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PLA-based biodegradable and tunable soft elastomers for biomedical applications

PLA-based biodegradable and tunable soft elastomers for biomedical applications

Amine Harrane¹, Adrien Leroy, H el ene Nouailhas, Xavier Garric, Jean Coudane and Benjamin Nottelet²

Faculty of Pharmacy, Max Mousseron Institute of Biomolecules (IBMM), UMR CNRS 5247 University of Montpellier 1, University of Montpellier 2, 15 Av. C. Flahault, Montpellier 34093, France

E-mail: benjamin.nottelet@univ-montp1.fr

Abstract

Although desirable for biomedical applications, soft degradable elastomers having balanced amphiphilic behaviour are rarely described in the literature. Indeed, mainly highly hydrophobic elastomers or very hydrophilic elastomers with hydrogel behaviours are found. In this work, we developed thermoset degradable elastomers based on the photo-cross-linking of poly(lactide)-poly(ethylene glycol)-poly(lactide) (PLA-PEG-PLA) triblock prepolymers. The originality of the proposed elastomers comes from the careful choice of the prepolymer amphiphilicity and from the possible modulation of their mechanical properties and degradation rates provided by cross-linkers of different nature. This is illustrated with the hydrophobic and rigid 2,4,6-triallyloxy-1,3,5-triazine compared to the hydrophilic and soft pentaerythritol triallyl ether. Thermal properties, mechanical properties, swelling behaviours, degradation rates and cytocompatibility have been evaluated. Results show that it is possible to generate a family of degradable elastomers covering a broad range of properties from a single biocompatible and biodegradable prepolymer.

1. Introduction

In an attempt to provide alternative biomaterials to the classical aliphatic polyesters used in drug delivery or tissue-engineering applications, biodegradable elastomers have recently attracted growing attention. Indeed, their ability to provide a structural support for the regeneration of soft tissues such as blood vessels or ligaments, with mechanical properties similar to those of native tissues in dynamic environment, and their ability to recover their shape after high deformation make them of a particular interest [1, 2]. Besides, if properly designed, they can provide a dimensionally stable

soft structure with tunable degradation rates, which makes them suitable for a large field of applications, including drug delivery. These biodegradable elastomers can be prepared as both thermoplastics (TPs) or thermosets (TSs), each family having advantages and disadvantages.

TP elastomer properties result from physical cross-links which are typically obtained from ABA linear copolymers where A and B are immiscible polymers segregated in phase-separated domains. One phase acts as a cross-linker, generally due to its crystallinity, whereas the second one is amorphous and possesses a low glass transition temperature. A classical method to get TP is to use polymers of high molecular weight for improved entanglement [3, 4]. However, chain extension with highly reactive reactants, like isocyanates, is usually preferred as it allows an easier process. Degradable TP

¹ Present address: Department of Chemistry, Faculty of Sciences, University of Oran Es-Senia, Oran 31000, Algeria.

² Author to whom any correspondence should be addressed.

based on ϵ -caprolactone (CL) and lactic acid (LA) linear and star copolymers have been prepared with Young's modulus (E) in the range 8–30 MPa and elongation at breaks (ϵ_{break}) above 500% [5–7]. To modulate these properties, these copolymers have been combined with various co-monomers including poly(ethylene glycol) [8, 9], butanediol [10–12] or butylene succinate [13]. Alternatively, a new class of materials prepared by polycondensation of polyols and citric acid [14] or sebacic acid [15] with low cross-linking density have also been described for further enlargement of degradable TP properties. TP are generally easily processed and complex shapes can be designed; however, their crystallinity leads to heterogeneous degradation and release profiles as well as nonlinear loss of properties with degradation, which limits their use in controlled drug delivery applications [8, 16, 17].

TS elastomers, on the opposite, are cross-linked via covalent bonds and can be prepared from amorphous prepolymers. As a result of their high cross-linking density, TS cannot be remolded by heating, and thus the preparation of complex 3D shapes is not always possible, depending on the nature of cross-linking process [4]. In addition, non-toxic cross-linkers should be chosen to guarantee the final biocompatibility. Despite these drawbacks, TSs are of interest since they generally degrade by combination of bulk and surface erosion, which assures a constant 3D structure throughout the hydrolysis process as well as a linear drug release profile [16, 18]. Cross-linking of the prepolymers is generally obtained by thermal activation of radical reactions, by post-polycondensation reactions or by photocuring. Like TP, many structures of degradable TS have been reported so far, including highly cross-linked polyesteramides [16, 19, 20], or cross-linked (co)polyesters based on ϵ -CL, LA and glycolic acid [18, 21–26]. A broad range of mechanical behaviours is offered by these structures with E in the range 0.2–800 MPa and ϵ_{break} in the range 5–600%. However, these materials present some drawbacks. For the former ones, a high temperature is required during a few days for the curing process and it is difficult to control the final cross-linking density. For the latter ones, a very slow hydrolytic degradation rate is observed, with less than 10% weight loss after 10 weeks [19, 22, 23, 25]. To increase this degradation rate while controlling the cross-linking density, Sheares *et al* recently proposed amorphous unsaturated aliphatic polyesters based on trans- β -hydromuconic acid and oligo(ethylene glycol) with a linear degradation of 100% in 30 days [17]. In another strategy, elastomer hydrophilicity is increased by addition of poly(ethylene glycol) (PEG) in the structure to accelerate the degradation. This strategy has been used to produce cross-linked hydrogels for drug delivery purposes. These hydrogels based on poly(lactide)-poly(ethylene glycol)-poly(lactide) (PLA-PEG-PLA) are soft, swelling materials which completely degrade within 8–9 weeks [27–30]. Although having some elastomeric properties, they cannot be used in applications requiring both elasticity and shape recovery, due to their very high swelling ratio resulting from the use of long PEG blocks (DP 100–200) or very short PLA blocks (DP 3) used to guarantee the formation of hydrogels. Typically, DP ratios between PEG

and PLA blocks are in the range 3.5–17, and the corresponding triblock copolymers are freely water soluble. To the best of our knowledge, the only example with a lower hydrophilicity has been described by Lee *et al* with acrylated PLA₂₁-PEG₁₀₀-PLA₂₁ used to form hydro-nanogels [29].

Our group, involved for many years in the study of PLA-PEG-PLA triblocks, including hydrogels [31–33], micelles and stereocomplexes [34–36], describe in this work the preparation of degradable elastomers based on short photo-cross-linked methacrylated PLA-PEG-PLA triblocks. A careful choice of the triblock copolymers has been done to ensure an amphiphilic balance and provide intermediate degradation times and linear degradation profiles to the elastomers. In addition, we would like to illustrate the possibility to obtain various mechanical behaviours from the same initial triblock, depending on the presence and the nature of cross-linkers. Two cross-linkers, 2,4,6-triallyloxy-1,3,5-triazine (TAC) and pentaerythritol triallyl ether (PETAE), already used for biomedical applications [37–42], have been chosen for their structural differences: rigid versus soft, hydrophobic versus hydrophilic. Elastomers based on PLA-PEG-PLA triblocks cured by UV with either TAC or PETAE have been prepared. Their mechanical properties in dry and hydrated states have been evaluated as well as their degradability. Finally their cytocompatibility has been assessed by the cell viability test with L929 fibroblasts.

2. Materials and methods

2.1. Materials

Dihydroxy PEG (PEG₄₅, 2000 g/mol⁻¹), tin(II) 2-ethylhexanoate (Sn(Oct)₂, 95%), triethylamine (99%), TAC (97%), PETAE (70%), methacryloyl chloride (>97%), diethyl ether and dichloromethane were purchased from Sigma-Aldrich (St-Quentin Fallavier, France). D,L-lactide (D,L-LA) was purchased from Purac (Lyon, France). 1-hydroxycyclohexyl benzophenone (Irgacure[®] 184) was kindly provided by Dr C Joly-Duhamel from the Ecole Nationale Supérieure de Chimie de Montpellier. PrestoBlue[™], modified Eagle's medium (MEM), horse serum, penicillin, streptomycin, Glutamax and Dulbecco's phosphate buffered saline (DBPS) were purchased from Invitrogen (Cergy Pontoise, France). Cellstar[®] polystyrene tissue culture plates (TCPS) were purchased from Greiner Bio-One (Courtaboeuf, France). All chemicals and solvents were used without purification with exception of dichloromethane which was dried over calcium hydride before distillation and use.

2.2. Characterizations

Molecular weights were determined by size exclusion chromatography (SEC) using a Waters equipment fitted with a 60 cm long 5 μ m mixed C PLgel column as the stationary phase, tetrahydrofuran (THF) at 1 ml min⁻¹ flow rate as the mobile phase, and a Waters 410 refractometric detector. Typically, the polymer (10 mg) was dissolved in THF (2 ml) and the resulting solution was filtered on a

0.45 μm millipore filter before injection of 20 μL of sample solution. \overline{M}_n and \overline{M}_w were expressed according to calibration using polystyrene standards. ^1H and ^{13}C NMR spectra were recorded at room temperature using an AMX300 Bruker spectrometer operating at 300 MHz. Deuterated chloroform and deuterated dimethylsulfoxide were used as solvents, and chemical shifts were expressed in ppm with respect to tetramethylsilane. Infrared spectra were recorded on a Perkin–Elmer Spectrum 100 FT-IR spectrometer. Differential scanning calorimetry (DSC) measurements were carried out under nitrogen on a Perkin Elmer Instrument DSC6 thermal analyser. Samples were submitted to a first heating scan followed by a fast cooling ($20\text{ }^\circ\text{C min}^{-1}$) to $-65\text{ }^\circ\text{C}$ and a second heating scan at a $10\text{ }^\circ\text{C min}^{-1}$ to $180\text{ }^\circ\text{C}$. Glass transition temperature (T_g) was measured on the second heating ramp. The partition coefficients ($\log P$) of TAC and PETAE were calculated using the AlogPS2.1 software (VCCLAB, Virtual Computational Chemistry Laboratory, <http://www.vcclab.org>, 2005). PrestoBlueTM absorption was quantified with a Thermo Scientific Multiscan[®] FC microplate photometer.

2.3. PLA-PEG-PLA triblock copolymers' syntheses (TC)

Triblocks were synthesized following a procedure previously described by our group [34]. Typically, predetermined amounts of D,L-LA and PEG₄₅ were introduced into a flask, the initial molar ratio of ethylene oxide to lactyl repeat units (EO/LA) was 2.5. Sn(Oct)₂ (0.1 wt%) was then added. After degassing, the flask was sealed under vacuum and the polymerization was allowed to proceed at $140\text{ }^\circ\text{C}$. After 3 days, the copolymer was recovered by dissolution in CH_2Cl_2 and precipitation in cold diethyl ether. Finally, the product was dried under reduced pressure to constant mass. PLA-PEG-PLA triblocks were obtained with a typical yield of about 90%. ^1H NMR: (300 MHz; CDCl_3): δ (ppm) = 5.2 (m, 1H, CO-CH(CH₃)-O), 4.3 (m, 1H, CO-CH(CH₃)-OH) and 2H CH₂-CH₂-OH, 3.6 (s, 4H, CH₂-CH₂-O), 1.5 (m, 3H, CO-CH(CH₃)-O).

The polymerization degree ($\overline{\text{DP}}$) of PLA blocks was calculated using equation (1):

$$\overline{\text{DP}}_{\text{PLA}} = \frac{1}{2} \times \left(\frac{\overline{\text{DP}}_{\text{PEG}}}{\frac{\text{EO}}{\text{LA}}} \right) \quad (1)$$

with EO/LA being the ratio of ethylene oxide and lactyl units calculated based on the NMR spectra.

Molecular weight (\overline{M}_n) of the synthesized triblock copolymer was calculated using equation (2):

$$\overline{M}_n = 2 \times (\overline{\text{DP}}_{\text{PLA}} \times 72) + \overline{M}_{\text{PEG}} \quad (2)$$

with 72 being the molecular weight of a lactic acid unit.

2.4. Methacrylation of PLA-PEG-PLA (MC-TC)

PLA-PEG-PLA was dissolved in freshly distilled CH_2Cl_2 (20% w/v). Triethylamine (4 eq./chain) was added and the copolymer solution was cooled down in an ice bath. Methacryloyl chloride (4 eq./chain) was then added dropwise

from a dropping funnel and the reaction was maintained under stirring at $0\text{ }^\circ\text{C}$ for 6 h in the dark. The reaction was then carried out at room temperature for 66 h in the dark. The reaction medium was filtered and the copolymer precipitated in cold diethyl ether. The precipitate was dissolved in acetone and precipitated in cold diethyl ether before drying under reduced pressure to constant mass. Methacrylated PLA-PEG-PLA triblock copolymers (MC-TC) were obtained with a methacrylation yield of 88% and kept in a dark place. ^1H NMR: (300 MHz; CDCl_3): δ (ppm) = 6.1 and 5.7 (s, 2H, CH₂ = C(CH₃)) 5.2 (m, 1H, CO-CH(CH₃)-O), 4.3 (m, 1H, CO-CH(CH₃)-OH) and 2H CH₂-CH₂-O(CO)), 3.6 (s, 4H, CH₂-CH₂-O), 1.9 (s, 3H, CH₂ = C(CH₃)) 1.5 (m, 3H, CO-CH(CH₃)-O).

Methacrylation efficiency was calculated using equation (3):

$$\text{Efficiency} = \frac{\left(\frac{I_{5.7-6.1}}{2} \right)}{\left[\left(\frac{I_{5.7-6.1}}{2} \right) + \left(I_{4.3} - 4 \times \frac{I_{3.6}}{(\overline{\text{DP}}_{\text{PEG}} \times 4)} \right) \right]} \quad (3)$$

2.5. Elastomers photo-cross-linking and gel content

Typically, MC-TC (1 g) was dissolved in CH_2Cl_2 (1.4 mL) with predetermined amounts of Irgacure[®] 184 as photoinitiator and PETAE or TAC as cross-linkers. Chemical structures are shown in figure S1 (see supplementary data available at stacks.iop.org/BMM/6/065006/mmedia). The obtained viscous solutions were poured in silicon vessels and let to dry slowly under a hood for 24 h in the dark. The resulting films were further dried at room temperature under reduced pressure (10^{-1} bar) for 6 h. The 0.9–1.1 mm thick films obtained were cross-linked for 10 min under the UV light system FUSION UV equipped with a FUSION F300S UV lamp (120 W cm^{-2}) and a LC-6 BENCHTOP conveyor belt running at 5 m min^{-1} . The overall residence time of the films under the UV lamp was 7 min, and each film was turned upside down after 3.5 min.

Sol-gel analysis was conducted by swelling the films in CH_2Cl_2 at room temperature. Initial CH_2Cl_2 was replaced few times by fresh solvent over a 24 h period to allow full extraction of unreacted prepolymers. The solvent was removed, the films were dried and the (Gc) was estimated by calculating the ratio between the films weights before and after extraction.

2.6. Mechanical analyses of elastomers

Elastomer samples ($20 \times 7 \times 1\text{ mm}^3$) were prepared for tensile mechanical analyses. Instron 4444 was used at a crosshead speed of 1 mm min^{-1} and at room temperature. Each sample was analysed in triplicate and Young's modulus (E , MPa), ultimate stress (σ_{break} , MPa), ultimate strain ($\varepsilon_{\text{break}}$, %), yield stress (σ_{yield} , MPa) and elastic limit ($\varepsilon_{\text{yield}}$, %) were expressed as the mean value of the three measurements. E was calculated using the initial linear portion of the stress–strain curve (0–5% strain).

2.7. Elastomers' swelling and degradation

Samples of elastomer films were weighed and placed in a phosphate buffer solution (PBS, pH 7.4) at 37 °C. The swelling percentage was calculated based on the initial dry samples weights according to the following equation:

$$Q = \frac{(W_h - W_0)}{W_0} \times 100, \quad (4)$$

where W_h is the weight of the hydrated sample after t hours in PBS and W_0 is the initial dry weight of the sample. Each result was expressed as the mean value of three measurements.

Degradation was carried out in PBS at 37 °C under stirring for various periods of time. After incubation, the sample was gently dried on absorbent paper, weighed and further dried under reduced pressure at 40 °C. The degradation was assessed using water uptake and weight loss. The water uptake was calculated based on the dry samples' weights after degradation using the following equation:

$$WU = \frac{(W_h - W_d)}{W_d} \times 100, \quad (5)$$

where W_h is the hydrated weight and W_d is the dry weight of the sample after a defined period of time in PBS. The weight loss was calculated using the following equation:

$$WL = \frac{(W_0 - W_d)}{W_0} \times 100, \quad (6)$$

where W_d is the dry weight of the sample after a defined period of time in PBS and W_0 is the initial dry weight of the sample before degradation. Each result was expressed as the mean value of three measurements.

2.8. Elastomer cytocompatibility

Mouse L929 fibroblasts (L929) were cultured in MEM containing 10% horse serum, penicillin (100 $\mu\text{g mL}^{-1}$), streptomycin (100 $\mu\text{g mL}^{-1}$) and Glutamax (1%). Elastomer films were disinfected in ethanol (95%) for 30 min before immersion in a solution of sterile PBS containing penicillin and streptomycin (1 mg mL^{-1}) and incubation for 48 h at 37 °C. Films were then rinsed three times with sterile PBS before soaking for 12 h in sterile PBS. Before drying, swelled sterile elastomer films were stamped to fit the size of the wells of 24-well cell culture plates. The *in vitro* cytocompatibility of the elastomers was assessed by following the proliferation of L929 on the surface of elastomer films. Films were placed in polystyrene 24-well tissue culture plates (TCPS) and seeded with 5000 cells. Cell viability after 4, 7 and 10 days was evaluated using the PrestoBlueTM assay that reflects the number of living cells present on a surface at a given time point. PrestoBlueTM is a cell-permeable resazurin-based viability reagent close to AlamarBlue[®] (supplementary data available at stacks.iop.org/BMM/6/065006/mmedia). At scheduled time points, the culture medium was removed and replaced by 1 mL of fresh medium containing 10% of PrestoBlueTM. After 2 h of incubation at 37 °C, aliquots of 100 μL were taken and analysed for UV absorbance at 570 and 595 nm. All data points and standard deviations correspond to measurements in triplicate.

3. Results and discussion

3.1. Elastomer synthesis

We were interested in the preparation of a soft elastomeric degradable material to guarantee a good biocompatibility and compliance towards soft tissues but, at the same time, with sufficient mechanical properties to guarantee the shape recovery and elastic behaviour required for some tissue-engineering or medical devices applications like, for example, in the fields of vascular prostheses or cartilage repair. Consequently, our strategy was based on the use of well-known PLA and PEG block copolymers. Our group recently described water-soluble PLA-PEG-PLA triblock copolymers with short PLA chains used for micelles' and hydrogels' formations [32, 34–36, 43]. Based on this previous work, we synthesized a triblock copolymer with crystalline PEG₄₅ ($M_n = 2000 \text{ g mol}^{-1}$) as the hydrophilic block and amorphous PLA₅₀ chains with a polymerization degree of 9 ($M_n = 650 \text{ g mol}^{-1}$) as hydrophobic blocks. This short copolymer presents an amphiphilic balance suitable for the purpose of this work.

Composition of the triblock copolymer was determined using ¹H NMR spectroscopy as reported in the literature [34, 36]. A typical NMR spectrum is shown in figure S2 (see supplementary data available at stacks.iop.org/BMM/6/065006/mmedia). The EO/LA ratio was determined from the integrations of protons of PEG block at 3.6 ppm and those of PLA blocks at 5.2 ppm. The ratio EO/LA was 2.5, in good agreement with the theoretical values. The polymerization degree of PLA blocks was calculated using equation (1) and was found equal to 9 in agreement with the expected theoretical value. The molecular weight of the synthesized triblock copolymer, noted PLA₉-PEG₄₅-PLA₉, was calculated using equation (2) and was found equal to $M_{n\text{NMR}} = 3280 \text{ g mol}^{-1}$. Chromatograms resulting from SEC analysis were monomodal and used to confirm the absence of PLA homopolymer ($M_{n\text{SEC}} = 6100 \text{ g mol}^{-1}$, $I_p = 1.4$). The apparent difference between $M_{n\text{NMR}}$ and $M_{n\text{SEC}}$ is attributed to the amphiphilic character of the block copolymer [44].

The synthesis of photo-cross-linkable triblock copolymers was achieved by the reaction between PLA₉-PEG₄₅-PLA₉ and methacryloyl chloride. A methacrylation efficiency of 88% was calculated from the integrations of NMR resonances belonging to the alkenyl protons at 6.1 and 5.7 ppm, and to the PEG and non-methacrylated PLA chain ends at 4.3 ppm using equation (3). SEC analysis was carried out and a molecular weight $M_{n\text{SEC}} = 5500 \text{ g mol}^{-1}$ was found with a polydispersity of 1.4. The little molecular weight decrease observed before and after methacrylation is also attributed to the modification of the amphiphilic character of the block copolymer.

Elastomeric materials with various formulations were then prepared with the two chosen cross-linkers, namely TAC and PETAE. Elastomer formulations are listed in table 1. Cross-linkers' molar concentrations ranging from 0% to 100%, with respect to the alkene groups, have been used. In most cases, Irgacure[®] 184 was also added as a photo-initiator at

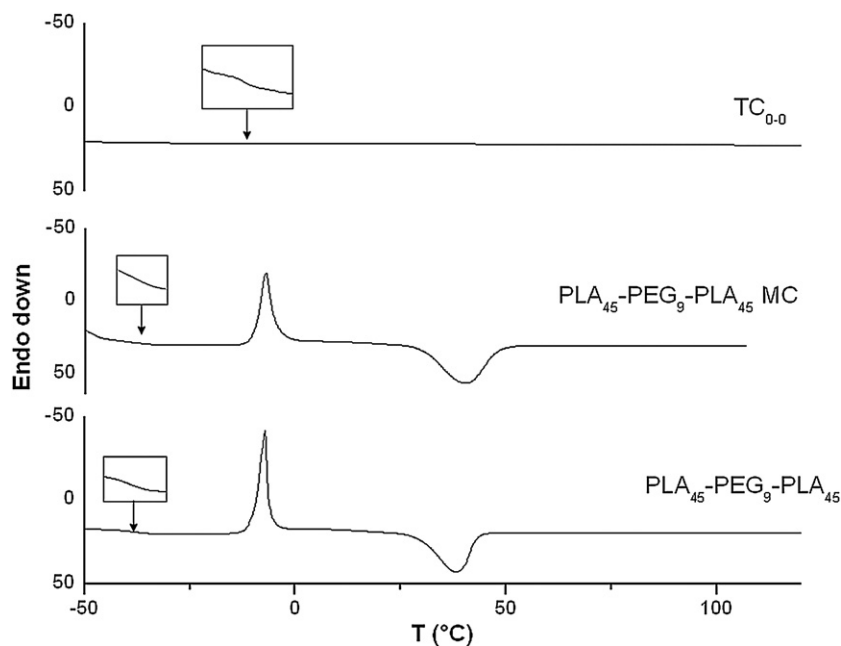


Figure 1. Thermograms of the tribloc copolymer, methacrylated tribloc copolymer and TC₀₋₀ (second heating ramp).

Table 1. Elastomers' formulations.

Sample name	Irgacure [®] 184 (mol%/alkene)	TAC (mol%/alkene)	PETAE (mol%/alkene)
TC ₀₋₀	0	0	0
TC _{I-0}	25	0	0
TC _{I-TAC25}	25	25	0
TC _{I-TAC50}	25	50	0
TC _{I-TAC100}	25	100	0
TC _{I-PETAE50}	25	0	50
TC _{I-PETAE100}	25	0	100

a concentration of 25%, with respect to the alkene groups. After UV cross-linking, elastomeric films have been swelled in CH₂Cl₂ for 24 h at room temperature to remove the non-reacted MC-TC. Gc in the range 70–80% was found for all samples, which corresponded to a cross-linking efficiency in the range 80–90%. This efficiency was similar in all cases, with no significant differences between the formulations. In particular, the cross-linking extent was the same in the presence or absence of photo-initiator.

Thermal properties were investigated by DSC, as shown in figure 1 and figure S3 (see supplementary data available at stacks.iop.org/BMM/6/065006/mmedia) and listed in table 2. As expected, T_g increased with the cross-linking. For TC and MC-TC, T_g was -38 and -37 °C, respectively, but increased to -12 °C for the sample cross-linked with TAC (TC_{I-TAC100}) and -30 °C for the one cross-linked with PETAE (TC_{I-PETAE100}). In accordance with known elastomer behaviours, T_g s increased with the cross-linker ratio as we can see that $T_g = -23$ °C for TC_{I-TAC25} and $T_g = -12$ °C for TC_{I-TAC100}. Interestingly, T_g was lower of about 20 °C when the soft PETAE cross-linker was used instead of the more rigid TAC. Besides, the measured T_g s being below room and body temperatures, they

Table 2. Elastomers' Gc, cross-linking efficiencies and thermal properties.

Sample name	Gc (%)	Cross-linking efficiency (%)	T_g (°C)	T_m (°C)	ΔH_m (J g ⁻¹)
TC	–	–	-38	38	51
MC-TC	–	–	-37	40	50
TC ₀₋₀	77.9 ± 0.9	87.4	-12	30	<1
TC _{I-0}	73.7 ± 1.5	83.8	-16	31	<1
TC _{I-TAC25}	78.8 ± 0.5	89.5	-23	30	<1
TC _{I-TAC50}	79.1 ± 0.9	89.9	-19	30	<1
TC _{I-TAC100}	80.0 ± 0.6	90.9	-12	30	<1
TC _{I-PETAE50}	70.0 ± 0.7	79.5	-31	30	<1
TC _{I-PETAE100}	73.7 ± 0.3	83.8	-30	34	<1

guarantee the soft elastomeric behaviours of the samples under physiological conditions. It can be noted that despite the cross-linking, a little crystallinity could be found in elastomers with typical melting temperatures (T_m) around 30 °C. However, the associated enthalpy $\Delta H_f < 1$ J g⁻¹ is negligible in comparison to the one found for TC and MC-TC ($\Delta H_f \approx 50$ J g⁻¹) and the elastomers can be considered as quasi-amorphous.

3.2. Elastomers' mechanical properties

Ideally, the present degradable elastomeric materials should be prepared by a synthetic methodology allowing the control of mechanical properties and degradability over a broad range. That is why we based our strategy on the cross-linking of a single and simple prepolymer, MC-TC, the desirable versatility being obtained from the presence and the nature of the cross-linkers. The chosen cross-linkers, TAC and PETAE, have a great difference in their structures, and the former is more rigid and hydrophobic than the latter ($\log P$ TAC = 3.1 ± 0.9 and $\log P$ PETAE = 1.3 ± 0.4). These characteristics are responsible for the difference already found between the

Table 3. Elastomers mechanical properties in the dry and hydrated states: Young’s modulus (E), ultimate stress (σ_{break}), ultimate strain ($\varepsilon_{\text{break}}$) and elastic limit ($\varepsilon_{\text{yield}}$).

Dry state				
Sample name	E (MPa)	σ_{break} (MPa)	$\varepsilon_{\text{break}}$ (%)	$\varepsilon_{\text{yield}}$ (%)
TC ₀₋₀	2.2 ± 0.2	1.1 ± 0.2	42 ± 9	15
TC _{I-0}	2.7 ± 0.2	0.9 ± 0.1	34 ± 2	5
TC _{I-TAC25}	3.0 ± 0.4	0.8 ± 0.1	29 ± 2	5
TC _{I-TAC50}	3.9 ± 0.7	1.0 ± 0.1	26 ± 5	5
TC _{I-TAC100}	4.5 ± 0.7	1.0 ± 0.1	25 ± 3	8
TC _{I-PETAE50}	3.0 ± 0.2	1.9 ± 0.1	66 ± 6	15
TC _{I-PETAE100}	3.5 ± 0.4	1.8 ± 0.4	52 ± 6	13
Hydrated state				
TC ₀₋₀	2.2	1.3	90	30
TC _{I-TAC100}	3.5	1.0	42	12
TC _{I-PETAE100}	2.2	1.0	130	25

T_g s of TC_{I-PETAE100} and TC_{I-TAC100}. To further demonstrate the possibility to generate a family of elastomers having various properties, we evaluated their mechanical properties on dry films under static conditions as a function of two parameters: the cross-linker concentration and its nature. Elastic deformations have been evaluated on the linear part of the strain–stress curves and the results are listed in table 3.

The cured neat material TC₀₋₀, without the photoinitiator and curing agent, had a Young’s modulus of 2.2 MPa and an elongation at break of 42%. For a defined cross-linker, E increased with the increase of cross-linker concentration, as we can see that $E = 3.0$ MPa for TC_{I-TAC25}, and $E = 4.5$ MPa for TC_{I-TAC100}. On the opposite, the elongation at break decreased with the increase of cross-linker concentration with $\varepsilon_{\text{break}}$ decreasing by about 20% between TC_{I-PETAE50} and TC_{I-PETAE100} and by about 14% between TC_{I-TAC25} and TC_{I-TAC100}. No influence of the cross-linker concentration was found for the ultimate stress, as we can see values around 1 MPa for TAC and 2 MPa for PETAE. The effect of the cross-linker nature on the final properties is very pronounced as shown in figure 2(a). In more detail, at fixed cross-linker concentrations, the TAC-based samples presented the highest stiffness with about 30% higher modulus compared to the corresponding PETAE-based samples. They also exhibited the lowest elasticity as a result of the blocked structure of the TAC aromatic ring. On the other hand, PETAE-based samples were the most deformable ones with an ultimate strain above 50% and elastic behaviours up to 15% of strain. Figure 3 illustrates these elastic properties and shape recovery ability, which are attributed to the high flexibility of the ether bond of the PETAE.

These effects were even more remarkable in the hydrated state and typical strain–stress curves of the hydrated materials are given in figure 2(b). Samples were soaked in PBS and their swelling ratio Q was measured after 1, 2 and 18 h. No differences were found between these three time points, so that figure 4 shows the relative swelling of the elastomers after 1 h in PBS. It can be seen that the highest swelling is found for elastomers cured without cross-linkers with about 100% water uptake. Swelling decreases with the cross-linker concentrations and, as expected, it is higher for the

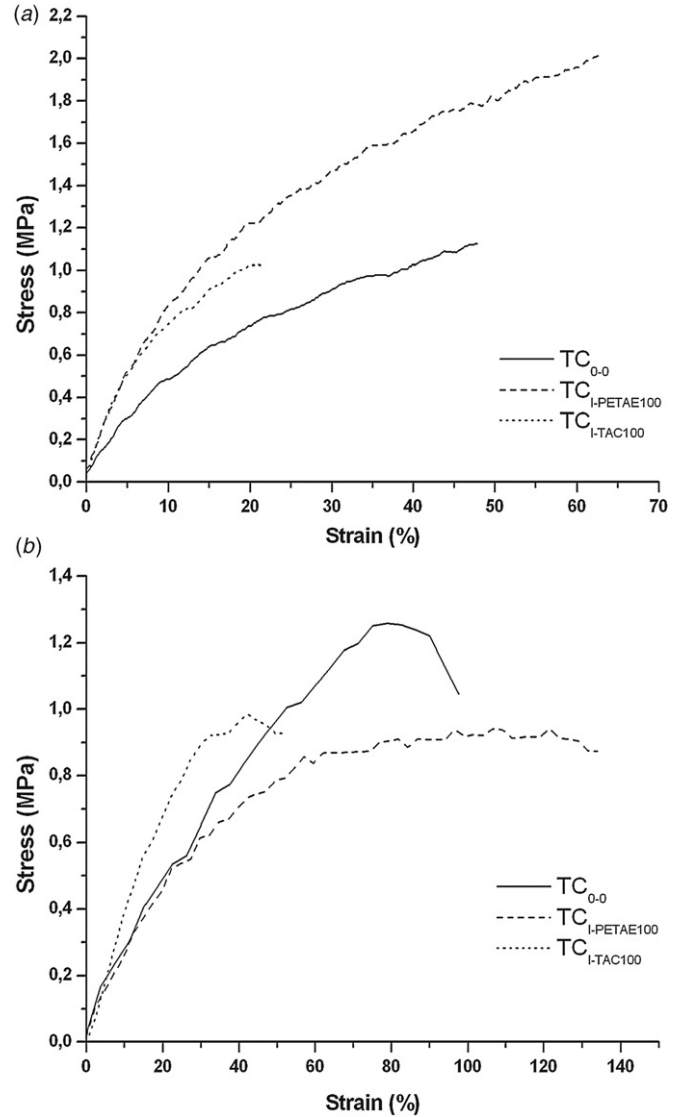


Figure 2. Typical strain–stress curves of elastomers in the (a) dry state and (b) hydrated state.

samples containing the less rigid, more hydrophilic PETAE. The choice of short triblock copolymers with a defined initial amphiphilicity is an advantage. Indeed, due to the balance between hydrophilic PEG and hydrophobic PLA segments ($EO/LA = 2.5$), the swelling is limited to about 100%. This limited swelling compared to other PEG/PLA-based structures found in the literature [27, 30, 45] is of importance to guarantee a relative dimensional stability of the elastomers when used in the surrounding of biological fluids. In addition, although influenced by swelling, the mechanical properties of the hydrated elastomers followed the same trends as the ones found for the dried ones.

The results are listed in table 3. To summarise, elastomers’ hydration led to slightly lower Young’s modulus with E decreasing to about 20% for TC_{I-TAC100} and about 35% for TC_{I-PETAE100}. More significant is the increased deformability under the hydrated state. As illustrated in figure 2(b), the strain values and elastic domains more or less doubled in

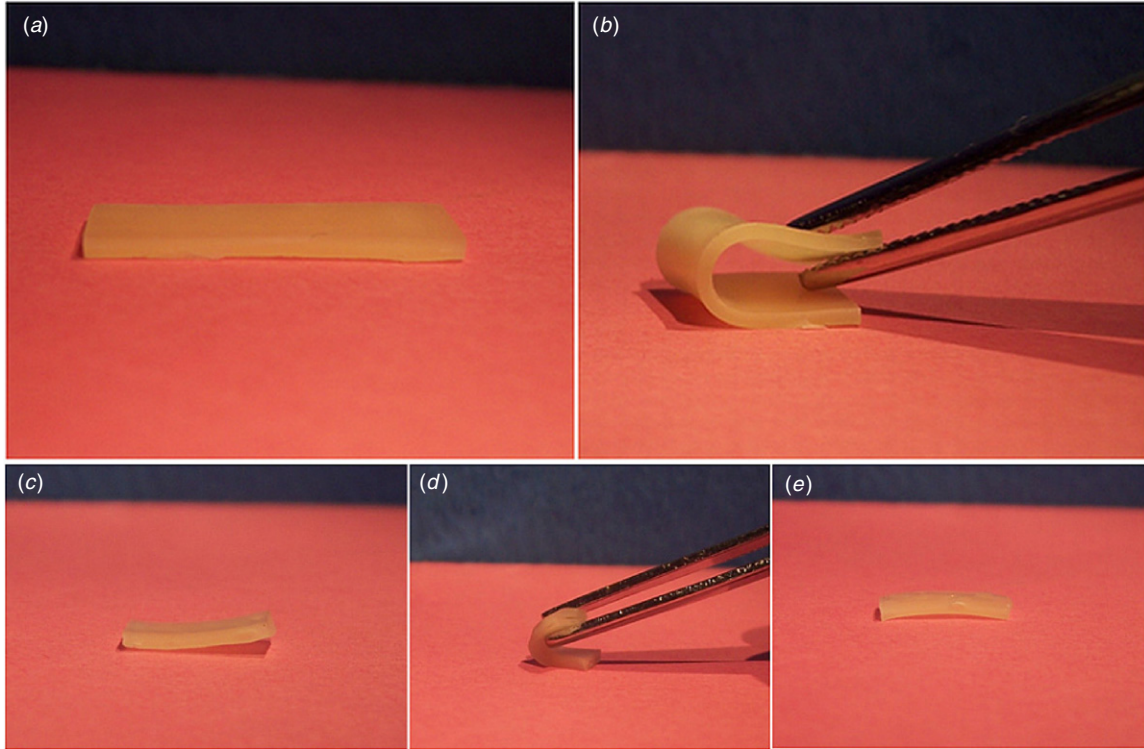


Figure 3. Typical pictures of the elastomer $TC_{I-PETAE100}$ in the dry state (a) and (b), and hydrated state (c)–(e) with shape recovery after mechanical strain.

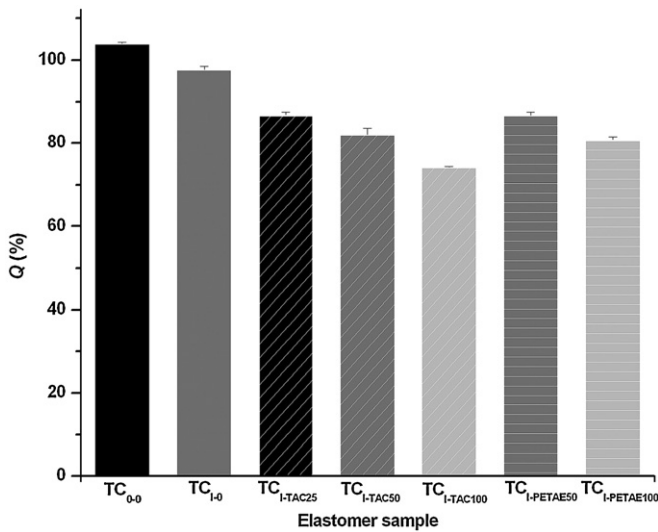


Figure 4. Swelling ratio of elastomers as a function of the cross-linking.

all cases. An ultimate strain of 130% for $TC_{I-PETAE100}$ was found instead of the original 52% for the dry sample and a reversible deformation of 30% for TC_{0-0} was found instead of the original 15%. Although already observed under the dry state, the influence of the cross-linker nature on mechanical properties was even more pronounced under the hydrated state. As expected, a stronger influence of hydration was found for the PETAE-based elastomers compared to the TAC-based ones, as a result of the higher hydrophilicity and flexibility of PETAE. The influence of hydration followed

the same order as the elastomers' hydrophilicity, with a stronger influence found for $TC_{I-PETAE100}$ compared to TC_{0-0} and $TC_{I-TAC100}$. This demonstrates the possibility to generate a family of elastomers covering a broad range of mechanical behaviours by choosing suitable cross-linkers. As expected, one has to note that the mechanical properties found for these elastomers are in the range of those found for soft natural tissues such as vascular vessels ($E \approx 1$ Mpa, $\epsilon_{break} \approx 100\%$) [46] or nasal cartilage ($E \approx 5$ Mpa, $\epsilon_{break} \approx 22.5\%$) [47] and, as such, may be suitable to prepare scaffolds for tissue engineering applications.

3.3. Elastomer degradation

TS elastomers generally degrade via a combination of bulk and surface erosion [16–18]. Their cross-linking maintains the elastomer shape constant during the degradation process until late stage. To evaluate these points, representative samples were selected to demonstrate the degradability of our materials. Each sample has been degraded in PBS at 37 °C over a 6 month period. As mentioned previously, the initial swelling slightly depends on the nature of the cross-linker. This observation was confirmed throughout the whole degradation process. The results are shown in figure 5.

In the absence of cross-linker (TC_{I-0}) and with PETAE ($TC_{I-PETAE100}$), water uptake was higher than with TAC ($TC_{I-TAC100}$). More in details, all samples presented a similar water uptake rate during the first month. Beyond this point, the difference was more pronounced with a slightly slower water uptake rate for the TAC-based sample. Final water uptakes of 260%, 420% and 480% were found for $TC_{I-TAC100}$, TC_{I-0}

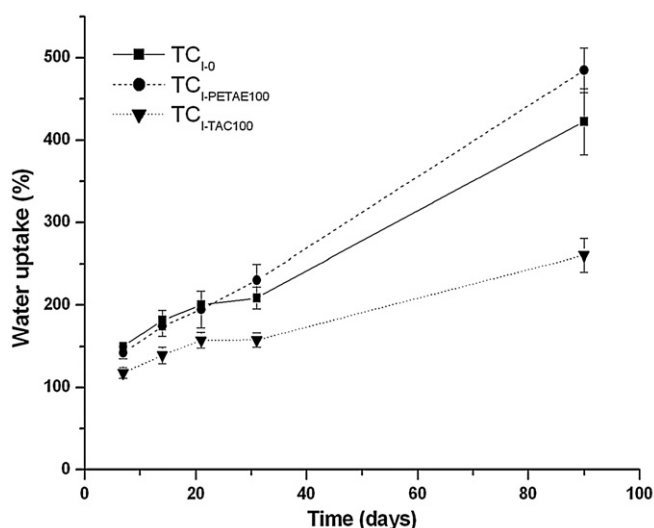


Figure 5. Water uptake of elastomers as a function of the cross-linker nature.

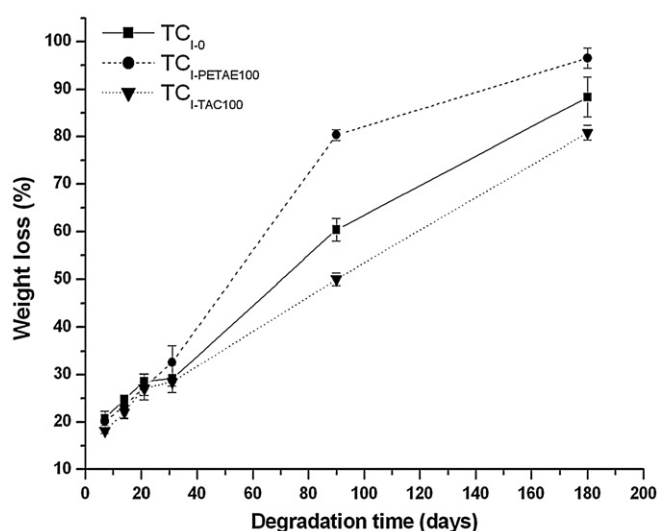


Figure 6. Weight loss of elastomers as a function of the cross-linker nature.

and TC_{I-PETAE100}, respectively, after 3 months in PBS. This corresponds to a final water uptake inferior by about 50% for the TAC-based material compared to the other materials. Due to their important degradation after 6 months and the difficulty to handle them, it was not possible to estimate the hydrated weight of the samples at this time point. It should be noted that a maximum hydration is rapidly obtained after soaking in PBS (cf swelling ratio) and that once this hydrated state has been reached, elastomers' shapes remain unchanged for at least 3 months. Water uptakes are in agreement with the swelling behaviour and led to different degradation rates. Indeed, like for water uptake, weight loss variations can be divided into two periods as shown in figure 6.

Up to 30 days, all elastomers degraded linearly at the same rate until all samples reach a weight loss of 30%. Beyond this point, degradation rates changed slightly as a function of the elastomers' structures, but still remained close from

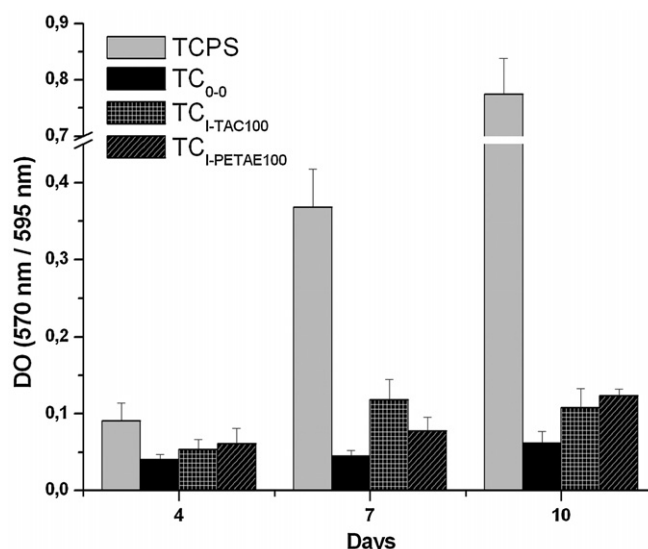


Figure 7. L929 fibroblast viability after 4, 7 and 10 days of culture on elastomers as a function of the cross-linker nature (PrestoBlue™ reagent; tissue culture polystyrene (TCPS) positive control).

a linear behaviour. The higher the hydrophilicity, the faster and more complete the degradation was. After 6 months, weight loss was almost complete for all samples, with values equal to 81%, 88% and 97% for TC_{I-TAC100}, TC₀₋₀ and TC_{I-PETAE100}, respectively. To the best of our knowledge, no other degradable elastomers have such a moderate degradation rate. Most structures described in the literature degrade either very slowly or very rapidly. Typically, slowly degrading elastomers, like PLA/PCL- [48, 49] or citrate/sebacate-based [19, 20] elastomers, exhibit less than 10% weight loss after 70 days. On the opposite, most examples of elastomers including PEG segments showed very fast degradation kinetics, full degradations being obtained within 30–60 days [17, 28, 30] or even less [14]. The herein proposed elastomers, with a 6 month degradation period, fulfil the gap between these two classes of compounds and might be useful for temporary applications requiring mid-term durability like nerve or vascular tissue engineering applications.

3.4. Elastomer cytocompatibility

As mentioned, the use of photoinitiators and cross-linkers in the synthesis of TS elastomers can be a problem for biomedical applications. In the present case, although PLA/PEG triblock copolymers are well known for their biocompatibility, the potential of elastomers containing TAC, PETAE and Irgacure® 184 residues had to be assessed. All these compounds have already been used for biomedical applications including dental cements [37], hydrogels [50], polymeric vectors [51] or medical devices [38–42], and are known to be non-toxic or known to exhibit very low toxicity [52–55]. To evaluate our elastomers, L929 fibroblasts were seeded on sterilized samples and cultured for 10 days to assess cell viability. The results are shown in figure 7.

The amount of cells found on elastomers was lower than for the TCPS positive control. Cells adhered and proliferated

slowly on all elastomers whatever the presence or the nature of cross-linkers. The slight increase of viability values indicates that elastomers' surfaces are compatible with cell culture. With an EO/LA ratio of 2.5, our elastomers have a hydrophilic nature which is probably responsible for the low adsorption of cell-binding protein present in the cell culture medium and the resulting hindered fibroblast adhesion [56, 57]. The release of acidic degradation compounds (lactic acid units) may also interfere with the cell proliferation although no drastic change of the medium colour was observed. Surprisingly, the number of cells appeared lower when no cross-linker was used. Again, this may be due to the higher swelling of TC₀₋₀ compared to that of the other elastomers, already shown in figure 4. This result confirms that the presence of cross-linkers do not cause any additional cytotoxic effect. Culture on TC_{I-TAC100} was comparable to the one of TC_{I-PETAE100}, and one can conclude that L929 behaved similarly regardless of the cross-linker type. Although suitable for cell culture, it might be interesting in the future to slightly change the hydrophilic/hydrophobic balance of these elastomers to facilitate cell adhesion and to enhance cell proliferation.

4. Conclusion

This study showed that mid-term degradable elastomers can be easily obtained by photo-cross-linking of PLA-PEG-PLA prepolymers having a chosen amphiphilic balance. Their properties can be advantageously tailored by the association of the prepolymers with suitable photo-cross-linkers. TAC and PETAE illustrated this diversity, with modulations of the mechanical properties and degradation profiles of the elastomers as functions of the photo-cross-linker nature and concentration. The typical values of 2–5 MPa for Young's moduli and 5–30% for the yield strains have been obtained and the various elastomers exhibit the degradation ratios of 80–100% after 6 months. Their intermediate degradation rate, scarcely found for degradable elastomers, as well as their cytocompatibility, makes them suitable for tissue engineering applications. The versatility of this approach should offer opportunities for all biomedical applications that require soft and mid-term degrading elastomeric materials.

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