In vitro degradation of thin poly(DL-lactic-*co*-glycolic acid) films

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Abstract: This study was designed to investigate the *in vitro* degradation of thin poly(DL-lactic-*co*-glycolic acid) (PLGA) films for applications in retinal pigment epithelium transplantation and guided tissue regeneration. PLGA films of copolymer ratios of 75:25 and 50:50 were manufactured with thickness levels of 10 μm (thin) and 100 μm (thick). Degradation of the films occurred during sample processing, and thin films with a higher surface area to volume ratio degraded faster. Sample weight loss, molecular weight loss, dimensional, and morphological changes were analyzed over a 10-week period of degradation in 0.2 *M* of phosphate-buffered saline (PBS), pH 7.4, at 37°C. All PLGA films degraded by heterogeneous bulk degradation. Sample weights remained relatively constant for the first several weeks and then decreased dramatically. The molecular weights of PLGA films decreased immediately upon placement in PBS and continued to decrease throughout the time course. PLGA 50:50 films degraded faster than 75:25 films due to their higher content of hydrophilic glycolic units. The results also demonstrated that thick films degrade faster than corresponding thin films with the same composition. This was attributed to the greater extent of the autocatalytic effect, which further was confirmed by heterogeneous gel permeation chromatograms. These studies suggest that the degradation rate of thin films can be engineered by varying film thicknesses. © 1999 John Wiley & Sons, Inc. J Biomed Mater Res, 46, 236–244, 1999.

Key words: poly(DL-lactic-*co*-glycolic acid) (PLGA); thin film; degradation; biodegradable polymer; retinal pigment epithelium transplantation; guided tissue regeneration

INTRODUCTION

Synthetic biodegradable polymers have become very important as biomaterials for applications in tissue engineering and controlled drug delivery. Among these materials, poly(DL-lactic-*co*-glycolic acid) (PLGA) copolymers have been widely utilized either as temporary scaffolds for cell transplantation to regenerate various tissues or as carriers for delivery of bioactive molecules.[1] They can be easily processed into desired configuration and their physical, chemical, mechanical, and degradative properties can be engineered to fit a particular need.[2] The biocompatibility of PLGA also has been demonstrated in many biological sites.[2]

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PLGA copolymers in the form of thin films previously have been shown to provide suitable substrates for human retinal pigment epithelium (RPE) cell culture *in vitro*.[3] RPE cells are essential in the maintenance of normal functions of photoreceptors.[4] Alteration in RPE structure and function is implicated in a variety of hereditary and degenerative retinal diseases, including age-related macular degeneration (ARMD) and Stargardt's disease.[5] Thin PLGA films therefore may be useful as temporary carriers for subretinal implantation of organized sheets of RPE. In addition, they potentially are applicable in guided tissue regeneration (GTR). PLGA films can serve as barriers to seal off a maxillofacial defect to prevent other tissues from interfering with the regeneration of periodontal ligament and alveolar bone.[6] This has a further beneficial effect due to the osteoconductivity of PLGA.[7]

Degradation properties are of crucial importance in biomaterial selection and design. The rate of degradation may affect a range of processes, such as cell growth, tissue regeneration, drug release, and host response. PLGA has been known to degrade by simple

hydrolysis of the ester bonds into lactic and glycolic acid, which are removed from the body by normal metabolic pathways. PLGA molecular weight, copolymer ratio, specimen size and configuration, and environmental conditions have been identified as important factors affecting the kinetics of degradation.[8–16] However, the degradation of thin PLGA films has not been studied in detail. This work evaluates the effects of film thickness on the *in vitro* degradation behavior of PLGA thin films. Sample weight loss, molecular weight loss, dimensional, and morphological changes were investigated throughout 10 weeks of degradation in simulated body fluids.

MATERIALS AND METHODS

Raw materials

Poly(DL-lactic-*co*-glycolic acid) (PLGA) of copolymer ratios of 75:25 (Birmingham Polymers, Birmingham, Alabama) and 50:50 (Medisorb®, Alkermes, Cincinnati, Ohio) were used in this study. The weight average molecular weights were 67,700 ± 1,100 [polydispersity index (PI) = 3.8 ± 0.2] for PLGA 75:25 and 43,900 ± 900 (PI = 4.1 ± 0.7) for PLGA 50:50, as determined by gel permeation chromatography. The PI is equal to the ratio of weight average to number average molecular weight (Mw/Mn).

Film fabrication

PLGA films were manufactured using a solvent casting technique, as previously described.[3] Briefly, PLGA solution in chloroform (Fisher Scientific, Pittsburgh, Pennsylvania) with a known concentration was prepared. A certain amount of this solution then was cast onto a glass coverslip (diameter 12 mm; Fisher) placed on a leveled table in the fume hood. The samples were air-dried for 20 h and subsequently placed under high vacuum (10 μm Hg) for 24 h to remove any remaining solvent. Four types of PLGA films prepared using this method are detailed in Table I.

The films (on glass) were soaked in distilled deionized water (ddH_2O) for 90 min, and then carefully lifted off the glass with a razor blade. The films subsequently were air- and vacuum-dried to obtain the initial samples.

TABLE I
Four Types of PLGA Films Prepared Using a Solvent Casting Technique

Film Code	PLGA Copolymer Ratio	Concentration of Casting Solution (mg/mL)	Volume of Casting Solution per Coverslip (μL)
F1	75:25	15	75
F2	75:25	88	115
F3	50:50	17.5	70
F4	50:50	110	115

Experimental design

The initial PLGA films were placed in glass scintillation vials (Fisher), each containing 20 mL of 0.2 *M* of phosphate-buffered saline (PBS; pH = 7.4; Gibco, Grand Island, New York). The samples were stored in a 37°C environment with shaking (~100 rpm) for various time periods up to 10 weeks. The PBS was changed every 8 h for the first 2 days, daily for the remainder of the week, on day 10 and day 14, and then weekly for the rest of the time frame. The pH of the PBS was monitored during the course of degradation. At the end of each time point, five samples were removed from PBS and the diameter measured immediately. These samples then were air-dried overnight and vacuum-dried for 24 h. The weight and Mw (and PI) of these samples then were recorded using five and three samples, respectively. All measurements were expressed as means ± standard deviation (SD) relative to the initial values.

Scanning electron microscopy (SEM)

Cross-sections of initial samples were gold-coated using a sputter coater (Pelco Sputter Coater 91000, model 3, Ted Pella, Redding, California) set at 20 mA for a total time of 120 s (coating thickness, approximately 40 nm). The sections then were observed with the SEM (JEOL JSM-5300 Scanning Microscope, Boston, Massachusetts) operated at 20 kV. Degraded samples were air- and vacuum-dried, and their surfaces were prepared for observation with the SEM.

Gel permeation chromatography (GPC)

The molecular weights of the initial films and degraded samples were determined using the GPC equipped with a differential refractometer (Waters, Model 410, Milford, Massachusetts) and an absorbance detector (Waters, Model 486). The samples were dissolved in chloroform (Sigma Chemical Co., St. Louis, Missouri) and eluted through a Phenogel 5-guard column (Model 1063376, 50 × 7.8 mm, 5 μm particle diameter, Phenomenex, Torrance, California) and a Phenogel 5-linear column (Model 106338, 300 × 7.8 mm, 5 μm particle diameter, Phenomenex) at a flow rate of 1 mL/min. Polystyrene standards (Polysciences, Warrington, Pennsylvania) were used to obtain a primary calibration curve. The values of the Mark-Houwink constants for PLLA ($K = 5.45 \times 10^{-3}$ mL/g and $\alpha = 0.73$) were utilized to determine the molecular weights of PLGA samples.[17]

RESULTS

Initial films

Using the solvent casting technique previously described, four types of PLGA films were manufactured (Table II). The weight average molecular weight (Mw)

TABLE II
Properties of PLGA Films at Day 0

Film Code	Weight (mg)	Mw (Da)	Mn (Da)	PI	Thickness (μm)	Diameter (mm)
F1	1.25 ± 0.02	62,900 ± 2,400	4,300 ± 650	14.8 ± 1.9	5–10	12
F2	12.76 ± 0.87	58,200 ± 1,900	9,200 ± 1,200	6.4 ± 0.8	85–100	12
F3	1.35 ± 0.01	37,300 ± 1,000	4,200 ± 500	8.9 ± 1.3	5–10	12
F4	13.35 ± 0.35	34,300 ± 300	7,600 ± 150	4.5 ± 0.1	85–100	12

and polydispersity indices (PI) of these films were determined after fabrication. The thin PLGA 75:25 films (F1) were Mw = 62,900 ± 2,400, PI = 14.8 ± 1.9; and the thick PLGA 75:25 films (F2) were Mw = 58,200 ± 1,900, PI = 6.4 ± 0.8. The thin PLGA 50:50 films (F3) were Mw = 37,300 ± 1,000, PI = 8.9 ± 1.3; and the thick PLGA 50:50 films (F4) were Mw = 34,300 ± 300, PI = 4.5 ± 0.1. Polymer degradation during processing resulted in a decrease in Mw and Mn and an increase in PI relative to the values of the raw materials. For the same polymer composition, the thin films had a lower Mn than the corresponding thick ones, indicating increased degradation of the thin films during sample preparation. The thickness levels were 5 to 10 μm for thin PLGA films and 85 to 100 μm for thick films. All the films maintained a diameter of 12 mm after fabrication.

Weight loss

The dynamics of weight loss for all the PLGA films were similar to each other [Fig. 1(a,b)]. Initially the weight remained relatively constant for several weeks; then a dramatic decrease in mass was observed. Thin PLGA 75:25 films (F1) maintained 89.0 ± 1.2% of the day 0 value after 6 weeks of degradation in PBS, but only 64.4 ± 1.9% remained at 10 weeks [Fig. 1(a)]. The weight for thick PLGA 75:25 films (F2) was 84.0 ± 8.0% at 6 weeks, which reduced to 28.9 ± 1.9% by 10 weeks due to a significant decrease in mass after 6 weeks [Fig. 1(a)]. Thick PLGA 50:50 films (F4) also showed faster mass loss than thin films (F3). After 6 weeks of degradation, 75.8 ± 4.3 and 34.6 ± 1.8% of their day 0 mass remained for F3 and F4, respectively [Fig. 1(b)]. No further measurements were performed for F3 due to the breakage of the thin PLGA 50:50 films during retrieval. In addition, PLGA 50:50 films (F3 or F4) showed faster and greater mass loss compared to PLGA 75:25 films (F1 or F2) of a similar thickness level.

Molecular weight loss

Unlike the profile for mass loss, the molecular weight of all the PLGA films decreased immediately after placement in PBS and continued to decrease

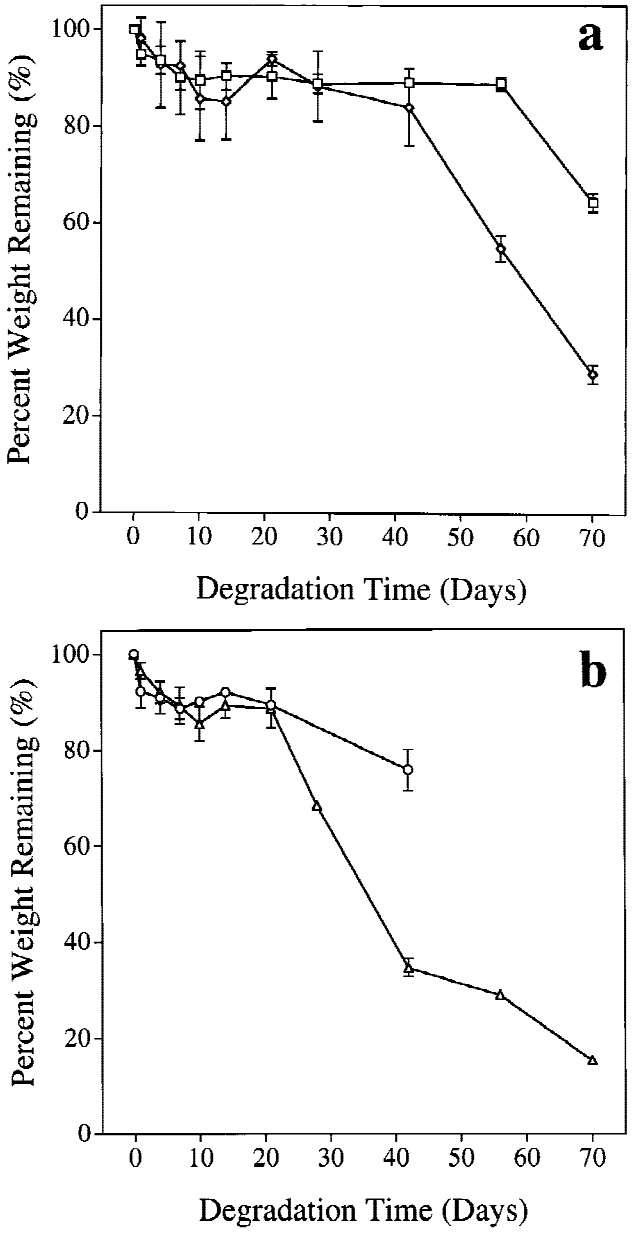

Figure 1. Percent of weight remaining compared to day 0 values as a function of degradation time for (a) PLGA 75:25 and (b) PLGA 50:50 films: F1 (□), F2 (◇), F3 (○), and F4 (△). The different types of PLGA films are presented in Table I. Error bars represent means ± SD for $n = 5$.

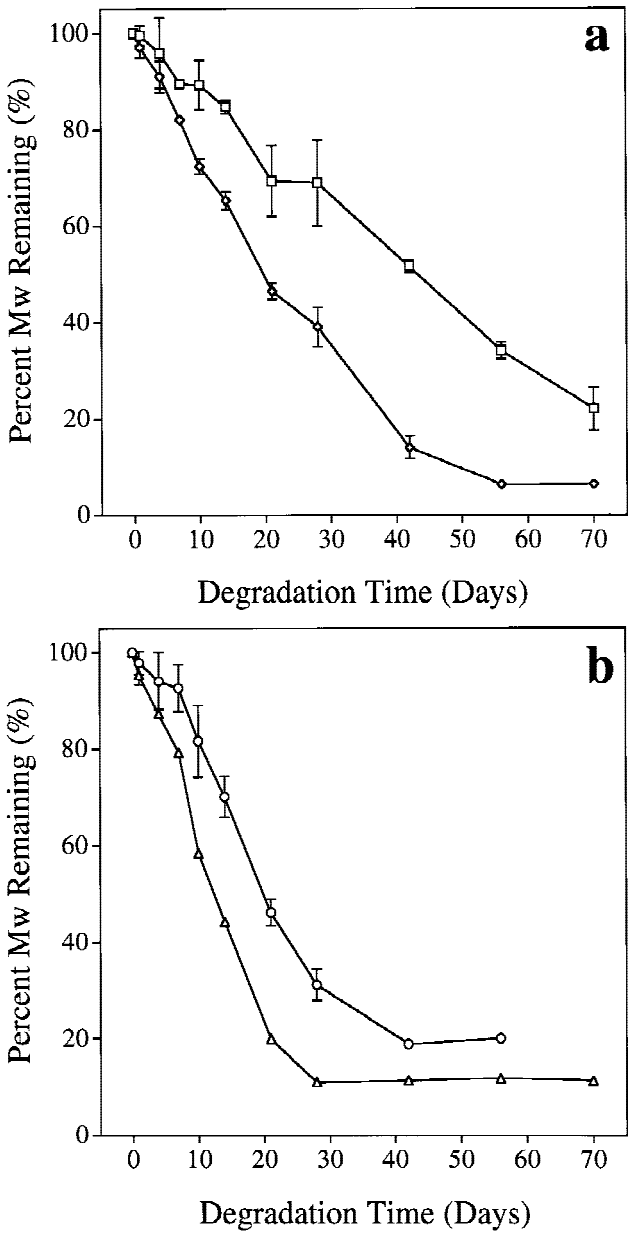

Figure 2. Percent of Mw remaining compared to day 0 values as a function of degradation time for (a) PLGA 75:25 and (b) PLGA 50:50 films: F1 (□), F2 (◇), F3 (○), and F4 (△). The different types of PLGA films are presented in Table I. Error bars represent means ± SD for $n = 3$.

throughout the time course [Fig. 2(a,b)]. Significant loss of Mw was observed for PLGA 75:25 films, with only 22.1 ± 4.5 and 6.4 ± 0.3% remaining for F1 and F2, respectively, after 10 weeks of degradation [Fig. 2(a)]. The Mw of F4 also decreased to 11.3 ± 0.6% of the day 0 value. The Mw of F3 was measured only up to 8 weeks (20.0 ± 0.5%). In addition, thick films (F2 or F4) showed a faster and greater decrease in Mw for both PLGA 75:25 and 50:50 compared to thin ones (F1 or F3). At 4 weeks, 68.9 ± 8.9% of its day 0 Mw remained for F1, and only 39.0 ± 4.0% remained for F2. Similarly, 31.1 ± 3.2 and 11.0 ± 0.1% of day 0 Mw remained for F3 and F4, respectively. The molecular weight loss for PLGA 50:50 films also was faster than it was for PLGA 75:25 films, provided the film thickness was similar.

The gel permeation chromatograms of the degraded PLGA 50:50 films suggest that degradation proceeded heterogeneously for both thin and thick films [Fig. 3(a,b)]. Similar chromatograms were observed for PLGA 75:25 (data not shown). Thin PLGA 50:50 (F3) had a broad single peak at 33,300 before degradation while bimodal peaks at 19,100 and 2,000 were observed for films after 21 days of degradation in PBS and 11,700 and 700 after 56 days [Fig. 2(a)]. This trend was not prominent for thick PLGA 50:50 films (F4) [Fig. 3(b)], probably due to the overlapping of peaks with close molecular weights. However, on day 56 a secondary peak was detected at 700 in addition to the main peak at 3,700. These results indicate the presence

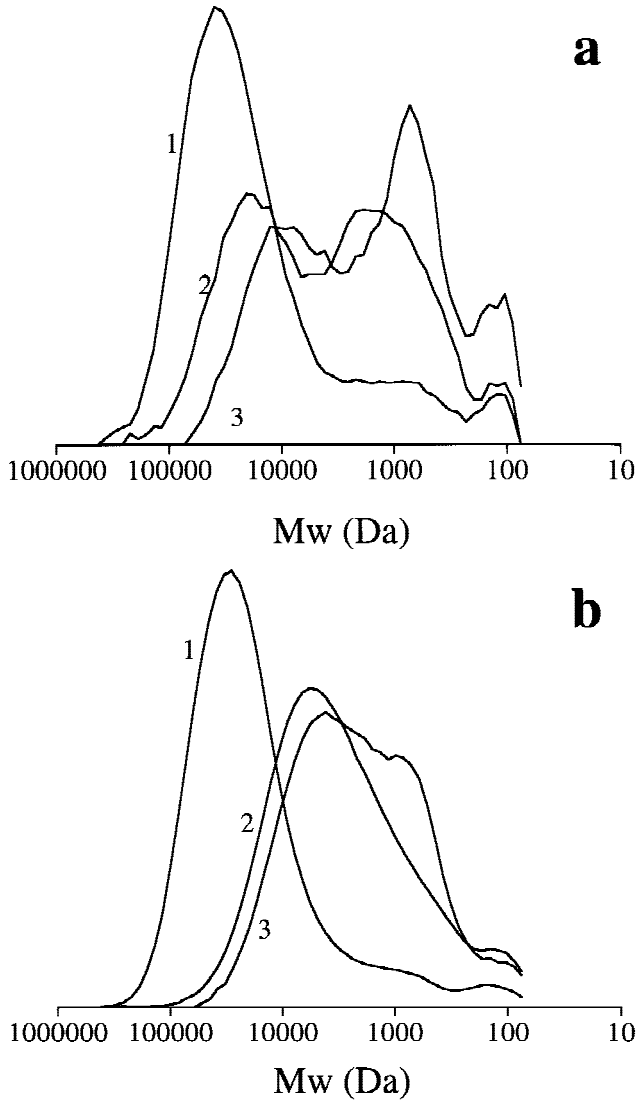

Figure 3. Gel permeation chromatograms of (a) thin and (b) thick PLGA 50:50 films showing the changes in the molecular weight distribution during degradation: at day 0 (1), after 21 days (2), and 56 days (3).

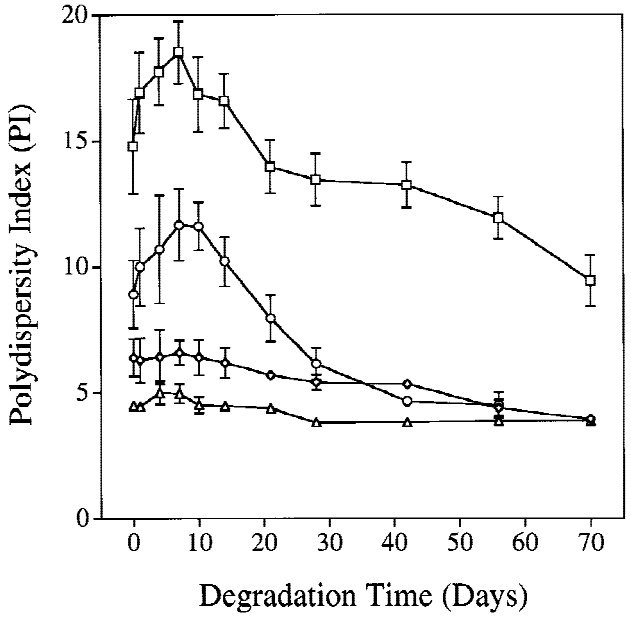

Figure 4. Variation of polydispersity indices of PLGA films with degradation time: F1 (□), F2 (◇), F3 (○), and F4 (△). The different types of PLGA films are presented in Table I. Error bars represent means ± SD for $n = 3$.

of both fast and slowly degrading domains, corresponding to the inner and surface film layers. A faster peak shift towards a lower molecular weight for F4 further supports the observation that thick films degraded faster than thin ones. In addition, the broad molecular weight distribution in the range of a few hundred to a thousand was seen for day 0 films compared to the narrower distribution of the raw material. The presence of secondary peaks for degraded samples in this range suggests that the change in molecular weight distribution during film processing follows the same mechanism as sample degradation in aqueous solution.

The polydispersity indices of the PLGA films also changed during degradation (Fig. 4). Thin PLGA films (F1 or F3) exhibited much broader molecular weight distribution than corresponding thick ones (F2 or F4) after processing. The PI of F1 and F3 increased to a maximum of 18.5 ± 1.3 and 11.7 ± 1.4 after 7 days and decreased gradually to 9.4 ± 1.0 (10 weeks) and 4.5 ± 0.5 (8 weeks), respectively. The initial increase in PI was a result of random chain scission during degradation, and the subsequent decrease was due to the decrease in Mw and the release of some of the degradation products. Little variation of PI was measured for thick films, and the PI of F2 and F4 decreased to 4.0 ± 0.2 and 3.9 ± 0.0, respectively, after 10 weeks.

pH variation

Little change in pH of the PBS solution was measured for up to 8, 6, 6, and 3 weeks for PLGA film types F1, F2, F3, and F4, respectively [Fig. 5(a,b)]. This was followed by a rapid drop in pH due to the release of acidic polymer degradation products in the solution. The time course of rapid pH drop corresponded roughly to the dramatic weight loss shown in Figure 1.

Dimensional change

All the fabricated PLGA films had diameters of 12 mm (the diameter of the coverslip used for solvent

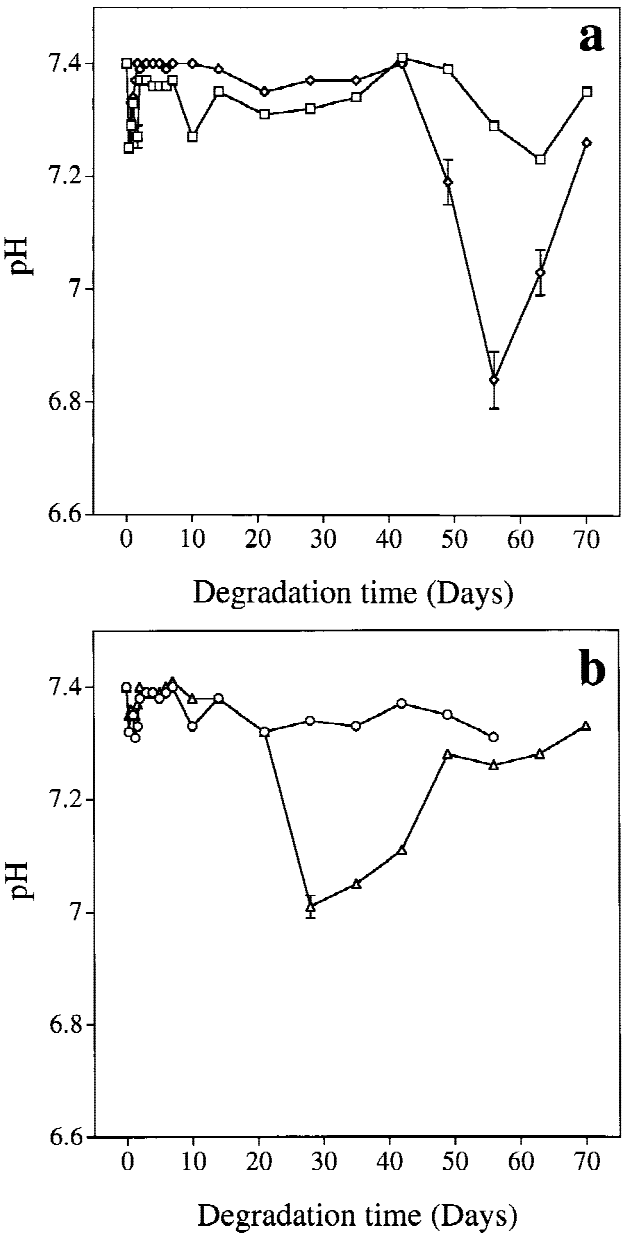

Figure 5. Variation of pH of the PBS solution with degradation time for (a) PLGA 75:25 and (b) PLGA 50:50 films: F1 (□), F2 (◇), F3 (○), and F4 (△). The different types of PLGA films are presented in Table I. Error bars represent means ± SD for $n = 5$.

casting). The diameter of thin PLGA 75:25 films (F1) decreased gradually during degradation, with a relatively faster decrease after 6 weeks [Fig. 6(a)]. A slight decrease in diameter also was observed for thick PLGA 75:25 films (F2) for the first 4 weeks, followed by a rather rapid decrease up to 8 weeks. A slight swelling of F2 samples then occurred, which was not seen for F1 samples due to the short time frame. By 10 weeks, the diameter had decreased to 87.6 ± 3.5 and 79.2 ± 7.6% of the initial value for F1 and F2, respectively. A relatively rapid initial shrinkage of both PLGA 50:50 films was measured [Fig. 6(b)]; and a slight swelling for thin films (F3) also was seen, followed by a rapid decrease in diameter. Significant swelling occurred at 6 weeks, probably due to the rapid release of degradation products. This phenomenon also was observed for thick films (F4) at an earlier stage of 4 weeks, followed by little change in sample diameter up to 10 weeks. The measurable sample diameter at the end of degradation was 9.7 ± 0.3 and 11.1 ± 0.4 cm for F3 (6 weeks) and F4 (10 weeks), respectively.

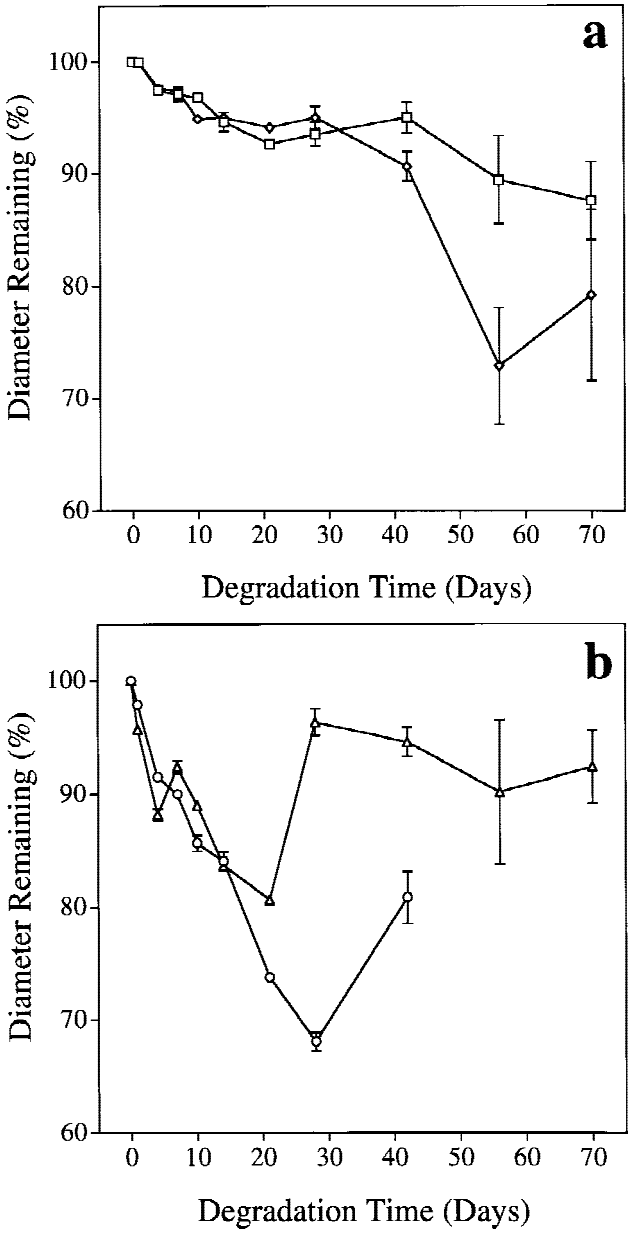

Figure 6. Variation of film diameter with degradation time for (a) PLGA 75:25 and (b) PLGA 50:50 films: F1 (□), F2 (◇), F3 (○), and F4 (△). The different types of PLGA films are presented in Table I. Error bars represent means ± SD for $n = 5$.

Film morphology

The gross appearance of all the PLGA films changed over time during degradation (Fig. 7). The initially transparent films became whitish due to water absorption. Thin and thick PLGA 75:25 films (F1 and F2) appeared whitish after 42 and 7 days, respectively. Thin PLGA 50:50 films (F3) remained clear until 28 days. Thick PLGA 50:50 films (F4) appeared whitish as early as 1 day in PBS. This change was reversible after vacuum drying until day 21, after which the absorbed water is believed to be bound to the polymer matrix.[18] All the films became more stiff and brittle after placement in PBS. However, F1 and F2 remained intact after 28 days while F3 and F4 started to break up from day 21 and day 10, respectively. The fragments of F3 could not be fully retrieved for further investigation beyond 6 weeks except for Mw measurement. Thick films (F2 and F4) changed to loose structures with macropores at the late stages of degradation.

All four types of PLGA films initially were nonporous, with smooth surfaces, as examined under scanning electron microscopy [representative micrograph

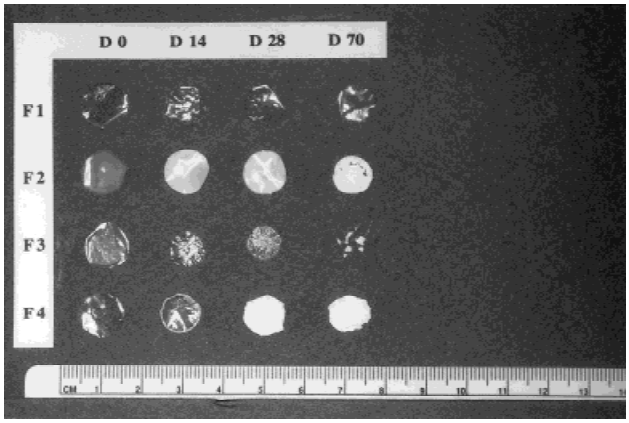

Figure 7. Gross appearance of dried PLGA films (F1, F2, F3, and F4) at day 0, after 14, 28, and 70 days of degradation in PBS. The different types of PLGA films are presented in Table I.

for F2 is shown in Fig. 8(a)]. However, extensive micropores were developed during degradation. The cross-section of F2 revealed numerous pores in the range of 10 to 40 μm after 42 days of degradation [Fig. 8(b)]. However, the top surfaces of both F1 and F2 were nonporous [Fig. 8(c,d), respectively]. The PLGA 50:50 films were more brittle compared to 75:25 films. The porous inner layers of F3 and F4 films were revealed in Figure 8(e,f), respectively, due to the breakage of some part of the surface layer. Part of the non-

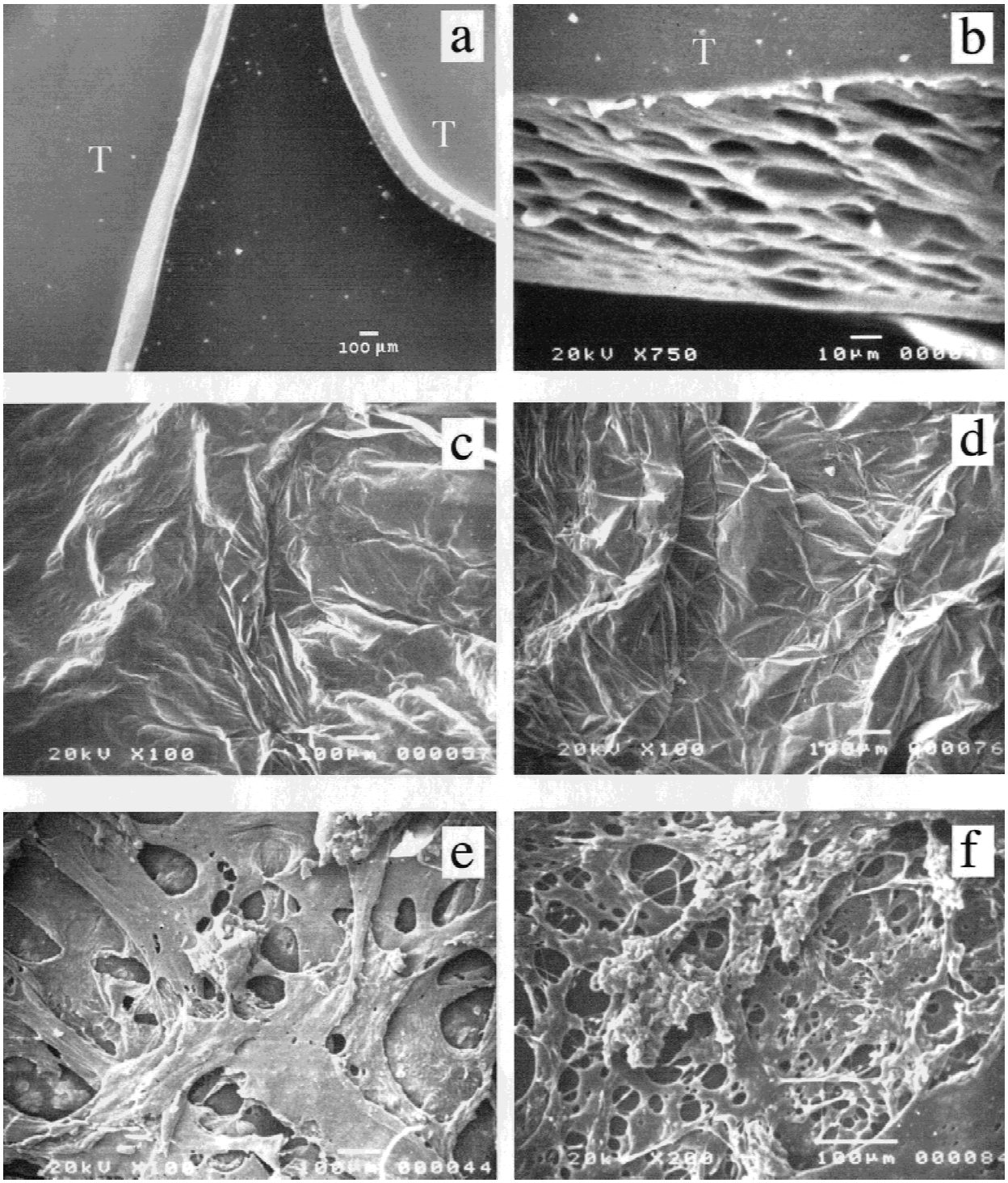

Figure 8. Scanning electron micrographs of four types of PLGA films: cross-sections of F2 at (a) day 0 and (b) after 42 days of degradation in PBS, and top surfaces of (c) F1, (d) F2, (e) F3, and (f) F4 on day 42. The different types of PLGA films are presented in Table I. The micrographs (a) and (b) were taken at an angle to show also the top surfaces (T) of the films.

porous skin clearly can be seen in Figure 8(f). The inner layer of F4 exhibited pores of a broad size, ranging from a few to 100 μm. These results further suggest the heterogeneous bulk degradation of the PLGA films.

DISCUSSION

This study was designed to measure the changes in sample weight, molecular weight, dimension, and morphology of thin PLGA films over a 10-week period of *in vitro* degradation in PBS to determine the effects of copolymer ratio and film thickness on degradation. Specifically, four types of PLGA films of copolymer ratios of 75:25 and 50:50, with thickness levels of 10 and 100 μm were used for investigation.

Changing the PLGA copolymer ratio from 75:25 to 50:50 without altering the film thickness increased degradation. The higher content of hydrophilic glycolic units in PLGA 50:50 facilitated the absorption and diffusion of water and thus hydrolysis of the ester bonds. This is consistent with the results published by other investigators using different specimen configurations.[8,9]

The effects of film thickness on the degradation profiles of both PLGA 75:25 and 50:50 films depended on the material treatment. Degradation occurred during film fabrication due to the sample's exposure to air (solvent casting) and water (film lifting). Thin PLGA films degraded faster than thick ones with the same copolymer ratio because thin films had a greater surface area to volume ratio and thus a greater extent of water uptake. This was confirmed by the observation that at day 0, the thin films (F1 or F3) had a much broader molecular weight distribution than the corresponding thick films (F2 or F4). In addition, although the processed thin films had a slightly higher Mw, their Mn was significantly lower than the thick ones. These results also suggest that for thin PLGA films, the fabrication process should be carefully controlled since it has a great effect on film degradation.

Increasing the film thickness level from 10 to 100 μm, however, resulted in faster degradation in PBS over the 10-week period for both PLGA 75:25 and 50:50 films. This was evident from the accelerated weight and molecular weight loss profiles. The faster degradation of thick films can be explained by the greater extent of the autocatalytic effect. The intermediate degradation products were trapped inside the film before their molecular weights decreased to a critical value of about 1,100 and became soluble in water.[13] The accumulation of carboxylic groups over time in the specimen center led to faster central degradation and therefore to overall film degradation. This was less evident for thin films, as expected. The differences in initial molecular weights were taken into account by using the normalized weights and molecular weights relative to the day 0 values.

All the PLGA films degraded by heterogeneous bulk degradation. The bimodal GPC curves may be explained by the presence of slowly degrading surface layers and fast-degrading central layers, which were confirmed by their differential morphology under SEM. This phenomenon previously has been demonstrated using large parallelepiped specimens of 2 mm in thickness.[10] The difference in degradation between specimen surface and center typically results in an empty shell with a thickness of about 200 μm after several weeks of degradation. In this study, much thinner PLGA films with thickness levels of 10 and 100 μm were used, and the autocatalytic effect was still observed.

A qualitative model based on diffusion-reaction phenomena previously was proposed for the degradation of poly(α-hydroxy esters).[19] The model claims that heterogeneous bulk degradation, and thus skin-layer formation, occurs only when the size of the specimen is above a critical value. The critical thickness (or diameter) for poly(DL-lactic acid) (PDLLA) films (or microspheres) was determined to be 200–300 μm.[19] This conclusion was based mainly on the observation of unimodal molecular weight distribution during degradation when sample size was smaller than the critical value.

The results obtained from our study do not support this model. This may be because of the different polymer used. However, other studies using PDLLA and PLGA microspheres did not agree with this model either.[13,20,21] Heterogeneous bulk degradation was observed for PDLLA and PLGA 50:50 microspheres with diameters of less than 10 μm.[13,20] In addition, the same phenomenon was demonstrated for both PLGA 75:25 and 50:50 microspheres with diameters ranging from 50 to 70 μm.[21]

Degradation properties of thin PLGA films are important for their applications. Based on Mw, the half-lives of F1, F2, F3, and F4 are 6, 3, 3, and 2 weeks, respectively. Thin PLGA 50:50 could be used as temporary carriers for subretinal implantation of organized sheets of retinal pigment epithelium. These films would limit distortion of the retina and minimize the amount of degradation products released. Compared to thin PLGA 75:25 films, which also were shown as suitable substrates for RPE cell culture *in vitro*,[3] their rapid degradation would be beneficial in allowing the re-association of regenerated RPE layers with the surrounding tissues. In addition, all biodegradable PLGA films potentially are useful as barriers in guided tissue regeneration. The selection of a particular film for the regeneration of periodontal ligament or alveolar bone depends mainly on its degradation rate. A significant amount of tissue needs to be

regenerated before the polymer is completely degraded.

CONCLUSIONS

Poly(DL-lactic-*co*-glycolic acid) films were formulated with varying copolymer ratios and thickness levels for an *in vitro* degradation study. Both parameters were seen to have a significant effect on the weight loss and molecular weight loss over 10 weeks of degradation in PBS. PLGA 50:50 degraded faster than 75:25 films of similar thickness. Increasing the thickness levels from 10 to 100 μm accelerated both the weight and the molecular weight loss over this time frame. All the PLGA films degraded by heterogeneous bulk degradation. The differential morphology of the porous inner layer and the nonporous surface layer was due to autocatalysis in the specimen center. These thin PLGA films potentially may be useful in retinal pigment transplantation and guided tissue regeneration.

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