Poly(DL-lactide)/Poly(ethylene glycol) Copolymer Particles. I. Preparation and Characterization

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SYNOPSIS

In this study, poly(DL-lactide)/poly(ethylene glycol) (PDLLA/PEG) copolymers were synthesized. First, PDLLA homopolymers with three different molecular weights (Mw_n: 7,300, 12,100 and 21,900) were synthesized by the ring opening polymerization of the dimer (i.e., DL-lactide) by using stannous chloride as catalyst. Average molecular weights of PDLLAs were determined by gel permeation chromatography (GPC). They were characterized by Fourier transform infrared and differential scanning calorimetry (DSC). These PDLLA homopolymers were then transesterified with PEG with a molecular weight range of 3,300–4,000. By changing the ratio of PEG to PDLLA, block copolymers with different chain structures were synthesized. DSC and GPC studies were performed to characterize these PDLLA/PEG copolymers. PDLLA and PDLLA/PEG particles in the size range of 2–10 μm were prepared by a modified solvent evaporation technique by using methylene chloride as solvent and methyl cellulose as emulsifier within the aqueous dispersion medium. Particle size was controlled by changing the solvent/polymer ratio, PDLLA molecular weight, and PEG content. Degradation of polymeric particles was investigated in a phosphate buffer at pH 7.4 and at 37°C. Particles prepared with low-molecular-weight PDLLAs degraded much faster. Introduction of PEG within the polymeric matrix caused a pronounced increase in the degradation rate. Bulk degradation was the dominant mechanism. © 1996 John Wiley & Sons, Inc.

INTRODUCTION

Poly(α-hydroxy acids) is the most widely known synthetic polymer family used for the production of biodegradable biomaterials. Some members of this family, namely poly(lactic acids) (or polylactides) (PLA) and poly(glycolic acids) (or polyglycolides) (PGA), and their copolymers have been studied intensively as biomaterials.[1-7]

In our recent studies, we attempted to synthesize homopolymers of lactides and/or glycolides, and their copolymers with poly(ethylene glycol) (PEG), and to process these polymers into particle or fiber forms for diverse biomedical applications including drug delivery systems.[8-16]

PLA and PEG copolymers were studied by a number of investigators. Zhu and colleagues performed the pioneering investigations on these types of copolymers.[17-19] They synthesized PLA/PEG copolymers firstly by using DL-lactide and ethylene oxide as the monomers. Later, they attempted to prepare PLA/PEG from DL-lactide and PEG. They were also able to synthesize star-shaped PLA/PEG copolymers by using star-shaped PEG and DL-lactide as the starting materials and stannous octoate as the catalyst. The average molecular weights and PEG contents of the copolymers that they produced were around 2×10^4 and 10%, respectively. Cohn and Younes also investigated PLA/PEG block copolymers, which were prepared from L-lactic acid and PEG, with antimony oxide and phosphoric acid as the initiators.[20] Their copolymers contained high amounts of PEG on the backbone (up to 70% molar ratio), therefore, they showed substantial hydrophilicity. Deng and coworkers reported the synthesis of PLA/PEG copolymers with low molecular weights (about 8,000) with PEG contents around 5% by using DL-lactide and PEG as the starting materials,

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Journal of Applied Polymer Science, Vol. 61, 1439–1446 (1996)
 CCC 0021-8995/96/091439-08

with a variety of initiators.[21] Carrai and Tricoli synthesized PLA/PEG copolymers by using L-lactide and PEG as the starting materials without using any initiator, in order to enhance the biocompatibility of the materials.[22] The PLA/PEG copolymers with high molecular weights (about 2×10^5) and high PEG content (up to 70% molar ratio) were reported. Jedlinski and colleagues reported the synthesis of triblock ABA copolymers by using poly(ethylene glycol–alcoholates) as the macroinitiator and L-lactide as the monomer.[23] Hu and Liu conducted detailed investigations on the morphology of PLA/PEG copolymers prepared from L-lactide and PEG, with stannous octoate as the initiator.[24] Recently, Gref and coworkers reported preparation of injectable nanoparticulate carriers made of copolymers containing about 10% PEG.[25]

In our recent studies related to the design of polymeric carriers for drug delivery, firstly, we prepared rifampicin containing poly(D,L-lactide) (PDLLA) homopolymer particles and investigated their drug loading and *in vitro* drug release characteristics in detail.[9,11,13] We also synthesized PDLLA/PEG copolymers from PDLLA and PEG by transesterification. In order to obtain micelle-forming copolymers we kept the molecular weight of PDLLA lower than 2,000 and the PEG content higher than 15%. In that novel approach, we investigated adramycin loading and release from these micelles.[8,12,14] In the present study, we aimed to prepare PDLLA/PEG copolymeric particles (not in micelle form, but in particle form) as drug carriers. Studies related to drug (i.e., rifampicin) loading and release were presented elsewhere.[26] Here, we report our results related to preparation and characterization of homo- and copolymers, and their particles.

MATERIALS AND METHODS

Synthesis of PDLLA Homopolymers

The dimer, i.e., DL-lactide, and the catalyst, i.e., stannous chloride ($SnCl_2$-$2H_2O$) were purchased from Purac Biochem (Gorinchem, The Netherlands) and BDH (British Drug Houses, Poole, UK), respectively. All other solvents and reagents were obtained from Merck (Frankfurt, Germany) and were used without further purification.

The ring-opening polymerization of DL-lactide in bulk was carried out by using a similar procedure described earlier.[8,9,27–30] Polymerizations were conducted in pretreated ampoule bottles (diameter: 25 mm, volume: 25 mL). For pretreatment, the bottle was filled with aqueous solutions of potassium dichromate/sulfuric acid, and left for 24 h at room temperature. Then they were thoroughly washed with distilled water several times, and with acetone, and finally dried overnight at 120°C. For polymerization, the pretreated bottle was cooled down to room temperature with a stream of dry nitrogen. Lactide, 3.6 g, was transferred to the bottle under dry nitrogen atmosphere, and 0.5 mL of a freshly prepared stannous chloride solution in ethyl ether was added by using a dry glass pipet. The bottle was connected via an adaptor to a purge valve system with access to vacuum or dry nitrogen. It was evacuated for about 5 min, refilled with dry nitrogen, and then heat-sealed and placed in an oven with temperature controlling system. The dimer was melted by preheating to the temperature of 160°C, and polymerization was started. After the desired polymerization period, the ampoule bottle was cooled down to stop the reaction immediately.

For purification and removing the unreacted dimer and low-molecular-weight polymer residuals, the product was dissolved in chloroform to make concentration about 10% (w/v). PDLLA was precipitated by adding this solution to the precipitation medium, i.e., a mixture of acetone/heptane (with a ratio of 1/2, v/v), by vigorous stirring. Precipitated polymer was filtrated and dried in vacuum at 30°C for 48 h.

In order to synthesize PDLLAs with different molecular weights, the polymerization time was changed in the range of 40–120 min.

Synthesis of PDLLA/PEG Copolymers

For synthesis of PDLLA/PEG copolymers we used the PDLLA homopolymer with three different number average molecular weights, namely, 7,300, 12,100, and 21,900.[28] The second component was PEG with a molecular weight range of 3,300–4,000 (BDH, UK). The homopolymers were dried in a vacuum oven at 30°C for about 4 days, then stored in a dessicator until use.

The PDLLA/PEG copolymers were synthesized by transesterification.[8,28] In order to have an homogeneous mixture, PDLLA and PEG were dissolved in acetone (1 g of polymers in 1 mL acetone). Transesterifications were performed in ampoule bottles. The polymer solution was placed into the bottle and nitrogen was continuously flowed through the solution. The solvent was evaporated at 100°C in about 2 h. The medium temperature was then raised to 190°C, and transesterification was con-

ducted at this constant temperature in about 6 h under nitrogen atmosphere.

Copolymer chains with different compositions were obtained by changing the initial ratio of PDLLA/PEG. Note that for convenience, instead of this ratio we used the definition of "PEG content" (i.e., PEG %) which is defined as follows:

$$\text{PEG Content (\%)} = (\text{g PEG/g PEG + PDLLA}) \times 100$$

Determination of Average Molecular Weights and Heterogeneity Indices

The molecular weights and molecular weight distributions of the homo- and copolymers were also determined by a high pressure liquid chromatography (HPLC) system (Waters, Milford, MA, USA). The gel permeation chromatography (GPC) unit, consisting of a Waters model 510 HPLC pump and a Waters U6K injector, was equipped with two Ultrastyragel columns (Waters, 10^4 Å and 500 Å) in series and a Waters 486 Tunable Absorbance Detector (at 241 nm). HPLC-grade chloroform (Fluka, Buchs, Switzerland) was used as both the solvent and the eluent. Eluation was performed at a temperature of 30°C and at a flow rate of 1 mL/min, using a Waters 510 HPLC pump. The polystyrene (PS) standards (Mw_n: 2,500–20,000, Polyscience, Warrington, PA) were used for PDLLA homopolymers to obtain the primary calibration curves. Both the PS and PEG standards were used for PDLLA/PEG copolymers. However, since the PEG contents of the copolymers were 15% or less, the results obtained with the PS standards are reported here. The average molecular weights and the heterogeneity indices were then evaluated by using the Mark–Houwink constants for PDLLA ($K = 1.29 \times 10^{-5}$, and $a = 0.82$).[31–33]

Structural Analysis with DSC

Five mg of the polymer sample was pressed in a sample capsule. The thermogram was then recorded with a differential scanning calorimeter (DSC, Thermal Analysis 2000, Version 4.1, Dupont , Wilmington, DE, USA), at a heating rate of 10°C/min, and in the temperature range from −80 to 250°C.

Homo and Copolymer Particles

Preparation

The spherical homo- and copolymeric particles in the size range of 2–10 μm were produced by a modified solvent evaporation method.[9,13] In a typical procedure, 0.1 g of the homo or copolymer was dissolved in 5 mL of methylene chloride (Merck, Frankfurt, Germany) and this solution was then added dropwise to 50 mL of distilled water (i.e., the dispersion phase) containing 0.5 g of the emulsifier (i.e., methyl cellulose, BDH, USA), while the medium was stirred both with a mechanical stirrer at 2,000 rpm and a bath-type sonicator (power: 250 W; operating frequency: 50 kHz) (Bransonic 221, Branson Europa, B. V., Soest, The Netherlands), at room temperature. The solvent was evaporated under these conditions in 2 h. The spherical particles were separated by centrifugation at 4,000 rpm for 10 min and were washed two times with distilled water.

In this group of experiments, we investigated the effects of the organic solvent/polymer ratio, the PDLLA molecular weight, and the PEG content on the average particle size.

Size Determination

The size and size distribution of the polymeric particles were determined from the micrographs taken with a scanning electron microscope (SEM, JEOL, Tokyo, Japan). A 100-μL aqueous suspension of particles was dried on a metal support *in vacuo* at room temperature for 4 h and the samples coated with gold; then SEM micrographs were obtained. Diameters of all of the particles on the micrographs (each containing about 100–200 particles) were measured and average sizes with standard deviations were evaluated.

Degradation

Degradations of PDLLA and PDLLA/PEG particles were investigated in phosphate buffer solutions at pH 7.4 and at 37°C. In a typical procedure, 100 mg of polymeric particles were suspended in 25 mL of a phosphate buffer solution, and the suspension was then placed in a shaking bath maintained at a constant temperature. To follow the degradation, 5 mL suspension periodically taken from the medium was centrifuged at 4,000 rpm for 10 min and the supernatant was removed. Particles were washed with distilled water in the manner described earlier and dried overnight in a vacuum oven at room temperature. The average molecular weights of precipitated polymers were determined by viscosimetry.

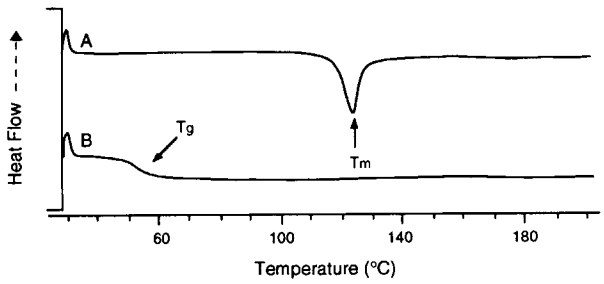


Figure 1 DSC thermograms of (A) DL-lactide and (B) PDLLA.

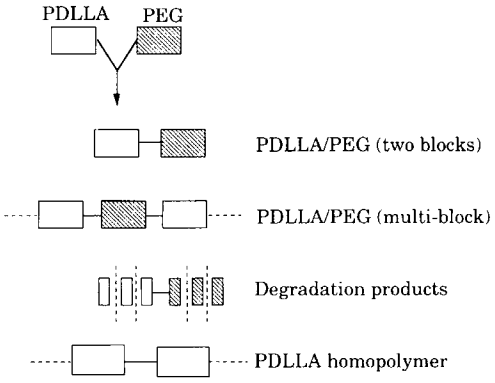
RESULTS AND DISCUSSION

Properties of PDLLA Homopolymers

DSC Studies

We used results of the DSC studies to show the purity of the PDLLA homopolymers, in other words, the existence of the dimer residuals (after purification steps) within the PDLLA matrix. Figure 1 shows the thermograms of DL-lactide and PDLLA. The thermograms were recorded by a DSC at a heating rate of 10°C/min and in the temperature range from −80°C to 250°C.

As seen in Figure 1, at the temperature range of −80 to 200°C there is only one thermal transition for PDLLA, which is the glass transition temperature (T_g) at 49–54°C, which shows that the matrix is amorphous, as also reported by others.[34,35] There is no melting point (no crystallinity) because the random distribution of D- or L-chiral carbon in the polymer chain backbones disrupts the regular configuration of the chains and causes the chains to be unable to fold regularly into crystalline lattice. In contrast, DL-lactide exhibits a thermal transition around 125°C, which is its melting point. Once again, comparing the thermograms of PDLLA and DL-lactide, we may say that there are no dimer residuals left in our PDLLA after the purification step.



Scheme 1 Products transesterification of PDLLA and PEG.

Average Molecular Weights and Heterogeneity Indices

The number and weight average molecular weights and the heterogeneity indices of the PDLLAs synthesized with different polymerization times (40–120 min) at a temperature of 160°C and with a dimer/catalyst ratio of 1,000 are given in Table I.

As seen here, the average molecular weights increased but the molecular weight distributions did not change with the increase in the polymerization time. Note that we aimed to produce PDLLAs with relatively low molecular weights in order to achieve high degradation rates, therefore we did not extend the polymerization time further.

Properties of PDLLA/PEG Copolymers

The PDLLA/PEG copolymers were synthesized by end-group transesterification reactions. The products of transesterification reactions may be highly complex mixtures of molecules with different structures (Scheme 1). There may be homopolymer chains with different lengths; copolymers which carry one PDLLA segment and one PEG segment (i.e., two-blocks copolymer); and/or multisegmental

Table I Average Molecular Weights of PDLLAs

Sample No.	t[a] (min)	M_n[b]	M_w[b]	Heterogeneity Index[c]
1	40	7,300 ± 300	15,900 ± 500	2.2
2	80	12,100 ± 400	25,900 ± 500	2.5
3	120	21,900 ± 400	47,600 ± 1500	2.2

[a] t: polymerization time.
[b] Mean ± SD of three measurements.
[c] The ratio of Mw/Mn.

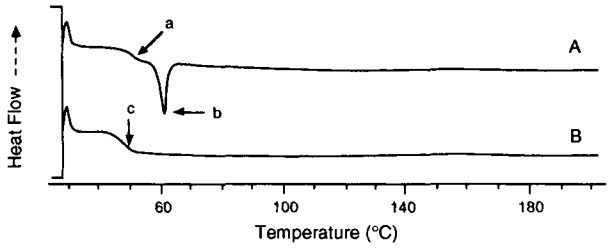


Figure 2 DSC thermograms of (A) DL-lactide and (B) PDLLA.

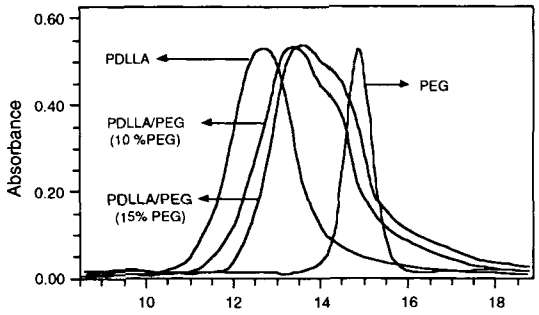


Figure 3 Absorbance–residence time curves of PDLLA, PEG, and PDLLA/PEG homo- and copolymers.

copolymer chains, again with different chain lengths and degradation products. The transesterification products were analyzed by the different techniques given below.

DSC Studies

Figure 2A and B show the DSC thermograms of a physical mixture of PDLLA and PEG (with 50 wt %), and a PDLLA/PEG copolymer sample, respectively. There are two thermal transitions on the thermogram of the PDLLA/PEG physical mixture, which are the T_g (49–54°C) of PDLLA and the melting point (T_m; 62°C) of PEG. However, there is only one transition on the thermogram of the copolymer, which is the T_g (44–50°C) of PDLLA/PEG. This difference may be used as an indication of the copolymer formation.

Average Molecular Weights and Heterogeneity Indices

The number and weight average molecular weights and the heterogeneity indices of the PDLLA/PEG copolymers synthesized with three different PDLLAs (Mw_n: 7,300, 12,100, and 21,900) and with two different PEG contents (10 and 15%) are given in Table II. Note that the molecular weight range of PEG used was 3,300–4,000.

As seen here, the average molecular weights of the copolymers are larger than those of PEG but smaller than PDLLA's, which may be because the thermal degradation occurred during the transesterification reactions. Figure 3, which gives one of the absorbance–residence time graphs (i.e., representing the molecular weight distributions) obtained by GPC directly, is clear evidence of this degradation (notice the tails of the curves for copolymers). These degradation products may be homo- or copolymers of PDLLA and PDLLA/PEG, as depicted in Scheme 1.

Properties of PDLLA and PDLLA/PEG Particles

Average Particle Size

The spherical homo- and copolymeric particles in the size range of 2–10 μm were produced by a modified solvent evaporation.[9,11,13] Both mechanical stirring and sonication were used to control dispersion of the organic phase (polymer solution in methylene chloride) within the aqueous dispersion medium containing methyl cellulose. In this group of experiments, we investigated the effects of the initial solvent/polymer ratio, the PDLLA molecular weight, and the PEG content on the particle size.

Table III gives the effects of the solvent/polymer ratio on the average particle size. In this group of experiments, the copolymer prepared from PDLLA with a number average molecular weight of 12,100

Table II Average Molecular Weights of PDLLA/PEGs Obtained by GPC

Sample No.	M_n (PDLLA)	PEG Content (%)	M_n[a]	M_w[a]	Heterogeneity Index[b]
1	7,300	15	6,400 ± 200	12,700 ± 400	2.1
2	12,100	15	11,000 ± 500	23,500 ± 600	2.1
3	21,900	15	19,700 ± 600	42,300 ± 1800	2.2
4	12,100	10	11,600 ± 500	24,000 ± 600	2.1

[a] Mean ± SD of three measurements.
[b] The ratio of Mw/Mn.

Table III Effects of Solvent/Polymer Ratio on Average Size of PDLLA and PDLLA/PEG Particles

Solvent/Polymer Ratio (mL/g)	PDLLA Particles[a] Average Size (μm)	PDLLA/PEG Particles[a] Average Size (μm)
10	10.6 ± 3.6	8.8 ± 2.0
50	3.0 ± 0.2	2.7 ± 0.2
100	2.6 ± 0.3	2.4 ± 0.4

[a] Mean ± SD.

and a PEG content of 15% was used. As seen here, the average size of the PDLLA microspheres decreased with increasing the solvent/polymer ratio. This can be explained by considering the viscosity of the initial polymer solution. More-viscous solutions were obtained when smaller amounts of solvent (low solvent/polymer ratio) were used.[9,11,13,28,36,37] It was more difficult to disperse solutions with higher viscosities, therefore larger particles were obtained. However, the effects of initial viscosity on the particle size were less pronounced when the initial solvent/polymer ratio was high (in the polymer solutions with low polymer concentrations). Notice that the PDLLA/PEG particles were smaller than the PDLLA particles prepared with the same solvent/polymer ratio. This may be due to the existence of the hydrophilic PEG segments in the polymeric chains, which resulted in better (easier) dispersion of the particles in the aqueous dispersion medium.

Table IV gives the effects of the PDLLA molecular weight on the average particle size. In this group of experiments, we used the copolymers prepared from PDLLA with a PEG content of 15%. The solvent/polymer ratio was 50 mL/g.

As seen here, the average size of both homo and copolymeric particles increased slightly with increased PDLLA molecular weight. As also mentioned above, when the PDLLAs with higher molecular weights were used, organic phases with higher viscosities were obtained.[28] Therefore, it was difficult to disperse these solutions in the dispersion medium, which led to larger particles. PDLLA/PEG particles were smaller than PDLLA particles prepared with the same PDLLA, which may be due to higher hydrophilicities of the copolymeric chains, as mentioned before.

Table V gives the effects of the PEG content on the average particle size. In this group of studies, the copolymers prepared from PDLLA with a number average molecular weight of 12,100 were used. The solvent/polymer ratio was 50 mL/g.

As seen here, the average size of the PDLLA/PEG copolymeric particles decreased slightly with increasing PEG content, possibly due to the existence of the hydrophilic PEG segments in the polymeric chains which led to easier dispersion of the particles in the aqueous dispersion medium, thus resulting in smaller particles. The incorporation of PEG in the polymeric chains did cause this slight change, but there was no difference when the PEG content was raised from 10 to 15%. Note that when the PEG content was higher than 15% the hydrophilicity of the copolymeric chains increased and they did form micelles, not the particles in the aqueous dispersion medium.[8,12,14]

Table IV Effects of PDLLA Molecular Weight on Average Size of PDLLA and PDLLA/PEG Particles

M_n of PDLLA	PDLLA Particles[a] Average Size (μm)	PDLLA/PEG Particles[a] Average Size (μm)
9,800	2.1 ± 0.2	2.1 ± 0.2
14,500	3.0 ± 0.2	2.7 ± 0.2
23,100	3.1 ± 0.6	3.2 ± 0.8

[a] Mean ± SD.

Table V Effects of PEG Content on Average Size of PDLLA/PEG Particles

PEG Content (%)	PDLLA/PEG Particles[a] Average Size (μm)
0	3.0 ± 0.2
10	2.7 ± 0.4
15	2.7 ± 0.2

[a] Mean ± SD.

Degradation

Degradations of PDLLA and PDLLA/PEG particles were investigated in phosphate buffer solutions at

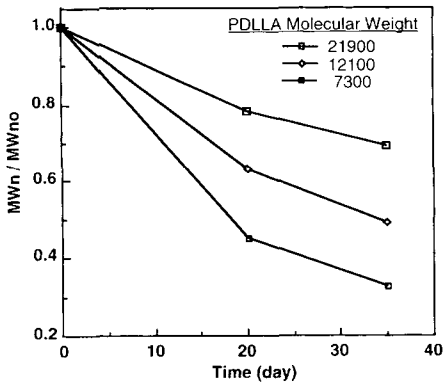


Figure 4 Degradation of PDLLA homopolymeric particles (in phosphate buffer solutions at pH 7.4 and at 37°C).

pH 7.4 and at 37°C, which simulate physiologic conditions. Figure 4 shows the degradation rates of PDLLA homopolymeric particles, prepared by using PDLLAs with three different molecular weights. Note that the number average molecular weights (obtained by viscosimetry) are given on the figure. Here, Mw_{n0} and Mw_n are the number average molecular weights of the PDLLAs at the beginning and at any time during degradation, respectively. For the production of these polymeric particles, the solvent/polymer ratio was kept constant at 50 m/g. As seen in this figure, PDLLAs with smaller chain lengths (lower average molecular weights) were degraded much faster than those with higher molecular weights. This may be because water molecules can penetrate much more easily within the matrices composed of low molecular weight polymer chains due to less entanglement and higher hydrophilicity (as a result of the higher number of end groups).

Figure 5 illustrates the effects of PEG content on the degradation of copolymeric particles. As seen here, the existence of PEG caused a pronounced in-

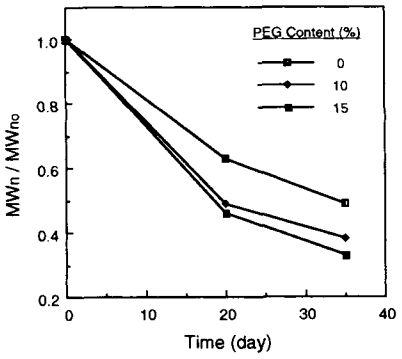


Figure 5 Degradation of PDLLA/PEG particles (in phosphate buffer solutions at pH 7.4 and at 37°C).

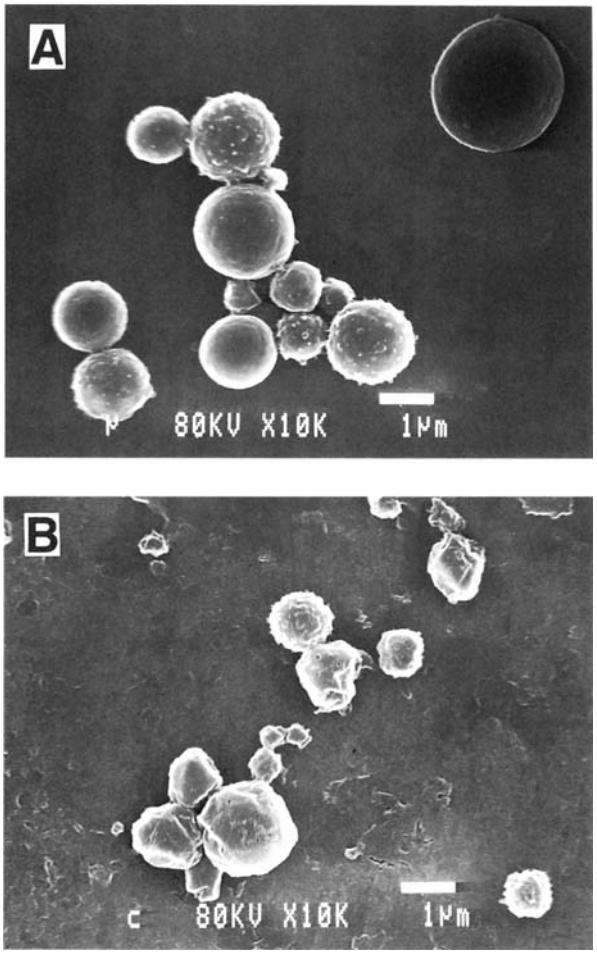


Figure 6 SEM micrographs of PDLLA/PEG particles: (A) freshly prepared; (B) after degradation of 35 days (in phosphate buffer solutions at pH 7.4 and at 37°C).

creased in the degradation rate. This may be because of the relative hydrophilicity of the copolymeric particles. Most probably the water molecules, which cause the degradation of the PDLLA segments, diffuse much more easily in the hydrophilic copolymeric matrices, thus resulting in higher degradation rates.

Figure 6 gives two representative SEM micrographs of the PDLLA/PEG copolymeric particles (with a PEG content of 15%). As seen in Figure 6(A), particles (freshly prepared, i.e., before degradation) are quite spherical and rigid and have smooth surfaces, although porosity on some of the particle surfaces is also observed. After 35 days degradation (in phosphate buffer solutions at pH 7.4 and at 37°C), particles seem to have collapsed [Fig. 6(B)]. This may be an indication of the bulk degradation, which empties the inner core of the polymeric particles; they become like balloons and

therefore collapse during the SEM preparation procedure. Bulk degradation of the polylactides was also reported by others,[9,19,38] and was attributed to the autocatalytic degradation mechanisms caused by the acidic character of the degradation products (i.e., monomers and oligomers) accumulated within the bulk of the polymeric matrix.

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Received August 22, 1995
Accepted January 12, 1996