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Polymer 46 (2005) 2068–2075
polymer
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Biodegradable multiblock PEO/PLA thermoplastic elastomers: molecular design and properties

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Received 21 September 2004; received in revised form 9 January 2005; accepted 9 January 2005

Abstract

Given the need for highly flexible biodegradable polymers, a series of poly(ethylene oxide)/poly(L-lactic acid) (PEO/PLA) (PELA) multiblock poly(ether-ester-urethane)s, were synthesized and characterized. The first step of the synthesis consisted of the ring-opening polymerization of L-lactide, initiated by the hydroxyl terminal groups of the PEO chain, followed by the chain extension of these PLA–PEO–PLA triblocks, using hexamethylene diisocyanate (HDI). The trimers comprised PEO segments in the 1000–10,000 molecular weight range, with the length of each PLA block covering the 200–10,000 interval. DSC and X-ray analyses revealed that, depending on their composition, amorphous matrices, monophasic crystalline materials and copolymers comprising two crystalline phases, were generated. The multiblock copolymers synthesized exhibited superior mechanical properties, with ultimate tensile strength values around 30 MPa, Young's moduli as low as 14 MPa and elongation at break values well above 1000%. Because of their phase segregated morphology, most of these multiblock copolymers displayed remarkable mechanical properties also when fully hydrated, with typical UTS values around 9 MPa.

Keywords: Poly(ethylene oxide); Poly(lactic acid); Biodegradation

1. Introduction

The interest in biodegradable polymers continues to grow, as their clinical use in new, more advanced areas steadily expands [1–3]. In addition to the classic α-hydroxy aliphatic polyesters introduced in the late sixties [4,5], other important biodegradable polymers were developed over the years, such as the poly(orthoester)s synthesized by Heller et al. [6] and the bioerodible poly(anhydride)s developed by Langer and co-workers [7]. The broad family of tyrosine-derived poly(carbonate)s [8] synthesized by Kohn et al., as well as the recently developed poly(glycerol sebacate) (PGS) [9], represent additional notable contributions to the field.

The most indispensable attribute of a biodegradable polymer pertains to its biocompatibility and that of the products of its degradation. In addition, since the stress field induced by the implant largely affects the healing and remodeling of the natural tissue surrounding it, tailoring the implant so that its mechanical behavior mimics that of the host tissue, is of utmost importance [10,11].

Because the vast majority of the biodegradable polymers in clinical use are rather stiff materials exhibiting limited extendibility, they are unsuitable for use in numerous applications, where these features are essential.

Aiming at expanding their clinical applicability, we developed a family of highly flexible biodegradable elastomers, tailored to meet different requirements, depending on their specific soft tissue application. Our working concept is based on creating multiblock polymeric backbones integrating segments that induce molecular flexibility, on one hand, and that comprise hydrolytically degradable moieties, on the other hand. These thermoplastic elastomers consist of biodegradable poly(ester) segments, which create the hard blocks of the copolymer, while flexible poly(ether glycol)s form the soft segments along the copolymeric backbone. Poly(caprolactone)/poly(ethylene oxide) (PCL/PEO) block copolymers, for example, were synthesized and their properties investigated [12].

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doi:10.1016/j.polymer.2005.01.012

Much of the work conducted in our laboratory focused on the development of copolymers, where poly(L-lactic acid) generated the hard blocks and poly(ethylene oxide) formed the soft segments along the copolymeric chain. In our earlier work [13–15], we synthesized these PEO/PLA (PELA) copolymers by reacting poly(ethylene glycol) chains with lactic acid via a hydroxyl-carboxylic acid condensation reaction, followed by a transesterification step, whereby high molecular weight polymers were produced. Presently, a family of PEO/PLA poly(ether-ester-urethane) multiblock copolymers has been developed following a two-stage reaction. PLA–PEO–PLA triblocks were synthesized first, followed by their chain extension with hexamethylene diisocyanate (HDI).

This article describes PELA multiblock copolymers differing in the segmental length of each of the two components, as well as in the ratio between them. Light will be shed on the relationship between their composition, morphology and mechanical properties. PELA elastomers already performed most satisfactorily as the absorbable component of highly compliant, selectively biodegradable filament wound vascular grafts implanted in the canine carotid artery for 90 days [16–18]. These polymers were also very successful in preventing post-surgical adhesions in various animal models [19,20] and are currently undergoing clinical studies.

2. Experimental

2.1. Materials

The different molecular weight poly(ethylene glycol) chains used (1000, 3200, 6000 and 10,000) and hexamethylene diisocyanate (HDI) were supplied by Aldrich (Milwaukee, USA). L-lactide was purchased from Boehringer (Ingelheim, Germany), while the stannous octanoate catalyst and dioxane were provided by Sigma (Steinheim, Germany).

2.2. Drying

Poly(ethylene glycol) was dried in a three-necked flask, under vacuum and magnetic stirring, at 105 °C, for 90 min.

2.3. Synthesis

The synthesis of these PEO/PLA multiblock copolymers consisted of a two-step polymerization reaction, in which the PLA–PEO–PLA triblocks initially produced, were then chain extended with HDI.

2.3.1. Triblock preparation

After drying, the calculated amounts of L-lactide (LD) and stannous octanoate, were added using a 400/1 LD/catalyst molar ratio. The first stage of the synthesis was carried out in 250 ml three-necked flasks, in the molten state (145 °C) for one hour, under a dry nitrogen atmosphere and mechanical stirring (~100 rpm).

2.3.2. Chain extension

The second stage of the synthesis was performed by reacting the triblock with hexamethylene diisocyanate, in a 1.0:1.1 Triblock:HDI molar ratio. Twenty grams triblock were dissolved in dry dioxane and HDI was added to the dissolved triblock, followed by 0.3 g of catalyst. The reaction was conducted at 82 °C for 3 h, under a dry nitrogen atmosphere and mechanical stirring (~100 rpm). The resulting polymer was precipitated into ether, dried and then dissolved in chloroform to generate a 7 wt% solution. Finally, 250 micrometer thick films were cast from the resulting solution, by evaporating the solvent at room temperature, followed by vacuum drying to optimize solvent removal.

2.4. Characterization

(a) *Gel permeation chromatography (GPC).* The average molecular weights and polydispersity were determined by gel permeation chromatography (Differential Separations Module Waters 2690 with refractometer detector Waters 410 and Millenium Chromatography Manager), using polystyrene standards between 472 and 360,000 Dalton.

(b) *Nuclear magnetic resonance spectroscopy (NMR).* ^{1}H-NMR spectra were recorded using a Bruker 300 High Resolution ^{1}H-NMR spectrophotometer. All spectra were obtained at room temperature from 15% (wt/v) $CDCl_3$ solutions. The composition of the copolymers was determined by ratioing the singlet at 3.65 ppm, corresponding to the protons of the EO repeating unit and the proton of the lactoyl methine peak (quartet), centered at 5.15 ppm.

(c) *Thermal analysis.* The samples were analyzed using a Mettler TA 3000 DSC thermoanalyzer. The thermograms ranged from −120 to 200 °C at 10 °C/min heating rate, under an inert nitrogen atmosphere. The heat of fusion was ratioed to the content (%wt) of the component crystallizing, PCL or PLA, in each specific copolymer.

(d) *X-ray diffraction analysis.* A Rigaku RU200 X-ray generator with Cu anode and a Rigaku D-Max/B diffractometer were used to obtain the X-ray diffraction patterns.

(e) *Mechanical properties.* The measurement of the mechanical properties was carried out on dogbone specimens using an Instron Universal Testing Machine (Model 4500), at a crosshead speed of 200 mm/min. A minimum of three specimens per sample were tested.

(f) *Water uptake.* In order to determine the equilibrium water content of the various polymers, 250 μm thick strips of dimensions 20×30 mm^2, were placed in 30 ml distilled water at 37 °C. Weights were recorded periodically, after blotting to remove surface water. Water uptake (%) was calculated as follows: $(w-w_0)*100/w_0$, where, w is the wet weight measured and w_0 is the weight of the dry sample.

2.5. Nomenclature

The poly(ether-ester-urethane)s described in this article are designated by relating to the composition of the basic PLA–PEO–PLA triblock, with the length of the PEO chain being denoted first, followed by the molecular weight of each lateral PLA block. Therefore, PELA6000/1,200, for example, denotes a copolymer based on triblocks comprising a PEO6,000 chain and two PLA blocks, each of them having a molecular weight of 1200. Also, since this study focused on L-lactide only, PLLA will be denoted simply as PLA.

3. Results and discussion

3.1. The working concept

Our work aimed at harnessing the distinctive phase segregated morphology and superior mechanical properties of thermoplastic elastomers [21], to the development of strong, highly flexible biodegradable polymers. As in typical poly(ether-urethane)s [22,23], the hard blocks formed strong domains that acted as physical crosslinks, while the soft segments rendered these multiblock copolymers with their remarkable flexibility and extendibility.

Because of their high mobility, amorphous PEO chains were selected to act as the flexible segments present along the copolymeric backbone [24]. Poly(L-lactic acid) is a rather stiff aliphatic polyester, with a glass transition around 55 °C and a melting point around 180 °C [25]. Due to these structural features, PLLA was chosen to create the hard blocks along these copolymers. In addition to their mechanical roles, each constituent fulfilled additional tasks. The PEO allowed to fine tune the hydrophilicity of the matrix, while PLLA afforded the biodegradability to the system.

The synthesis of the PELA copolymers was conducted following a two-stage reaction, as schematically described in Scheme 1.

First, PLA–PEO–PLA triblocks were synthesized by the ring-opening polymerization of L-lactide, initiated by the hydroxyl terminal groups of the poly(ethylene glycol) chain. The second stage involved the chain extension of the OH-terminated PLA–PEO–PLA trimers, using hexamethylene diisocyanate (HDI), whereby urethane groups were generated along the polymeric backbone.

In contrast to the triblocks synthesized by other groups [26–28], the multiblock nature of these high molecular weight copolymers, represents one of their fundamental attributes. That, since it allowed to tailor the morphology of the copolymer by fine tuning the composition of the basic triblocks, while attaining superior mechanical properties due to the high molecular weight of the chain extended multiblock copolymers.

3.2. The triblocks

The PEO and PLA segments covered a broad range of molecular weights, with PEO chains spanning from 1000 up to 10,000 and PLA blocks ranging from around 200 to approximately 3600. Predictably, this very broad compositional spectrum resulted in polymers displaying markedly different morphological features and mechanical properties.

GPC measurements revealed that the PLA–PEO–PLA triblocks had a rather narrow molecular weight distribution, as revealed by the low polydispersity values obtained (typically below 1.2). The composition of the triblocks was determined using NMR analysis, by ratioing representative peaks of the ethylene oxide and lactoyl units. The peaks chosen were the singlet centered at 3.6 ppm, assigned to PEO's methylene protons, and the quartet at 5.2 ppm, due to PLA's methine proton.

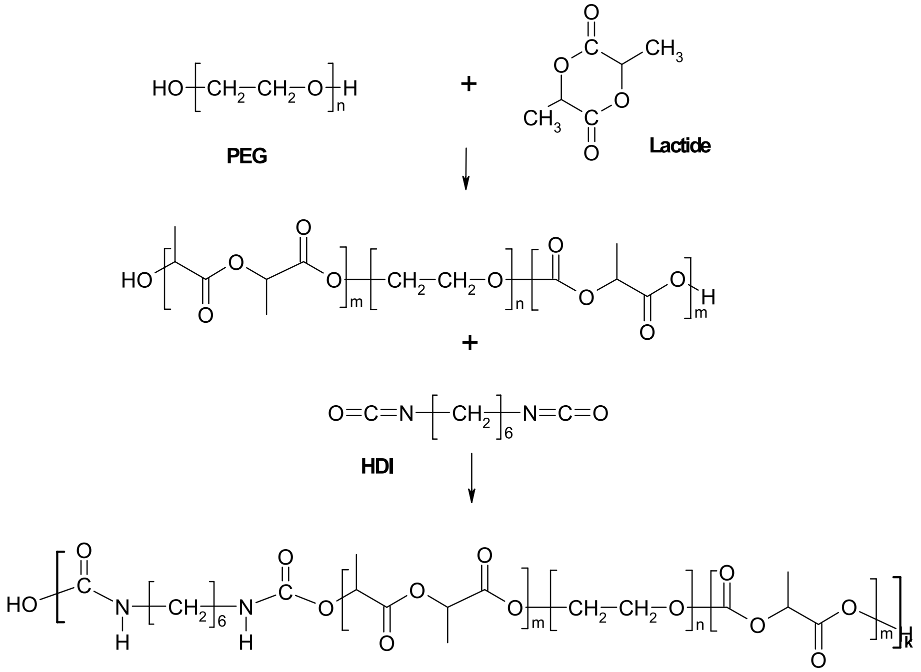
3.3. The copolymers

The multiblock copolymers generated by reacting the different triblocks with HDI, were categorized following two basic criteria: [A] their PEO content and [B] the length of the PLA and PEO segments, for a specific (EO/LA) ratio. Given the relatively high molecular weight of the triblocks (typically above 5000), the morphology of the chain extended polymer and that of the respective triblock are very similar. In the interest of conciseness, therefore, and since this study focuses on the chain extended polymers, the morphological data presented pertains only to the high molecular weight multiblock copolymers.

3.3.1. [A] Copolymers with different degrees of hydrophilicity

3.3.1.1. Same PEO segment with increasingly long PLA blocks. Fig. 1 presents the thermograms of three PELA polymers comprising the same PEO segment (6000), with increasingly long PLA blocks (from 12 to 17 and 36 lactoyl units).

As apparent from the thermograms shown, the PEO segment prevented the crystallization of the shorter PLA blocks, comprising 12 and 17 lactoyl units. It was only when the PLA blocks were sufficiently long (36 lactoyl units) that they were able to crystallize, albeit rather modestly ($\Delta H=$ 22.1 J/gr). Likewise, the ability to hamper PEO's crystallization increased with the length of the PLA segments, as revealed by the shift of PEO's melting endotherm, from 51 °C for PELA6000/850, down to 28 °C for



Scheme 1. Synthesis and structure of PELA block copolymers.

PELA6000/2600. Predictably, PEO's heat of fusion (normalized to its content in the copolymer) was also largely affected, decreasing from 100 J/gr for the former to 16 J/gr for the latter.

These findings were fully corroborated by X-ray diffraction analysis. The patterns shown in Fig. 2(a), reveal that the peaks appearing at 17.2° and 23.7° are representatives of PLA's and PEO's crystalline phases, respectively. The large and sharp peak displayed by PELA6000/850 at 23.7°, gradually decreased, as the molecular weight of the PLA block increased to 1200 and, even more so, when it raised further, to 2600 (Fig. 2(b)). Concomitantly, while the LA sequences present in both PELA6000/850 and PELA6000/1200 were amorphous, the longer PLA blocks were able to crystallize to some extent in PELA6000/2600, as revealed by the small peak detectable at 17.2°. The limited crystallizability of these PLA segments was demonstrated by both the calorimetric findings as well as the X-ray analysis.

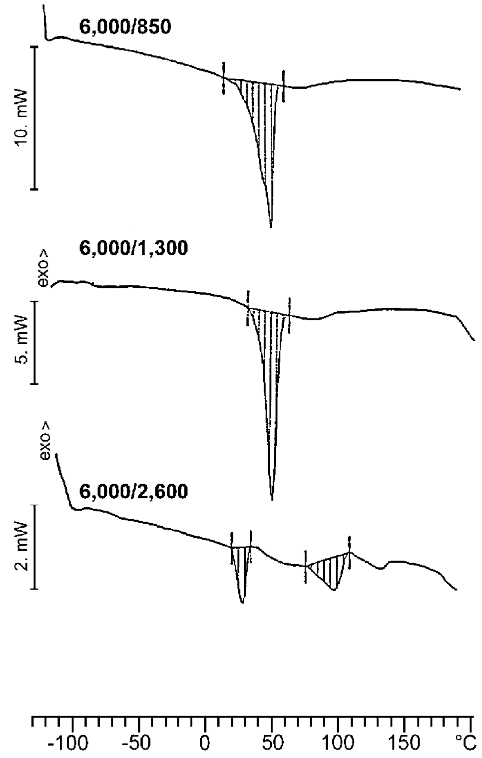


Fig. 1. DSC thermograms of three PELA polymers comprising the same PEO segment (6000) and increasingly long PLA blocks.

These hydrophilic polymers absorbed large amounts of water, the equilibrium uptake level rising from around 120% to 460%, as the PEO content increased, as shown in Fig. 3.

The mechanical properties of PELA copolymers were determined in the dry and hydrated states (after 2 h immersion in a buffer solution at 37 °C). When dry, these multiblock copolymers displayed high strength (between 26 and 31 MPa) and enhanced flexibility, with Young's moduli around 14 MPa and elongation at break values between 1200% and 1800%. Expectedly, once hydrated, the mechanical properties dropped substantially, especially for PELA6000/850, which was so weak that no measurements could be conducted. Having said that, the relatively long and partially crystallized hydrophobic PLA blocks present in PELA6000/2600 were able to reinforce the hydrophilic matrix, enabling the hydrated material to display a

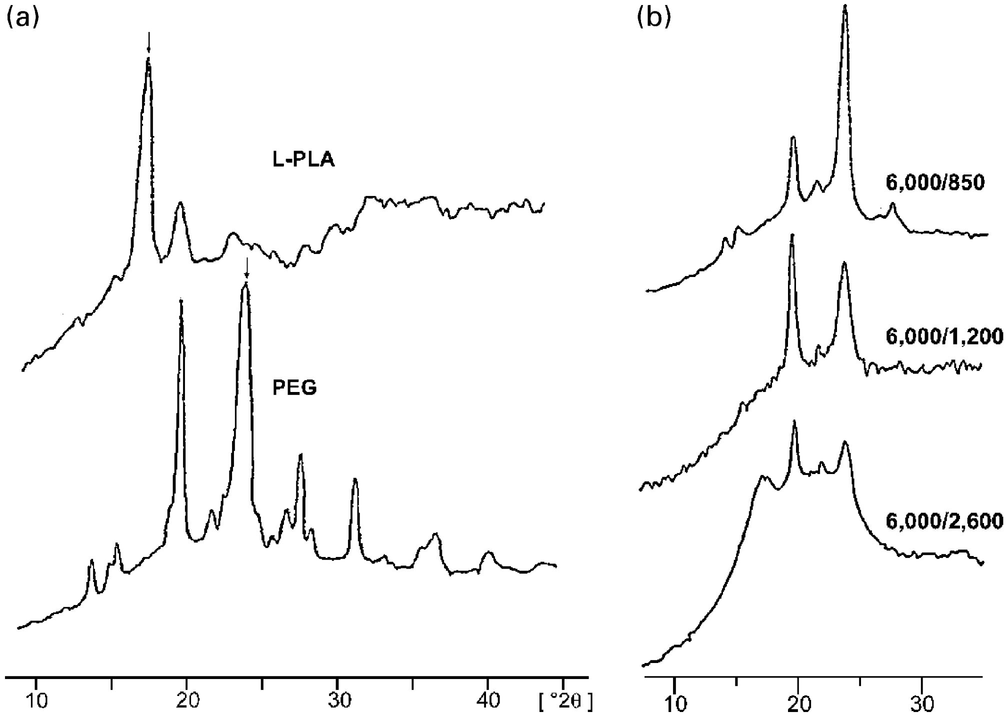


Fig. 2. (a) X-ray diffraction patterns of L-PLA and PEG. (b) X-ray diffraction patterns of three PELA polymers comprising the same PEO segment (6000) and increasingly long PLA blocks.

remarkable 9.0 MPa UTS level, with a Young's modulus of 8.5 MPa and 1200% strain to failure.

3.3.1.2. Same PLA block with increasingly long PEO segments. When the PLA length was kept constant (around 1250) and the PEO segment increased from 3200 to 6000 and 10,000, significant changes in the microstructure of the materials were obtained. Fig. 4 presents the thermograms of the following three PELA copolymers: 3200/1300, 6000/1200 and 10,000/1300. The PEO chains present in PELA3200/1300 were amorphous (T_g around −47 °C), while partially crystallized PLA segments showed a small melting endotherm at 88 °C. The other two copolymers were characterized by a PEO crystalline phase and an amorphous PLA component. PEO's melting endotherm shifted from 50 to 58 °C, as the length of the PEO chains increased from 6000 to 10,000, while the heat of fusion increased accordingly.

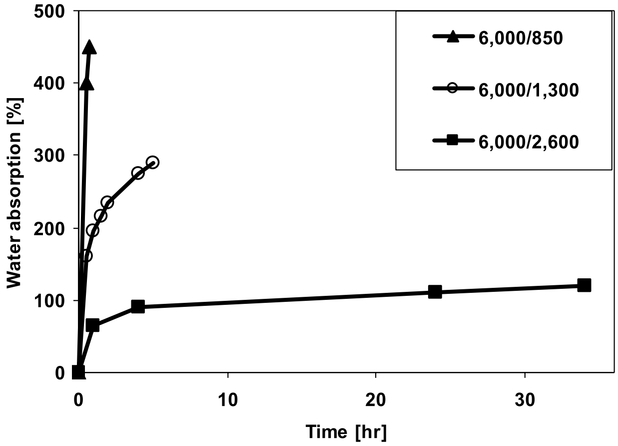


Fig. 3. Water absorption of three PELA polymers comprising the same PEO segment (6000) and increasingly long PLA blocks, as a function of time.

The different morphology of these materials reflected also on their mechanical response. Their Young's modulus, for example, increased from 18 MPa for PELA3200/1300, to 150 MPa and 220 MPa for PELA6000/1200 and PELA10,000/1300, respectively. The enhanced flexibility of the copolymer comprising the shortest PEO segment can be attributed to the essentially amorphous nature of the poly(ethylene oxide) chains. As the PEO became longer and was able to crystallize, the materials became stiffer.

The water absorption of the different copolymers depended markedly on their composition, with the highly hydrophilic PELA10,000/1300 absorbing 450% in 30 min, falling apart a few minutes later. PELA3200/1300 was the only copolymer of this group that displayed enhanced mechanical properties after being immersed in water, dropping from its dry UTS value of 30.0 MPa, down to 8.5 MPa once fully hydrated. Having said that, it is apparent from these data that several water swollen PELA copolymers displayed mechanical properties markedly superior to those exhibited by other biodegradable polymers, even when in their dry state. For example, poly(glycerol sebacate) (PGS), a slightly crosslinked biodegradable elastomer recently synthesized [9], attained ultimate tensile strength values only slightly above 0.5 MPa.

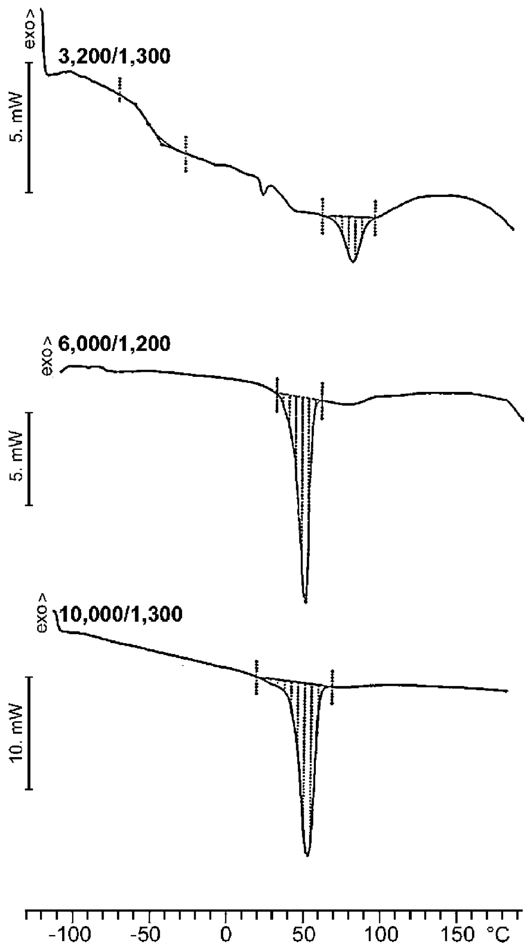


Fig. 4. DSC thermograms of three PELA copolymers comprising the same PLA block (around 1250) and increasingly long PEO segments.

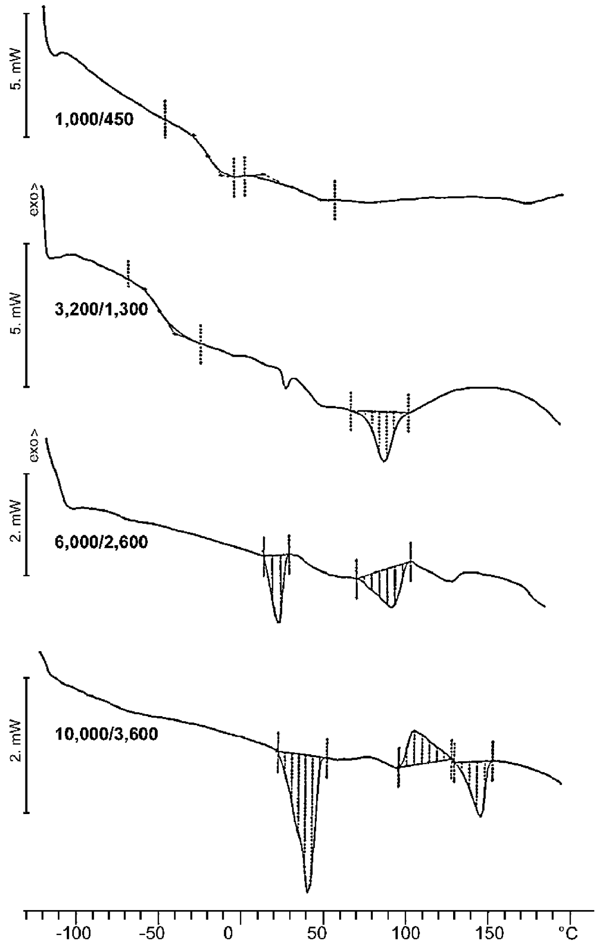


Fig. 5. DSC thermograms of four PELA copolymers having an (EO/LA) ratio of about two and increasingly long segments.

3.3.2. [B] Varying the length of the PEO and PLA blocks

This part of the study investigated the effect of the length of the blocks on the morphology of PELA copolymers, while keeping the (EO/LA) ratio constant. This issue will be illustrated for four copolymers having an (EO/LA) ratio of about 2: PELA1000/450, PELA3200/1300, PELA6000/2600 and PELA10,000/3600.

The thermograms shown in Fig. 5 revealed that the morphology of the copolymers differed markedly, depending on the length of the blocks.

This series of copolymers comprised one amorphous matrix (PELA1000/450), one monophasic crystalline material (PELA3200/1300) and two copolymers (PELA6000/2600 and PELA10,000/3600) where both components were able to crystallize. PELA1000/450 displayed one PEO-related glass transition around −20 °C, and a second one around 31 °C, attributed to PLA's amorphous phase. The marked shift of both glass transitions indicated that a substantial degree of phase blending took place between the relatively short segments of the two components. PELA3200/1300 was predominantly amorphous, displaying only a PLA-related melting endotherm at 88 °C, while PEO was unable to crystallize. As both segments increased further, they generated two distinct crystalline phases, as demonstrated by the two fusion peaks observed. While PEO6000 chains showed a melting endotherm at 28 °C, it shifted to 44 °C for PEO10,000. Similarly, PLA exhibited a melting endotherm centered at 101 °C, that moved up pronouncedly, to 149 °C, as the length of the degradable blocks increased from 36 to 49 lactoyl units, in PELA6000/2600 and PELA10,000/3600, respectively.

The X-ray diffraction patterns shown in Fig. 6 are in full accordance with the thermal data discussed above.

While PELA1000/450 displayed a pattern characteristic of amorphous matrices, the degree of crystallinity of the copolymers raised concurrently with their segmental length. The crystalline nature of the copolymer was especially well developed in PELA10,000/3600, which exhibited the sharp peaks at 17.2° and 23.7°, characteristic of PLA's and PEO's crystalline phases, respectively.

The data presented in Table 1 reveal that highly flexible, strong elastomers were obtained.

These findings demonstrate that the morphology of the

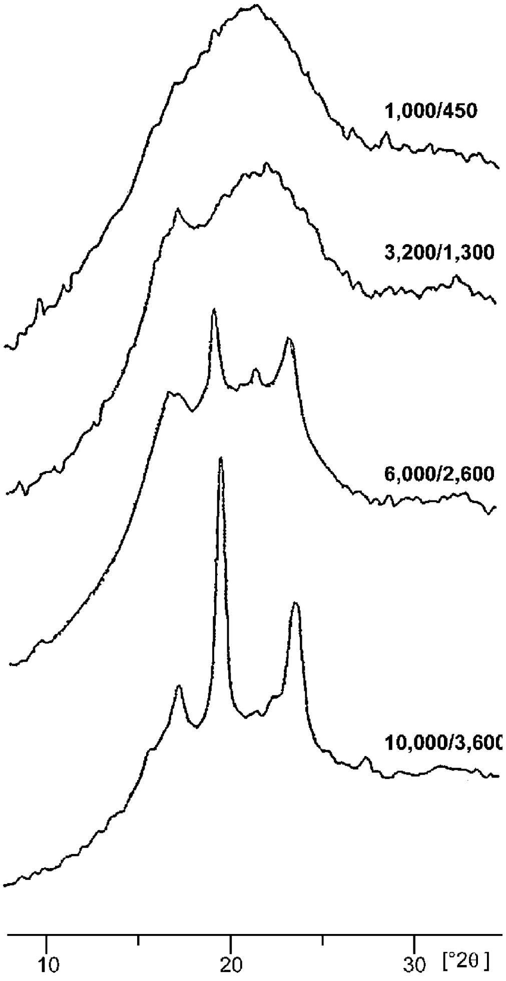


Fig. 6. X-ray diffraction patterns of four PELA copolymers having an (EO/LA) ratio of about two and increasingly long segments.

copolymers, as elucidated by DSC and X-ray analyses, played a fundamental role in determining their mechanical properties. This is shown most clearly by the high ultimate tensile strength (around 30 MPa) of the three crystalline copolymers, on one hand, and by the modest 3.5 MPa tensile strength attained by amorphous PELA1000/450, on the other hand. As the molecular weight of the segments raised, the polymers became gradually stiffer, with *E* values increasing steadily from 8.5 MPa for PELA1000/450 up to 214 MPa for PELA10,000/3600. All four copolymers displayed remarkable extendibility, that increased with the length of the blocks, until the PEO became substantially crystalline, in PELA10,000/3600. The longer the PLA and PEO segments, the more segregated the two phases, allowing the flexible, essentially amorphous PEO chains to render the materials with very high elongation at break values. Once the PEO segments were long enough to crystallize (Figs. 5 and 6), a sharp decrease in the strain at failure was apparent, concurrent with a sharp increase in the rigidity of the material.

These PELA copolymers absorbed substantial amounts of water (between 70% and 120% after 2 h immersion in a buffer solution at 37 °C) with the anticipated large effect on their mechanical performance, as shown in Table 1. While amorphous PELA1000/450 lost its mechanical integrity already after 3 h, the other copolymers performed much better. After absorbing around 80% water, PELA6000/2600, for example, displayed UTS and *E* values of 9.0 MPa and 8.5 MPa, respectively. Even though the strength of the hydrated polymers was typically about one third of that of their respective dry counterparts, these multiblock copolymers were still remarkably stronger than other biodegradable elastomers recently developed and most existing hydrogels [29–31].

4. Conclusion

A family of strong, highly flexible biodegradable polymers was developed, by capitalizing on the particular morphology and superior mechanical properties of thermoplastic elastomers. Calorimetric and X-ray studies revealed that amorphous matrices as well as materials comprising one or two crystalline phases, could be synthesized by fine tuning diverse compositional parameters. PEO/PLA multiblock copolymers displaying enhanced mechanical properties where tailored to generate a phase segregated microstructure, where the poly(ethylene oxide) amorphous chains performed as a molecular spring and the crystalline PLA blocks formed strong non-covalent crosslinking domains. These highly flexible thermoplastic elastomers attained ultimate tensile strength values as high as 30 MPa and elongation at break levels well above 1000%. Furthermore, the reinforcing effect of the crystalline and hydrophobic PLA domains enabled some of these copolymers (e.g. PELA6000/2600) to retain noteworthy strength (8–9 MPa), even when in their fully hydrated state.

Table 1
Mechanical properties of four PELA copolymers having an (EO/LA) ratio of about two and increasingly long segments

Polymer	UTS [MPa]		Modulus [MPa]		Strain at failure [%]	
	Dry	Wet	Dry	Wet	Dry	Wet
1000/450	3.5	–	8.5	–	1000	–
3200/1300	30.0	8.5	17.5	9.5	1200	1000
6000/2600	31.0	9.0	13.5	8.5	1800	1200
10,000/3600	30.0	6.0	214.0	10.4	900	450

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