany) for calibration. The samples were dissolved in tetrahydrofuran (THF) and filtered before injection. THF containing 0.1% trifluoracetic acid (TFA) was used as mobile phase at a flow rate of 1 ml/min. Two PSS® columns, 7.8 mm × 300 mm, with a pore size of 10^3 and 10^5 Å (Polymer Standard Service) connected in series were used to separate sample fractions at 30 °C. A differential refractometer (ERC 7510, Tokyo, Japan) was used for detection. Each sample was analyzed in duplicate and data were processed using ChromStar 4.1® software (SCPA, Stuhr, Germany).

2.4. Determination of glass transition temperature

Measurement of glass transition temperature (T_g) was performed using a differential scanning calorimeter (DSC 821, Mettler Toledo, Greifensee, Switzerland). Two samples (4–7 mg) were heated twice under nitrogen atmosphere. Thermograms covering a range of −20 to 200 °C were recorded at a heating or cooling rate of 10 K/min. Calibration of the system was performed using gallium and indium standards. The onset temperature, which corresponds to the temperature at which the signal first derives from baseline was used to describe the phase transition and was evaluated from the second heating run (STARe® software 6.0, Mettler Toledo, Greifensee, Switzerland).

2.5. X-ray diffraction (XRD)

X-ray diffraction patterns were recorded with an automatic powder diffractometer D 5000® (Siemens, Munich, Germany) using a Cu Kα radiation source (40 kV, 30 mA) and a nickel filter (1.54 Å). The scanning speed was 0.2 degree/min. The maximum scattering angle (2θ) was 35°. Separate blank patterns were recorded to allow subtraction of air-scattering and sample holder. Sharp peaks or broad halos were observed in diffraction pattern of crystalline or amorphous film, respectively. Crystallinity was calculated using DiffracPlus 3.0® software (Bruker, Rheinstetten, Germany).

2.6. Degradation studies

Weighed film specimens were placed in previously weighed glass vials and immersed in 12 ml phosphate buffer (0.05 M, pH 7.4 containing 0.05% benzalconium chloride and 0.1% sodium azide). The samples were incubated at 37 °C for 4 weeks without agitation. Six parallel samples were tested for each type of film. The buffer solution was replaced after each sampling time in order to prevent pH changes due to polymer degradation. At different time-intervals, the films were removed, washed three-fold with water, and weighed after removal of surface water. The samples were then dried for at least 48 h in a lyophilizer.

Water absorption and mass loss were calculated using the following equations:

$$\text{Water absorption (\%)} = \frac{100(W_w - W_d)}{W_d}$$

$$\text{Mass loss (\%)} = \frac{100(W_0 - W_d)}{W_0}$$

where W_w and W_d represent the mass of film in wet and dry state, respectively. W_0 is the film weight determined initially.

SEC and DSC were applied to monitor the degradation of films whereas XRD was used to detect crystallinity in degraded polymer films.

3. Results and discussion

3.1. Physicochemical characteristics of PLGA/OLA films

Using the solvent-casting technique, five different PLGA films were produced. The properties of applied materials are listed in Table 1.

In order to clarify the miscibility of PLGA and D,L-lactic acid oligomer all films were analyzed by

Table 1
Characteristics of materials used

Code	Molecular weight (kDa)		$\bar{M}_w/\bar{M}_n$	T_g (°C)
	$\bar{M}_w$	$\bar{M}_n$		
OLA-1	1.7	0.96	1.8	15.6
OLA-2	3.2	1.5	2.1	26.8
PLGA	27.4	16.0	1.7	44.5

Table 2
Compositions and characteristics of produced PLGA films

Code	Oligomer	Composition (%)		Molecular weight (kDa)		$\bar{M}_w/\bar{M}_n$	T_g(°C)
		PLGA	OLA	$\bar{M}_w$	$\bar{M}_n$		
Reference	None	100	0	24.7	14.4	1.7	44.3
PLGA/OLA-1 10%	OLA-1	90	10	19.6	5.6	3.5	40.7
PLGA/OLA-1 30%	OLA-1	70	30	16.8	3.3	5.2	34.0
PLGA/OLA-2 10%	OLA-2	90	10	20.9	7.1	2.9	42.6
PLGA/OLA-2 30%	OLA-2	70	30	18.4	5.4	3.4	36.5

DSC. The presence of a single T_g in all blends confirmed that PLGA and oligo-D,L-lactides are miscible at all the given composition. Miscibility was also observed at higher oligomer concentrations, however, the mechanical strength of resulting films was insufficient. All films were characterized prior to erosion and results are summarized in Table 2. The acronyms are reflecting the nature of each film matrix.

The addition of low molecular weight oligomers resulted in a decrease of the apparent molecular weight of the films produced. This results mainly from the mixing of different molecular weights and less from degradation caused by incorporated oligomers (Mauduit et al., 1996).

It was observed that the number average molecular weight ($\bar{M}_n$) of oligomer-containing films decreased more than $\bar{M}_w$. This can be explained by the fact that $\bar{M}_n$ depends more on the fraction of low molecular weight than on the fraction of high molecular weight.

In parallel the polydispersity index (PI) increased in oligomer-containing films. The PI is defined as the ratio of $\bar{M}_w$ to $\bar{M}_n$ and describes the broadness of molecular weight distribution within a polymer. From Table 2 it can be seen that PI is a function of oligomer loading and of the average molecular weight of oligomer. The higher the oligomer loading and the lower $\bar{M}_w$ of oligomer the higher PI of film.

3.2. *In vitro degradation profiles*

The films listed in Table 2 were incubated in phosphate buffer pH 7.4 at 37 °C. As degradation parameters, water absorption, mass loss (both gravimetrically), and weight loss (SEC) were monitored. Morphological changes were detected by DSC and X-ray diffraction.

3.2.1. *Visual examination*

All prepared films were initially translucent and elastic depending on average molecular weight and percentage of oligomer in the film matrix. After 1 day incubation all films were white and no longer translucent. With increasing incubation time the diameter of all films increased dramatically. After freeze-drying all films were wax-like, wavy, and brittle.

3.2.2. *Water absorption and glass transition temperature*

Water absorption was detected from the beginning of incubation in buffer (Fig. 1a). The initial amount of absorbed water was a function of average molecular weight of oligomer and their percentage in PLGA film. Water absorption of all films increased steadily with time because degradation causes an increase in polymer hydrophilicity. The incorporation of oligomers increases the hydrophilicity of the film due to their hydroxylic and carboxylic end groups. In consequence, oligomer-containing films absorbed more water than the oligomer-free film. For PLGA/OLA-1 10 and 30% the amount of water absorbed after 3 days was 186 and 240%, respectively, compared to 41% in oligomer-free film as reference (Fig. 1a). However, after 5 days water absorption was higher in the PLGA/OLA-1 10% film than in PLGA/OLA-1 30% film. We assume that with an increasing amount of oligomer incorporated the leaching of OLA-1 increases and consequently the hydrophilicity of the remaining film decreases. In consequence degradation of polymers of the same chemical composition but different molecular weights is slower for the higher molecular weight compound (Belbella et al., 1996).

Comparing OLA-1 and OLA-2 the first has a lower average molecular weight and glass transition

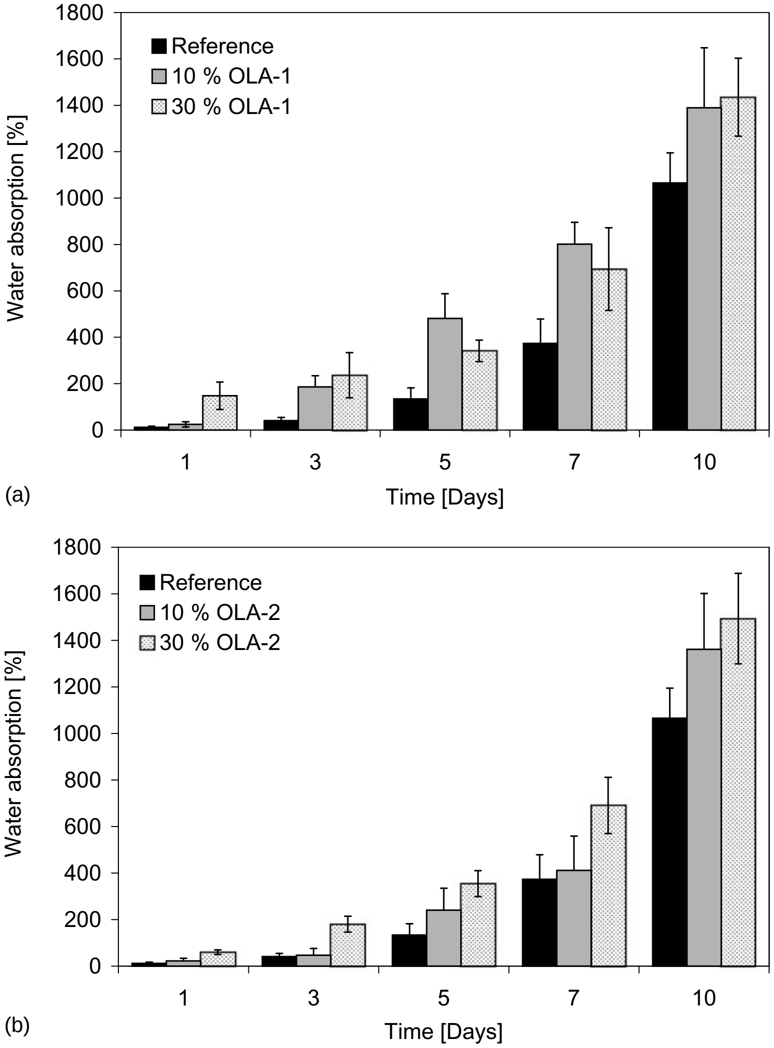

Fig. 1. Effect of addition of oligomers (0, 10, and 30%) on water absorption of PLGA 50:50 films during in vitro degradation: (a) for OLA-1 and (b) for OLA-2. The five types of films are presented in Table 2.

temperature whereas the latter is more lipophilic. Therefore initial water uptake was reduced in films containing OLA-2. For PLGA/OLA-2 10 and 30% the amount of water absorbed after 3 days was only 47 and 180%, respectively (Fig. 1b). As expected water absorption of PLGA/OLA-2 films was a function of oligomer loading over the whole time period.

In parallel to water absorption the glass transition temperature of films was monitored as a function of oligomer molecular weight and oligomer loading during degradation (Table 3). It is known that a decrease of $\bar{M}_w$ leads to a decrease of T_g which is attributed to an easier chain mobility in polymers (Avgoustakis and Nixon, 1991). From Table 3 it can be seen that T_g decreased directly after incubation in buffer with one exception due to polymer degradation and water absorption (Bodmeier and Chen, 1989; Vert et al., 1994a,b). For PLGA films, containing 30% OLA-1 or OLA-2 an increase of T_g was observed after 3 days. This was caused by diffusion of a major part of the incorporated oligomers out of the film. The remaining

Table 3
Glass transition temperature of degraded PLGA films

Sample	T_g (°C)							
	0 day	3 day	5 day	7 day	10 day	14 day	18 day	21 day
PLGA	44.3	40.7	39.2	37.2	35.1	36.3	41.7	45.5
PLGA/OLA-1 10%	40.7	39.0	37.6	35.3	33.9	41.1	46.2	46.2
PLGA/OLA-1 30%	34.2	40.3	37.2	34.6	33.8	29.7	44.4	40.5
PLGA/OLA-2 10%	42.6	38.5	37.7	36.6	35.6	31.9	43.9	39.1
PLGA/OLA-2 30%	36.5	39.7	38.5	38.0	36.3	38.3	41.7	40.2

higher molecular weight fraction is characterized by a higher T_g as known from literature (Heller, 1987).

Surprisingly T_g started to increase in all films after 10 or 14 days and reached values greater than those in the beginning (Seo et al., 2002). In parallel with the observed increase of T_g an endothermic peak was detected in the first run of DSC experiment (Fig. 2). This was assigned to the melting of crystalline domains formed during degradation (Seo et al., 2002; Therin et al., 1992). X-ray diffraction was successfully used to confirm this assumption. All results demonstrated that incorporation of oligomers in PLGA film clearly enhanced their hydrophilicity (Geze et al., 1999).

3.2.3. Crystallinity

In all films no crystallinity was found at the beginning of degradation studies. The XRD pattern of initial films is as an example shown for PLGA/OLA-2 10% (Fig. 3a). The obtained halo pattern is typical for an amorphous polymeric compound and confirmed that all films were initially amorphous.

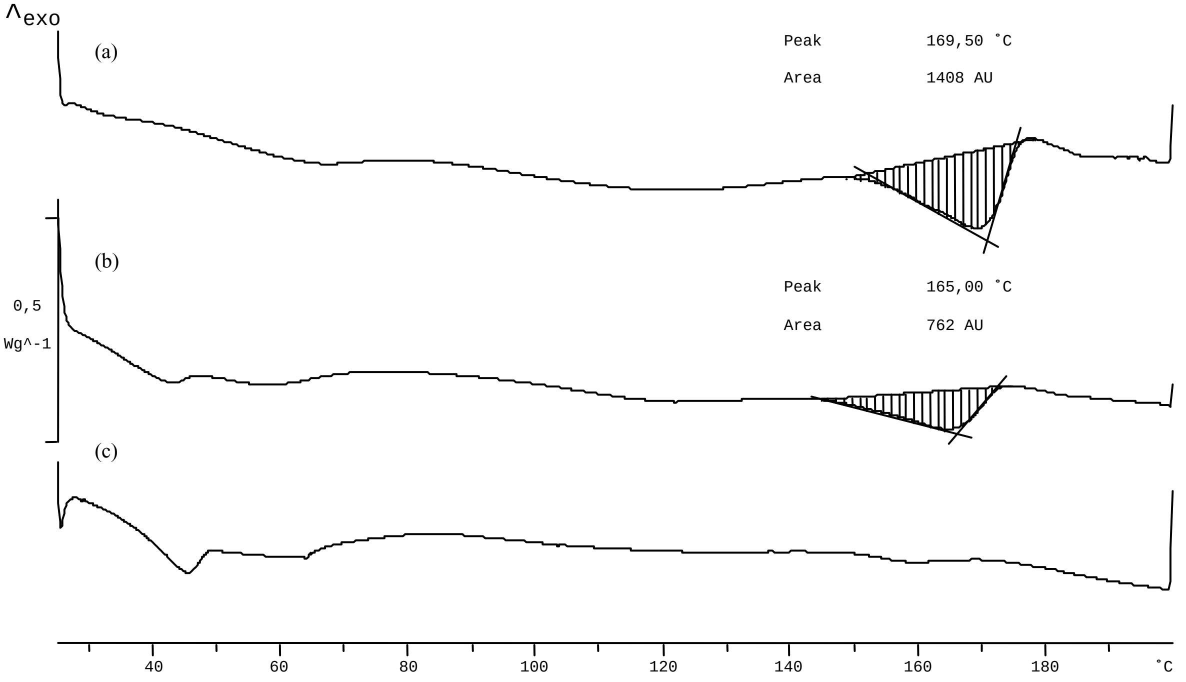

Fig. 2. DSC thermograms obtained after 14 days immersion in buffer pH 7.4: (a) PLGA/OLA-1 10%, (b) PLGA/OLA-2 10%, and (c) reference. AU means area units.

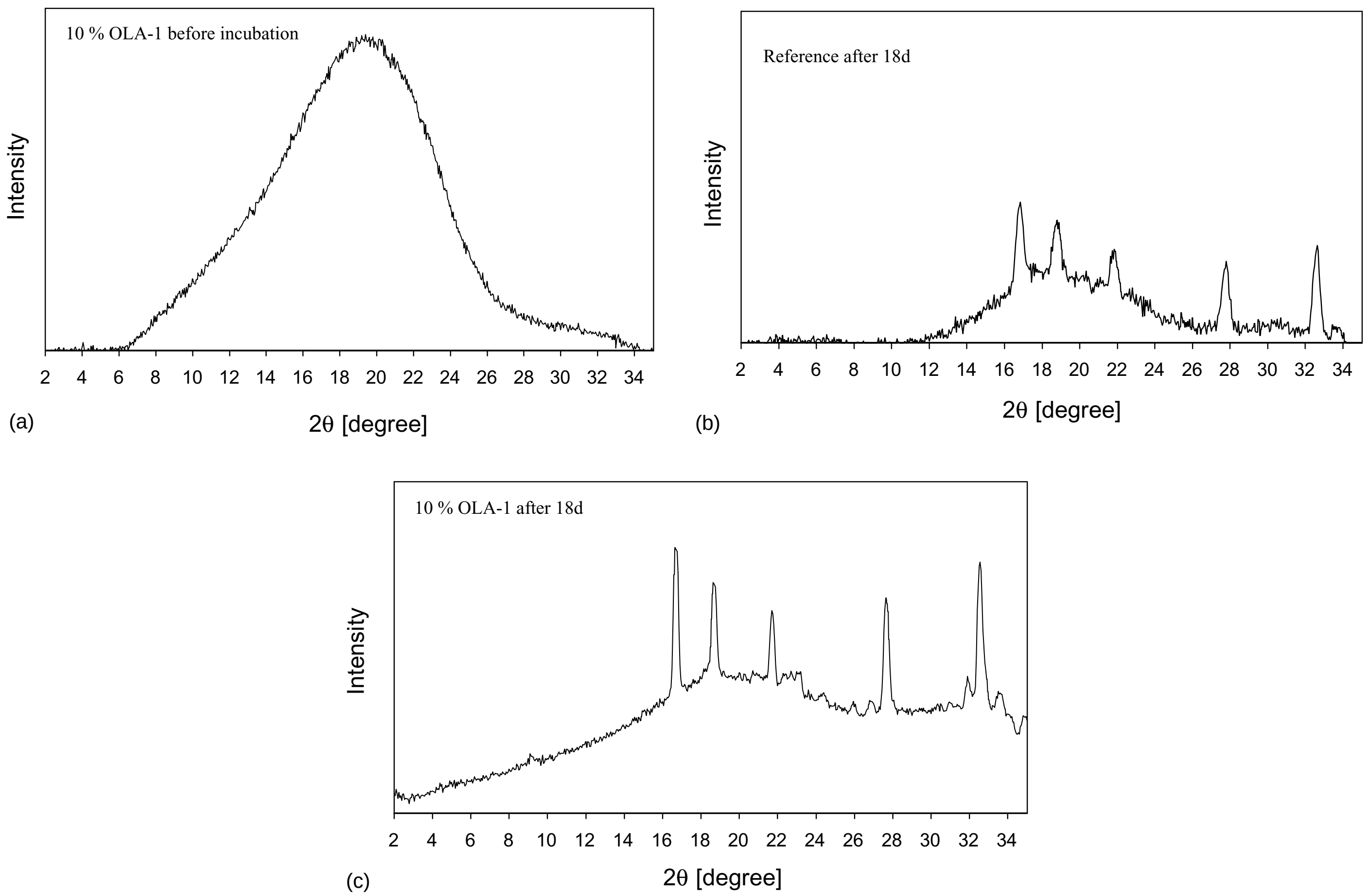

Fig. 3. X-ray diffraction pattern obtained for (a) PLGA/OLA-1 10% before immersion, (b) reference, and (c) PLGA/OLA-1 10% after 18 days immersion in buffer pH 7.4.

Table 4
Crystallinity of degraded PLGA films

Code	Crystallinity (%)			
	0 day	10 day	14 day	18 day
Reference	0	0	0	22
PLGA/OLA-1 10%	0	0	26	28
PLGA/OLA-1 30%	0	0	0	34
PLGA/OLA-2 10%	0	0	15	31
PLGA/OLA-2 30%	0	0	0	20

However, after 2 weeks of incubation crystallinity was detected in 10% oligomer-containing films indicating that oligomers contribute to morphological changes during degradation. This can be explained by the fact that with increasing water content, molecule chains in the polymer matrix become more flexible and mobile enough to crystallize under such conditions (Li and Vert, 1999).

It was found that the degree of crystallinity was higher in films containing OLA-1 ($\bar{M}_w$ 1700 Da) instead of OLA-2 ($\bar{M}_w$ 3200 Da) (Table 4). Based on this finding we conclude that the degree of crystallinity at this time point was depending on the average molecular weight of oligomer added.

With increasing incubation time crystallization occurred also in reference and 30% oligomer-containing films. The diffraction pattern of oligomer-free and oligomer-containing films obtained after 18 days of incubation are shown in Fig. 3b and c. Five sharp peaks were detected ($2\theta = 16.9, 18.9, 21.9, 27.7$, and 32.6°) which demonstrated the presence of crystalline domains within all polymer films. As expected crystallinity was higher in oligomer-containing films, confirming our hypothesis that oligomers affect directly or indirectly crystallization during degradation (Table 4). Unfortunately, after 3 weeks no X-ray pattern could be obtained due to the very small amounts of residual polymer mass.

The results show that the degree of crystallinity in oligomer-containing films depends on average molecular weight and percentage of incorporated oligomer. One can hypothesize that this finding is related to the differences in T_g and molecular weight between the two oligomers. These should influence the chain mobility and the reorganization of chains within the film (Göpferich, 1998).

However, crystallization was only observed at later stages of polymer degradation. The driving force for such morphological change is a closer packing of polymer chains with consequent enhancement of intermolecular attraction (Heller, 1987).

3.2.4. Mass loss and molecular weight changes

The $\bar{M}_w$ of oligomer-free film decreased with time (Fig. 4). In contrast $\bar{M}_w$ of oligomer-containing film

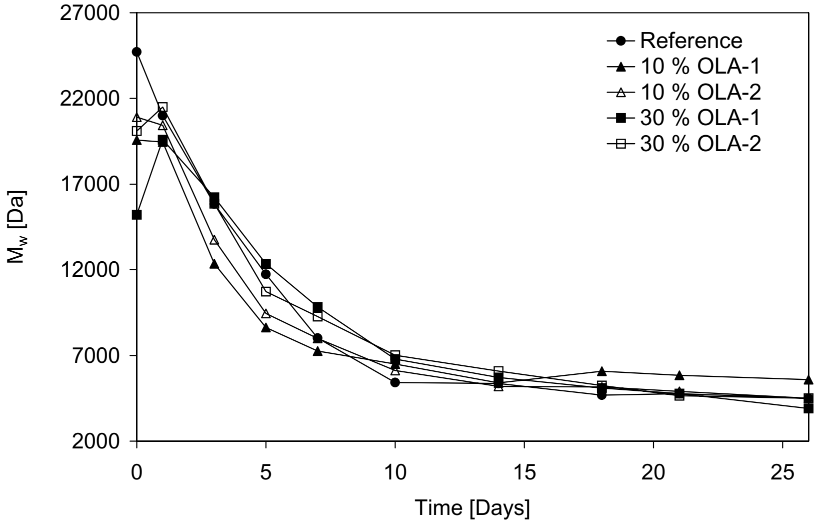

Fig. 4. Degradation profiles of oligomer-free and oligomer-containing films which are presented in Table 2.

was either unchanged (10% OLA) or increased (30% OLA) within the first 24 h. Due to the higher average molecular weight of OLA-2 the increase of $\bar{M}_w$ observed was smaller than for OLA-1 containing films. Beyond this $\bar{M}_w$ of all blends decreased with time as expected and reached a plateau after 2 weeks. This can be explained by the fact that films degrading for longer than 10 days in buffer, were partially insoluble in THF and thus excluded from analysis. In addition degradation products, which are small enough to be soluble, diffused out from the film and were also excluded from the analysis. As a consequence no further decline of $\bar{M}_w$ was observed until the end of the study. However, the best representation of the molecular weight progression is the PI.

As shown in Fig. 5a, the PI (closed symbols) of PLGA/OLA-1 10 and 30% decreased from 3.5 and 4.3 to 2.1 and 2.6, respectively, within the first 3 days. In contrast PI of reference increased slightly within these

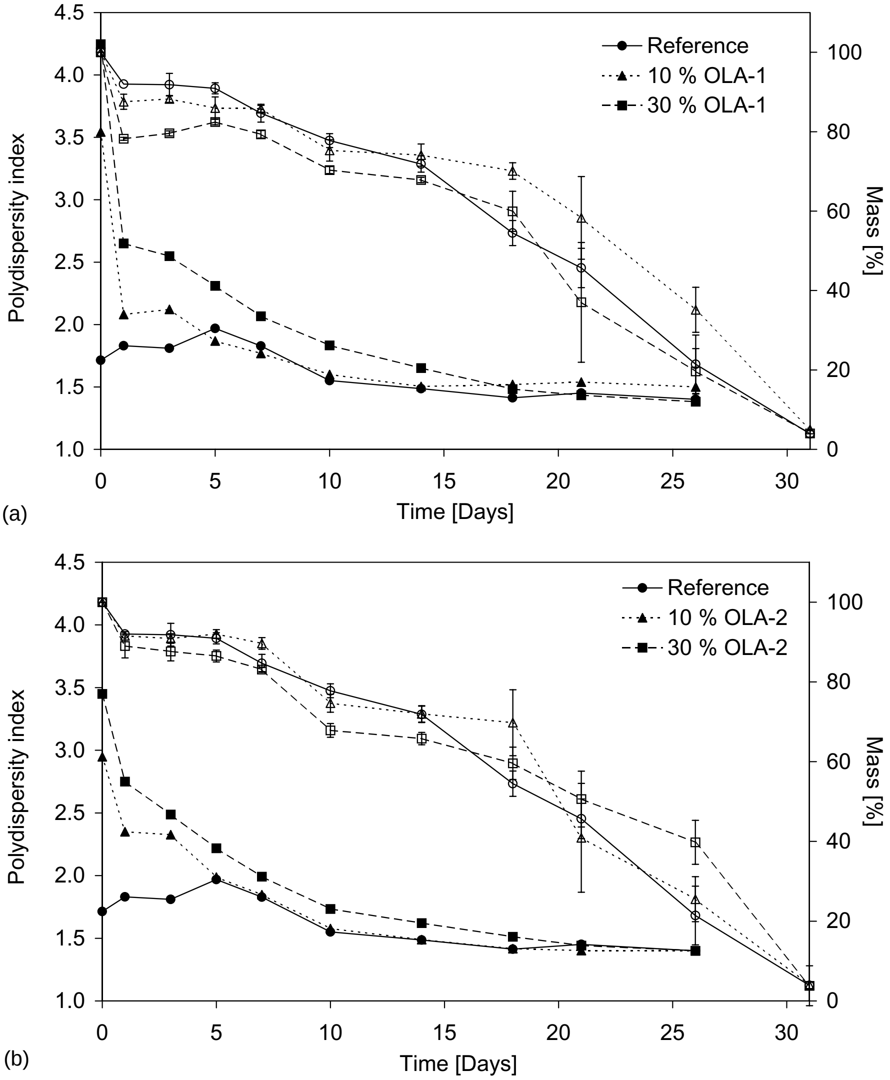

Fig. 5. Effect of addition of oligomers (0, 10, and 30%) on mass loss (open symbols) and polydispersity (closed symbols) of PLGA films: (a) PLGA/OLA-1 and (b) PLGA/OLA-2.

first days indicating that a smaller molecular weight fraction was formed.

Mass loss of films (open symbols, Fig. 5) was observed immediately after incubation in buffer. In general, mass loss was higher for films containing OLA-1 due to its smaller $\bar{M}_\mathrm{w}$ and consequently higher solubility. As expected initial mass loss increased with increasing amount of incorporated oligomer.

The initial mass losses were 8, 12, and 21% for reference, PLGA/OLA-1 10 and 30%, respectively (Fig. 5a). This can be assigned to the release of both residual acetone and incorporated oligomer. The initial mass loss observed, as well as the reduction of PI, confirmed our assumption that a great amount of low molecular weight fraction had left the film matrix within 3 days.

No remarkable mass loss was detected until the end of the week. After 10 days mass loss had reached 22, 24, and 30% compared to 15, 14, and 21% after 1 week for reference, PLGA/OLA-1 10 and 30%. The PI of these films decreased in combination with a loss of $\bar{M}_\mathrm{w}$, as shown in Fig. 4., indicating that most of the higher molecular weight fraction and incorporated oligomer were degraded and had partially left the film matrix. After 14 days mass loss of oligomer-free film was accelerated in comparison to 18 days found for PLGA/OLA-1 10 and 30% films.

In Fig. 5b mass loss and changes in molar weight distribution of PLGA/OLA-2 10 and 30% are shown. No differences were found between initial mass loss of reference and PLGA/OLA-2 10% compared to a slightly increased mass loss of PLGA/OLA-2 30% during the first 5 days. In parallel PI decreased from 2.95 and 3.45 to 2.3 and 2.5 for PLGA/OLA-2 10 and 30%, respectively. Mass loss increased after 1 week from 10 and 17% to 25 and 32% after 10 days for PLGA/OLA-2 10 and 30%, respectively, and was rather constant until day 18. From then on mass loss of PLGA/OLA-2 10 and 30% was accelerated which was also found for films containing OLA-1. At the end of the study the remaining mass of all films was less than 5%.

For all oligomer-containing films a prolonged lag phase up to the onset of accelerated mass loss was observed. This observation leads to the assumption that the duration of lag phase is influenced by oligomers. The extent upto which degradation is affected depends on both the average molecular weight of the oligomer incorporated and the amount of remaining oligomer.

4. Conclusion

The influence of the average molecular weight and the concentration of D,L-lactic acid oligomers added on the degradation rate and crystallinity of PLGA 50:50 film was investigated. The incorporation of polydisperse oligomers clearly enhanced the hydrophilicity of PLGA film. The initial mass loss and the amount of water absorbed were functions of average molecular weight and concentration of oligomer. For the same oligomer initial mass loss and water uptake was enhanced with increasing amount of oligomer in the film. However, an autocatalytic effect caused by the increased number of carboxylic end groups due to the incorporation of oligomers was not observed.

The degradation studies point to the fact that all initially amorphous polymer films changed into semi-crystalline films. Moreover, it was found that oligomers contribute to such morphological change due to their properties like low T_g, short chain length, low $\bar{M}_\mathrm{w}$, and hydrophilicity that facilitate crystallization. It was found that the time until crystallization occurred, as well as the degree of crystallization, depends on the average molecular weight of oligomers added and their remaining concentration in the film.

During this study no differentiation between surface and center was observed due to the small specimen size. However, the finding that oligomers cause direct or indirect crystallization during degradation of an initially amorphous PLGA matrix can be used to explain the surface/center differentiation in large specimens in accordance with described diffusion-reaction phenomena. In further studies the influence of oligomers on degradation rate and crystallinity in massive polymer devices will be assessed to test this hypothesis. A challenge for the future will be to visualize the distribution of oligomers incorporated during the degradation process.

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