

Multiblock Copolymers Based on Segments of Poly(D,L-lactic-glycolic acid) and Poly(ethylene glycol) or Poly(ϵ -caprolactone): A Comparison of Their Thermal Properties and Degradation Behavior

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Received 8 July 1999; accepted 2 February 2000

ABSTRACT: A comparison of the thermal properties of two classes of poly(D,L-lactic-glycolic acid) multiblock copolymers is reported. In particular, the results of differential scanning calorimetry, and thermogravimetric analysis of copolymers containing poly(ethylene glycol) (PEG) or diol-terminated poly(ϵ -caprolactone) (PCDT) segments are described. The influence of the chemical structure and the length of PEG and PCDT on thermal stability, degree of crystallinity and glass transition temperature (T_g) is discussed. Finally, an evaluation of the hydrolytic behavior in conditions mimicking the physiological environment is reported. © 2000 John Wiley & Sons, Inc. *J Appl Polym Sci* 78: 1721–1728, 2000

Key words: poly(lactic-glycolic acid); poly(D,L-lactic-glycolic acid); diol-terminated poly(ϵ -caprolactone); poly(ethylene glycol); block copolymers; bioerodible polymers; thermal properties; thermal degradation, hydrolytic degradation

INTRODUCTION

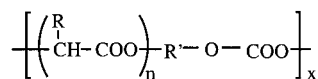
Poly(lactic-glycolic acid) (PLGA) constitute probably the family of bioerodible polymers most commonly employed at present in the biomedical field as surgical materials (bioerodible sutures, artificial skin), bone reparation systems, or matrices for implant of drug delivery systems.^{1–9} Also, recently their use to produce scaffolds in the regeneration of tissues has been considered with promising results.^{10–13} Depending on their structure (i.e., presence of D,L- or D,L-lactic acid, molar ratio of lactic to glycolic acid LA/GA and molecular weight), PLGAs with variable properties can be obtained. A further possibility to modulate their

characteristics is represented by the synthesis of copolymers.^{14–17} For instance, copolymers with poly(ϵ -caprolactone) and poly(ethylene glycol) are investigated actively to achieve better tuning of morphology, mechanical properties, degradation rate, and permeability.^{4,14,18–20}

In general, the biocompatibility, the swelling, and the degradation rate are obviously among the main characteristics that need to be considered when designing materials for biomedical applications. Morphology is another factor that must be properly investigated inasmuch as it affects extensively the hydrolytic behavior of the material.^{4,19} Furthermore, PLGAs can be molded by a number of technologies, some of them involving thermal treatments such as melt encapsulation,²¹ extrusion,¹⁰ and thermal sterilization,²² which can induce degradation processes with decrement of molecular weight²³ and loss of volatile prod-

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Journal of Applied Polymer Science, Vol. 78, 1721–1728 (2000)
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where:

R = H or CH₃

R' = $\left[(\text{CH}_2)_5 - \text{COO} \right]_a \text{CH}_2\text{CH}_2 \left[\text{OCO} - (\text{CH}_2)_5 \right]_b$ in PLGA-PCDT

R' = $-\text{CH}_2 - \left(\text{CH}_2\text{OCH}_2 \right)_m \text{CH}_2 -$ in PLGA-PEG

Scheme 1 Structure of PLGA-PCDT and PLGA-PEG multiblock copolymers.

ucts, depending on the processing temperature.^{24,25} Therefore, the calorimetric properties and thermal stability also play an important role from the technological point of view.

The aim of the present work is to investigate the thermal properties and susceptibility to thermal and hydrolytic degradation of two classes of multiblock copolymers containing PLGA and diol-terminated poly(ϵ -caprolactone) (PCDT) or poly(ethylene glycol) (PEG) segments, and to relate the molecular structure with the properties of these materials. The copolymers investigated are multiblock copolymers with poly(ester-carbonate) structure (see Scheme 1) synthesized by a chain extension reaction where oligomeric PLGA is reacted with PCDT or PEG bearing chloroformate end groups. It is worthwhile to notice that this process, whose synthetic pathway was reported in previous papers,^{26–28} allows the preparation of bioerodible materials with a wide range of properties by a proper selection of the PLGA composition and of the type and length of the segments.

EXPERIMENTAL

Instruments

The differential scanning calorimetry (DSC) analysis was carried out using a Mettler TC11 Thermal Analyser Processor equipped with a Low Temperature Cell DSC30. The DSC curves were obtained by heating a sample of about 10 mg from -100 to 100°C at $10^\circ\text{C}/\text{min}$ under nitrogen flow ($10 \text{ mL}/\text{min}$).

The thermogravimetric analysis (TGA) was run by a Mettler TC11 Thermal Analyser Processor equipped with a Mettler TG50 microbalance heating a sample of about 10 mg into alumina

crucible from room temperature to 650°C at $20^\circ\text{C}/\text{min}$ under nitrogen flow ($20 \text{ mL}/\text{min}$).

Methods

Preparation of Sheets

Sheets having size $1 \times 0.5 \times 0.14 \text{ cm}$, were obtained by plates prepared by compression molding at 80°C , and a nominal pressure of 2.5 MPa. In order to minimize bubbles and stress inside the specimen, the following scheme was adopted: step 1, compression (1 min); step 2, decompression (0.5 min); step 3, compression (10 min); step 4, cooling (15 min).

Conditions of the Degradation Tests

The degradation tests were carried out at 37°C in 0.025M phosphate buffer pH 7.4 brought to ionic strength 0.13 with sodium chloride, and under static conditions (about 80 mg copolymer in 5 mL of buffer).¹⁶ The phosphate buffer consisted of Na₂HPO₄ (17.22 g), NaH₂PO₄ (3.93 g), NaCl (35.4 g), and sodium azide (3.0 g), in water (6 L).

Weight Loss and Water Adsorption Determination

Weight loss (WL) and water adsorption (WA) were evaluated by weighing. The samples were first dried *in vacuo* at 25°C up to constant weight, then the WL was determined by

$$\text{WL} = 100(W_0 - W_t)/W_0 \quad (1)$$

where W_0 and W_t are the initial and residual weight of the dried sample at the time t , respectively. The water adsorption was deduced from

$$\text{WA} = 100(W_s - W_t)/W_t \quad (2)$$

where W_s is the weight of the swollen sheet at time t after surface wiping.

Dissolution Time Determination

The dissolution time was considered as the time at which no discrete particles were visually detectable either in suspension, or at the bottom of the reaction vessel.

Materials

PCDT samples were purchased from Aldrich Co. while PEG samples were purchased from Fluka Co. Oligomeric PLGA50/50, PLGA-PCDT, and

Table I Molecular Weight Characterization of Block Copolymers^a

| Code | Starting Oligomers: Diol | | Block Copolymers | | | |
|--------------------|--------------------------|-----------|-------------------|----------------------------|------------------------------|-------|
| | Type | \bar{M} | $[\eta]^b$ (dL/g) | $\bar{M}^c \times 10^{-3}$ | $\bar{M}_w^d \times 10^{-3}$ | D^e |
| PLGA50/50-PCDT530 | PCDT | 530 | 0.40 | 8.4 | 31.5 | 3.7 |
| PLGA50/50-PCDT1250 | PCDT | 1250 | 1.20 | 22.0 | 114.7 | 5.2 |
| PLGA50/50-PCDT2000 | PCDT | 2000 | 0.82 | 27.0 | 113.7 | 4.2 |
| PLGA50/50-PEG150 | PEG | 150 | 0.83 | 91 | 180 | 2.0 |
| PLGA50/50-PEG1000 | PEG | 1000 | 1.74 | 239 | 434 | 1.8 |
| PLGA50/50-PEG2000 | PEG | 2000 | 1.55 | 197 | 370 | 1.9 |
| PLGA50/50-PEG4000 | PEG | 4000 | — | 194 | 370 | 1.9 |

^a Note: an oligomeric PLGA with $\bar{M}_n = 1920$ was always used except for PLGA50/50-PEG150, which was synthesized from a PLGA with $\bar{M}_n = 2640$ (\bar{M}_n determined by end-group titration).

^b Intrinsic viscosity in chloroform at 32°C.

^c Number-average molecular weight evaluated by SEC using polystyrene narrow standards.

^d Weight-average molecular weight evaluated by SEC using polystyrene narrow standards.

^e Polydispersity index \bar{M}_w/\bar{M}_n .

PLGA-PEG block copolymers were synthesized as previously described.^{26–28}

RESULTS AND DISCUSSION

Tested materials have a multiblock structure in which every PLGA segment is bound through an ester or carbonate linkage to the neighboring PEG or PCDT blocks (Scheme 1); in practice, six copolymers having PLGA blocks with LA/GA = 50/50, $\bar{M}_n = 1920$ and PEG or PCDT segments of various lengths were studied. The composition, the length of the diol segments, and the average molecular weights of block copolymers, determined by size exclusion chromatography (SEC) using polystyrene standards,^{26–28} are summarized in Table I. For comparison purposes, starting PLGA50/50, PEG, and PCDT oligomers were investigated as well.

Differential Scanning Calorimetry

Oligomeric poly(D,L-lactic-glycolic acid) are amorphous materials whose T_g increases with the LA/GA ratio. In contrast, oligomeric PEGs are typical semicrystalline products having T_g in the range -80 to -20°C and melting point (T_m) between -15 and 65°C .²⁹ The T_m values increase with molecular weight, while the T_g exhibits a maximum for \bar{M}_n about 6000.²⁹

Differential scanning calorimetry data on some PLGA-PEGs and starting PEGs have been reported previously²⁷ and are summarized in Table

II. PLGA50/50-PEG150 and PLGA50/50-PEG1000 are amorphous materials with T_g at 30.0 and -5.7°C , respectively, while PLGA50/50-PEG2000 and PLGA50/50-PEG4000 are semicrystalline polymers. The former exhibits a T_g at -27.1°C , whereas no glass transition could be revealed under the analytical conditions used in PLGA50/50-PEG4000 as well as in starting PEGs. It may be noticed that the T_g values decrease with increasing the PEG length, i.e., its weight fraction. In the case of PLGA50/50-PEG150 and PLGA50/50-PEG1000, a good agreement was obtained between the experimental T_g 's and those evaluated from the Fox relationship³⁰ employing the T_g values of completely amorphous PEGs.^{29,31} In fact, the calculated T_g 's turned out to be 23°C for PLGA50/50-PEG150 and -6°C for PLGA50/50-PEG1000.

The melting points of PLGA50/50-PEG2000 and PLGA50/50-PEG4000 are located at 44.6 and 57.1°C , respectively, and are therefore depressed compared to starting PEGs ($T_m = 52.8$ and 59.9°C). The same trend was observed for crystallinity (see Table II), which was calculated with respect to the oligomeric diol content by means of

$$C\% = (\Delta H_m \cdot 100)/(w \cdot \Delta H_m^0) \quad (3)$$

where ΔH_m^0 (J/g) is the heat of fusion of the corresponding diol, ΔH_m (J/g) is the heat of fusion of the sample, and w is the weight fraction of the diol segments within the copolymer.

Also, oligomeric PCDTs are semicrystalline products having T_g in the range -80 to -60°C

Table II DSC Data of Starting Oligomers and of Block Copolymers^a

| Sample | Diol ^b (wt %) | T_g (°C) | mp ^c (°C) | ΔH_m^d (J/g) | C^e (%) |
|--------------------|--------------------------|------------|----------------------|----------------------|-----------|
| PLGA50/50 | | 31.5 | | | |
| PCDT530 | | -77.1 | 31.3 | 41.9 | |
| PCDT1250 | | -70.3 | 45.7 | 70.7 | |
| PCDT2000 | | -59.1 | 49.7 | 75.4 | |
| PEG1000 | — | — | 38.9 | 154.7 | — |
| PEG2000 | — | — | 52.8 | 179.2 | — |
| PEG4000 | — | — | 59.9 | 188.1 | — |
| PLGA50/50-PCDT530 | 22 | 25.7 | — | — | — |
| PLGA50/50-PCDT1250 | 39 | -57.9 | 40.3 | 16.6 | 59.7 |
| PLGA50/50-PCDT2000 | 51 | -45.3 | 49.4 | 24.4 | 63.6 |
| PLGA50/50-PEG150 | 5 | 30.0 | — | — | — |
| PLGA50/50-PEG1000 | 34 | -5.7 | — | — | — |
| PLGA50/50-PEG2000 | 51 | -27.1 | 44.6 | 42.2 | 46 |
| PLGA50/50-PEG4000 | 68 | — | 57.1 | 79.7 | 63 |

^a Under nitrogen (scanning rate: 10°C/min).

^b PCDT content (weight percentage).

^c Melting point.

^d Heat of fusion.

^e Percentage of crystallinity evaluated by means of the following equation: $C = \Delta H_m / 100w \cdot \Delta H_m^0$, where ΔH_m^0 is the heat of fusion of the starting PCDT, ΔH_m is the heat of fusion of the block copolymer and w is the PCDT weight fraction in the copolymer.

and T_m between 30 and 50°C, both increasing with molecular weight (see Table II). In all PCDTs two overlapping melting peaks are detected, probably related to two crystalline phases, in accordance with literature data.³² In Table II only the highest T_m value is reported.

As regards the multiblock copolymers, it should be noticed that PLGA50/50-PCDT530 is an amorphous material with T_g of +25.7°C. In contrast with the PLGA-PEG amorphous samples, the T_g evaluated from the Fox relationship is very different from the experimental data. The other samples (PLGA50/50-PCDT1250 and PLGA50/50-PCDT2000) are semicrystalline polymers with glass transition at -57.9 and -45.3°C, respectively. Their melting point (40.3 and 49.4°C) is displaced toward lower values compared to the PCDT oligomers. The crystallinity, which is also decreased in comparison with the diol, increases with the PCDT molecular weight, i.e., with the PCDT weight fraction. The depression in crystallinity, as well as in the melting points, in comparison with the starting PCDT is lower than in the corresponding PLGA-PEG copolymers. This suggests that the PLGA segments have a higher compatibility with the PEG rather than with the PCDT blocks.³⁰ Accordingly, PLGA50/50-PEG1000 exhibits no crystallinity, in contrast with PLGA50/50-PCDT1250, which has a comparable diol length. On the other hand, the presence of a possible second T_g related to the

PLGA-rich phase, which would provide further information on block compatibility, could not be revealed owing to the broadness of the diol melting peak.

Table III TGA Data of Starting Oligomers and of Copolymers^a

| Sample | Step (I) | | Step (II) | |
|--------------------|--------------|------------------|--------------|------------------|
| | T_i^b (°C) | ΔW^c (%) | T_i^b (°C) | ΔW^c (%) |
| PLGA50/50 | 311 | 95 | — | — |
| PLGA75/25 | 338 | 97 | — | — |
| PCDT1250 | 368 | 92 | — | — |
| PCDT2000 | 343 | 89 | — | — |
| PEG1000 | 405 | 98 | — | — |
| PEG2000 | 394 | 97 | — | — |
| PEG4000 | 394 | 97 | — | — |
| PLGA50/50-PCDT530 | 289 | 69 | 373 | 81 |
| PLGA50/50-PCDT1250 | 284 | 52 | 389 | 92 |
| PLGA50/50-PCDT2000 | 284 | 49 | 392 | 93 |
| PLGA50/50-PEG150 | 310 | 92 | — | — |
| PLGA50/50-PEG1000 | 287 | 59 | 378 | 33 |
| PLGA50/50-PEG2000 | 275 | 39 | 389 | 54 |
| PLGA50/50-PEG4000 | 310 | 27 | 384 | 74 |

^a Analysis conditions: sample of about 10 mg heated into alumina crucibles from room temperature to 650°C at 20°C/min under nitrogen flow (20 mL/min).

^b Temperature at the inflection point.

^c Total weight loss percentage at the end of the step.

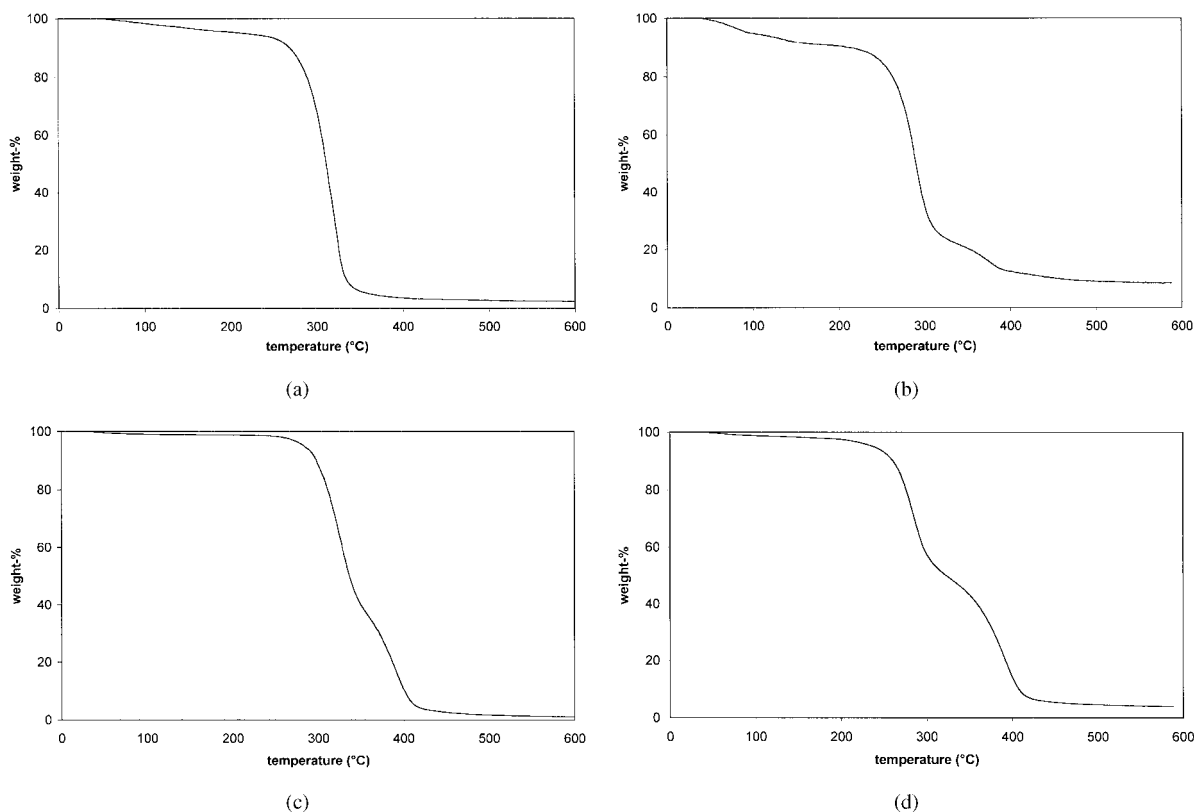


Figure 1 TGA traces of (a) oligomeric PLGA50/50, (b) PLGA50/50-PCDT530, (c) PLGA50/50-PCDT1250, and (d) PLGA50/50-PCDT2000.

Thermogravimetric Analysis

Thermal stability was evaluated running the thermogravimetric analysis in nitrogen atmosphere, in the range of 25–650°C and at a scanning rate of 20°C/min. In Table III the temperature at each inflection point (T_i) and the total weight loss (ΔW) calculated at the end of the each volatilization step are reported. The TGA traces of all copolymers analyzed as well as that of oligomeric PLGA are shown in Figures 1 and 2.

As regards starting PLGA [Fig. 1(a)], it exhibits lower thermal stability ($T_i = 311^\circ\text{C}$; $\Delta W = 95\%$) than the oligomeric diols (see Table III). Oligomeric PCDTs show lower thermal stability than PEGs with comparable molecular weight. In fact, the PCDT2000 and PEG2000 traces exhibit an inflection point at 343 and 394°C, respectively. This is consistent with the higher stability of ether compared to ester bonds.

In general, PLGA-PCDT and PLGA-PEG copolymers show two inflection points with the exception of the sample PLGA50/50-PEG150, where only a single step was observed [Fig. 29a], but in that case the low PEG content (5 wt %) might be a critical factor. The temperature values and, above all, the

comparison between the percentage of volatilized material after each step and the composition of the copolymer suggest that the first step can be essentially ascribed to the degradation of the PLGA portion and the second one to the PCDT or PEG portion. For instance, the PCDT content in the PLGA-PCDT copolymers is 22% (PLGA50/50-PCDT530), 39% (PLGA50/50-PCDT1250), and 51% (PLGA50/50-PCDT2000) (see Table II) while the weight loss of the second volatilization step for the same copolymers is 12, 40, and 44%, respectively (see Table III). In spite of the higher thermal stability of the PEG in comparison with the PCDT oligomers, no substantial difference in the stability among the various copolymers was observed. In fact, in all polymers the first degradation step was detected in the same temperature range (270–290°C) with the exception of PLGA50/50-PEG150 and PLGA50/50-PEG4000 where a higher T_i was noticed (310°C).

Water Adsorption and Degradation in Physiological Media

Water adsorption and degradation experiments were performed at 37°C in 0.025M phosphate

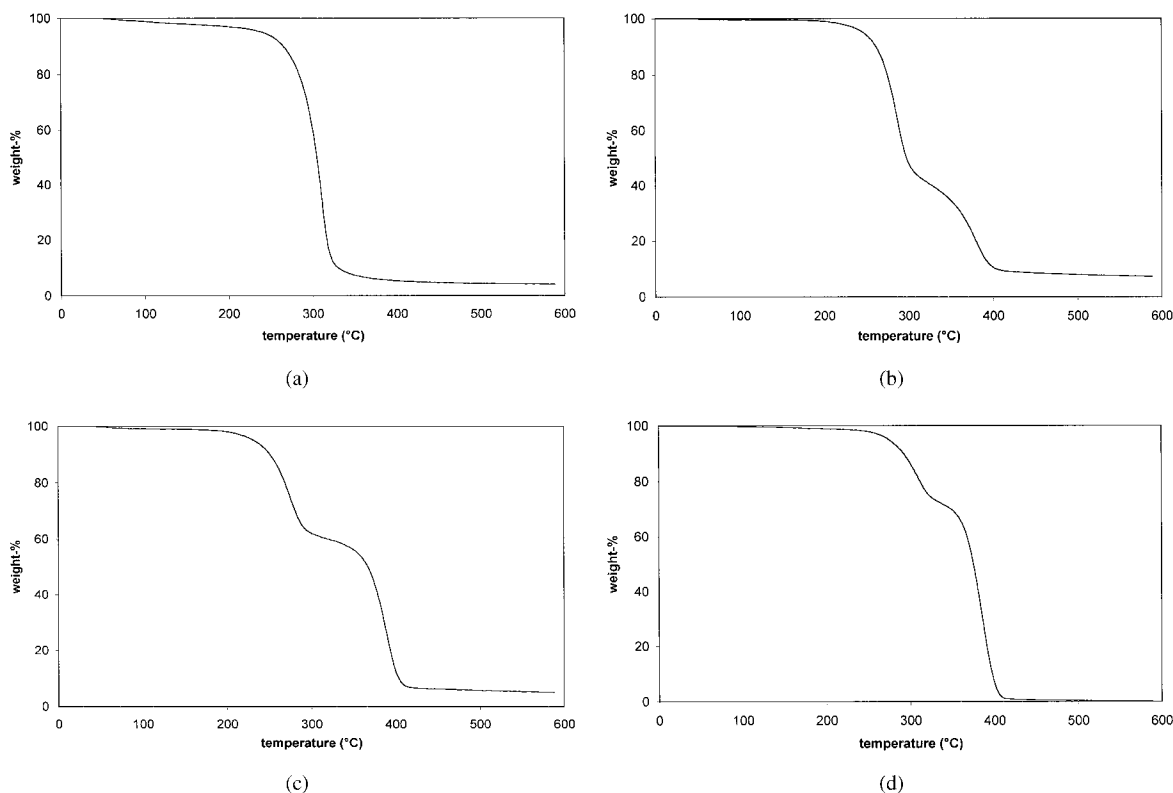


Figure 2 TGA traces of (a) PLGA50/50-PEG150, (b) PLGA-PEG1000, (c) PLGA50/50-PEG2000, and (d) PLGA50/50-PEG4000.

buffer (pH 7.4) on sheets prepared by compression molding (size: $10 \times 5 \times 1.4$ mm). The samples were weighed at different times and weight loss and water adsorption were evaluated according to eqs. (1) and (2).

Water adsorption vs time is reported in Figure 3(a) (PLGA-PCDT) and 3(b) (PLGA-PEG). Since PLGA50/50-PEG2000 and PLGA50/50-PEG4000 were very hydrophilic materials (WA = 360 and 1100 wt %, respectively) with poor mechanical characteristics in the swollen state, which made them difficult to handle, they were not considered in this test. The influence of the PCDT segment length was rather unexpected. In fact, the product deriving from PCDT1250 showed a lower water adsorption compared to that from PCDT 2000, although the latter has longer segments, i.e., a higher weight fraction, of the more hydrophobic component, and a higher degree of crystallinity. In all cases, water adsorption was not constant, but significantly increased with time, and some weight loss was observed. This indicates that a degradation process takes place also at short times. It may be noticed that while PLGA50/50-PEG150 showed a behavior similar to PLGA-PCDTs, a quite different behavior was exhibited by

PLGA50/50-PEG1000. In fact, its water adsorption strongly increased in short periods of time, which is symptomatic of a high degradation rate.

Degradation data (weight loss and dissolution time) are shown in Table IV. It is apparent that the dissolution times decrease in the order PLGA50/50-PCDT1250, PLGA50/50-PCDT2000 > PLGA50/50-PCDT530 > PLGA50/50-PEG150 > PLGA50/50-PEG1000 > PLGA50/50-PEG2000 > PLGA50/50-PEG4000. Therefore, the highest stability to hydrolysis was observed for PLGA-PCDT copolymers. In fact, the products containing PCDT1250 and 2000 did not completely dissolve even after very long times (> 8 months). This behavior can be explained by considering that PEG allows a higher accessibility of ester bonds to water molecules compared to PCDT. In fact, PEGs are more hydrophilic than PCDTs; therefore, PLGA-PEGs swell more in water than PLGA-PCDTs and the crystallinity of the PEG segments is rapidly lost, in contrast with PCDT materials. The dissolution times at 14 days of PLGA-PCDTs do not follow the same trend; on the other hand, the material morphology affects largely its hydrolytic behavior and the differences in composition, compatibility,

and degree of crystallinity related to the different molecular weight of the PCDT oligomers do not allow an easy explanation of the observed behavior.

CONCLUSIONS

From our investigations, it may be concluded that the crystallinity and calorimetric properties of PLGA-PEGs and PLGA-PCDTs are largely affected by the type of diol (PEG or PCDT) involved and its length. A higher compatibility of the PLGA toward the PEG blocks compared to the PCDT blocks was observed, although it decreased with the molecular weight of the diol.

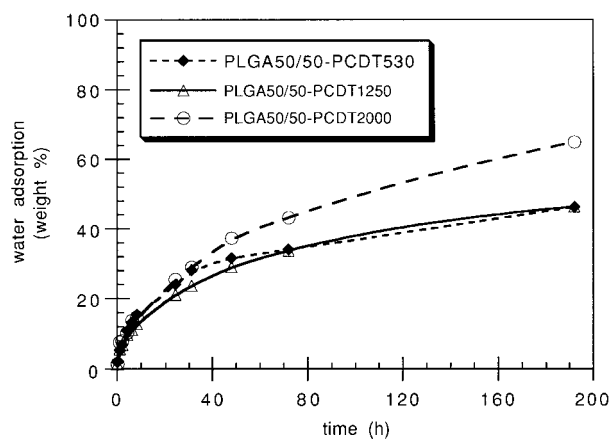
Evidence for the occurrence of two separate degradation processes in nitrogen atmosphere ascribable to the decomposition of PLGA and oligo-

Table IV Weight Loss and Dissolution Times of Block Copolymers

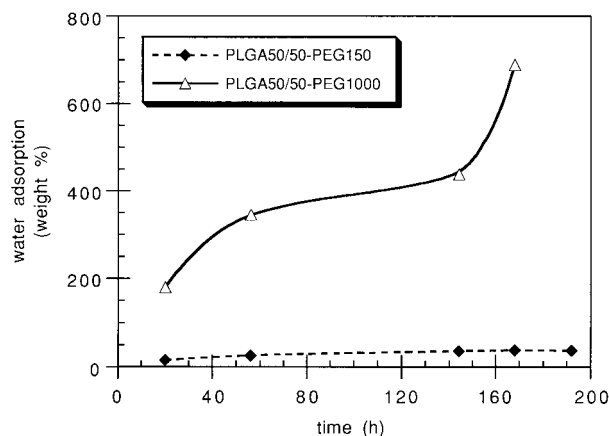
| Code | Weight Loss (wt %) ^a | Dissolution Times (days) |
|--------------------|---------------------------------|--------------------------|
| PLGA50/50-PCDT530 | 8.0 | 45 |
| PLGA50/50-PCDT1250 | 16.7 | nd ^b |
| PLGA50/50-PCDT2000 | 14.1 | nd ^b |
| PLGA50/50-PEG150 | 9.2 | 33 |
| PLGA50/50-PEG1000 | 100 | 12 |
| PLGA50/50-PEG2000 | 100 | 4 |
| PLGA50/50-PEG4000 | 100 | 2 |

^a After 14 days at 37°C.

^b Not dissolved after 8 months.



(a)



(b)

Figure 3 Water adsorption vs time in phosphate buffer for (a) PLGA50/50-PCDT copolymers and (b) PLGA50/50-PEG copolymers.

meric diol, respectively, were gathered. Any way, the thermal stability of the products investigated was comparable to that of a typical PLGA. This suggests that they can be processed by the same procedures as PLGAs. In this connection, studies on their rheological behavior are in progress and will be discussed in a subsequent paper.

The hydrolytic behavior of these materials is strongly dependent on the hydrophilicity and crystallinity of the oligomeric diol. Lower degradation times were observed with PLGA-PEGs increasing the PEG length while an opposite trend was exhibited by the more hydrophobic PLGA-PCDTs.

Considering the well-known biocompatibility of PLGA, PEG and poly- ϵ -caprolactone polymers constituting these materials, the possibility of modulating their degradation rate, and finally, their thermal stability similar to that of PLGA, it may be concluded that the PLGA-PEG and PLGA-PCDT multiblock copolymers investigated appear as promising classes of bioerodible materials potentially useful in the biomedical field with, in principle, a wider range of applications compared to PLGAs.

This research has been supported by Europeptides, Bt. Aristote-9, Avenue du Marais, 95100 Argenteuil, France.

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