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Tailored Mechanical Properties and Degradability of Polyesters by Controlled Molecular Architecture

*Maria Ryner, Ann-Christine Albertsson**

Department of Polymer Technology, The Royal Institute of Technology (KTH), SE-100 44 STOCKHOLM, Sweden
E-mail: aila@polymer.kth.se

SUMMARY: Advanced molecular architectures have been used as a tool for tailoring the mechanical properties and the degradation process of polymers for specific applications. Crosslinked poly(1,5-dioxepan-2-one), random poly(1,5-dioxepan-2-one-*co*-L-lactide), triblock poly(L-lactide-*b*-1,5-dioxepan-2-one-*b*-L-lactide) and triblock poly(ε-caprolactone-*b*-1,5-dioxepan-2-one-*b*-ε-caprolactone) have been synthesized and their thermal and mechanical properties as well as degradation times and degradation products have been characterized and compared. The stress at break of the synthesized polymers ranged from 4 MPa to 55 MPa and the elongation at break from 25% to 1200%. The degradation time varied from 70 days up to 360 days. These polymers are suitable as films or microspheres for controlled drug delivery or as temporary tissue replacements e.g. for tendons or nerve guides.

Introduction

There is an increasing demand for degradable polyesters with good elasticity, tensile strength and biocompatibility for use in medical applications. Ring-opening polymerization (ROP) is a versatile pathway leading to polymers with specific structures and purposes. Polyesters, polyanhydrides, polycarbonates and copolymers combining useful properties from several monomers can be synthesized. Most widely used are polymers from lactide and glycolide since their degradation products can easily be metabolized. Their homopolymers are crystalline and offer only a limited range in properties. Completely amorphous polymers like poly(1,5-dioxepane-2-one) (pDXO) are therefore very useful for copolymerization to improve the elasticity of a polymer. A careful design of the molecular structure is important for the polymer properties. Molecular architectures like linear, branched, star[1-2], comb[3], multiblock[4] and triblock[5-6] copolymers have been studied for different applications.

In this paper, we describe the synthesis of different polyesters possessing a wide range of mechanical and thermal properties by copolymerization and carefully design of the molecular structure. The original starting point was pDXO[7)]. This linear homopolymer is completely amorphous and, to improve the mechanical properties, the pDXO matrix was crosslinked.[8]

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DXO was also used for block and random copolymerization with L-lactide[9-10)] and ε-caprolactone[11] yielding very strong and elastic materials with an interesting future as biomaterials.

Experimental

Materials

L,L-lactide (Boeringer GmBH, Germany) was purified by recrystallization in dry toluene. The monomer was dried for 20 h under reduced pressure (10-2 mbar) at room temperature prior to polymerization. 1,5-dioxepan-2-one (DXO) was synthesized from tetrahydro-4H-pyran-4-one through Baeyer-Villiger oxidation according to the literature.[12)] Prior to polymerization, DXO was purified by distillation and recrystallized twice in dry diethyl ether. ε-caprolactone (ε-CL, Janssen, Belgium) was dried over calcium hydride (Aldrich, Germany) for 48 h and then distilled under reduced pressure before use. Stannous 2-ethylhexanoate ($Sn(Oct)_2$, Aldrich, Germany) was used as received. Crosslinking agent 2,2-bis(caprolactone-4-yl) (BCY) was prepared by oxidizing dicyclohexyl-4,4′-diol with Jones reagent followed by a Baeyer-Villiger oxidation.[13)] The BCY obtained was purified by recrystallization in ethyl acetate. 1,1,6,6-tetra-n-butyl-1,6-distanna-2,5,7,10-tetraoxacyclodecane was prepared from dibutyl tin oxide and ethylene glycol.[14-15)] Aluminum tri-isopropoxide (Aldrich) was purified by distillation under reduced pressure and dissolved in dry toluene.[11)]

Crosslinked DXO

DXO was polymerized with crosslinking agent BCY in bulk at 140°C for about 10h, using $Sn(Oct)_2$ as catalyst.[8)] The polymerization was performed in an aluminum forms with dimensions 70x70x0.7 mm and 10x20x0.5 mm.

Triblock copolymer of DXO and ε-CL

ε-CL was charged into a previously flamed and nitrogen-purged glass reactor in a dry box, under a nitrogen atmosphere. Dry THF or toluene, DXO and ε-CL were sequentially added to the reactor through a rubber septum using stainless steel capillaries or syringes. The polymerization was initiated by aluminum isopropoxide at 25°C with 1 molar equivalent (with respect to the initiator) of pyridine. The triblock copolymer obtained was recovered by precipitation in heptane and finally dried under reduced pressure at room temperature until no further change in weight was observed.

Random copolymer of DXO and L-LA

$Sn(Oct)_2$, DXO, L-LA and a magnetic stirring bar were added to the previously flamed and nitrogen-purged polymerization flask under an argon atmosphere. The flask was sealed with a rubber septum and immersed in a thermostated oil bath for 20h at 120°C.

Triblock copolymer of DXO and L-LA

DXO and initiator were weighed into a silanized round-bottomed flask under a nitrogen atmosphere inside a dry box. The flask was fitted with a magnetic stirrer bar and sealed with a three-way valve. Chloroform was transferred to the flask using a syringe. The polymerization flask was immersed in a thermostated oil bath at 60°C. The second monomer, L-LA, was charged into a round-bottomed flask. The monomer was dissolved in chloroform and transferred with a syringe to a reaction vessel containing the initiator-polymer complex after complete conversion of DXO. The polymer obtained was purified by three precipitations in a hexane-methanol (95:5) mixture.

Measurements

The molecular weights of the polymers were determined with a Waters 717plus autosampler and a Waters model 510 apparatus equipped with two PLgel 10μm mixed-B columns (Polymer Labs., UK), 300x7.5mm. Spectra were recorded with a PL-ELS 1000 evaporative light scattering detector (Polymer Labs., UK) connected to an IBM-compatible PC. Millenium32 version 3.05.01 software was used to process the data. Chloroform was used as eluent, at a flow rate of 1.0 mL/min. Narrow MWD polystyrene standards were used for calibration, range 1,700-706,000 g/mol.

The thermal properties of the synthesized polymers were analyzed by differential scanning calorimetry (DSC) using a Mettler-Toledo DSC instrument with a DSC 820 module. A scanning rate of 10°C/min was used and the samples were heated in a nitrogen atmosphere. The second scan was used to record the heat of fusion. When the degree of crystallinity in the different poly(DXO-co-L-LA) was evaluated, it was assumed that only poly(L-lactide) (pL-LA) segments contributed to the heat of fusion.

The mechanical characterization of the polymers was performed in an Instron 5566 equipped with a non-contacting video extensometer and pneumatic grips, controlled by a Dell 466/ME personal computer. The tensile measurements were performed with a crosshead speed of 150 mm/min. The elongation at break was calculated from the grip separation, due to the large elongation of the samples. The films had a thickness of approximately 0.5 mm and were preconditioned (48h at 50±5% RH and 23±1°C) before testing. Five samples from the same film were tested for each polymer. The procedures were according to ASTM D882-95A.

Results and discussion

Different thermal, mechanical and degradation properties were obtained by carefully designing the molecular structure of the polymer. The homopolymer of DXO is a completely amorphous and sticky polymer with a glass temperature of –37°C. DXO was copolymerized with a tetrafunctional ε-CL derivative (2,2-bis(caprolactone-4-yl)) giving a crosslinked rubbery material. The glass temperature of crosslinked poly(1,5-dioxepan-2-one) (pDXO) increases from –31°C to –6°C with increasing degree of crosslinking. PDXO degrades slowly (50% weight loss after 200 days) and the degradation products were shown to correspond to the linear form of the monomer. The elongation at break for crosslinked pDXO ranged from 25±3 % with a crosslinking density of 8 % to 120±3 % for a crosslinking density of 44%, Tab. 1. The exceptionally long degradation time for this polymer makes it suitable as a cell-seeding scaffold, although the mechanical properties need to be improved for applications that demand higher elasticity and strength. Another advantage of this material is its completely amorphous matrix. Semi-crystalline materials are known to produce a more severe foreign body reaction than amorphous materials.[16)]

Table 1. Elastic properties of synthesized polymers.

Polymer	Stress at break [MPa]	Elongation at break [%]
pDXO		
crosslinking density 8%		120±3
crosslinking density 44%		25±3
random poly (L-LA-co-DXO)		
75/25 mol%	21±1.5	420±63
triblock poly (L-LA-co-DXO)		
35/65 mol%	23±1.4	555±41
27/73 mol%	42±4.5	828±72
12/88 mol%	4.4±0.6	463±21
triblock poly (ε-CL-co-DXO)		
37/63 mol%	52±6.7	1070±50
30/70 mol%	53±3	1210±67

PDXO is very important as a building block in degradable materials. The hypothesis was that the amorphous phase of pDXO together with the crystalline phase of for example pL-LA or poly(ε-caprolactone) (pCL) could result in a stronger and more flexible material. Random poly(L-LA-co-DXO) was synthesized with $Sn(Oct)_2$ as catalyst. The difference in reactivity ratio between DXO and L-LA (r_{DXO}=0.1 and $r_{L\text{-}LA}$=10) resulted in a blocky copolymer that after transesterification had a more randomized structure. The glass temperature, crystallinity and mechanical properties of this copolymer were strongly dependent on the composition. The glass temperature increased from −36°C up to 58°C when the L-LA/DXO ratio was changed from 0/100 to 100/0. The crystallinity of the copolymer increased from 3% at a 50/50 ratio of L-LA/DXO up to 33% at a 96/4 ratio of L-LA/DXO, using a value of ΔH^0_m = 106 J/g.17) The copolymer of L-LA/DXO with a composition of 75/25 exhibited a stress at break of 21±1.5 MPa and an elongation at break of 420±63 %, Tab. 1.

The degradation of this copolymer was studied both in vitro and in vivo. The degradation time was found to depend mainly on the composition. A copolymer of 80/20 L-LA/DXO had a weight loss of 50% after 230 days (in vitro), whereas a copolymer of 20/80 L-LA/DXO had a weight loss of only 20% after the same degradation time (in vitro).16,18) The degradation process was found to be hydrolysis through ester bond cleavage. The in vivo degradation study showed a less pronounced foreign body reaction for a copolymer of low crystallinity. The random poly(L-LA-co-DXO) had significantly higher elasticity than the crosslinked pDXO and the synthetic pathway is much simpler. The polymer still degrades slowly and can be useful for controlled drug delivery systems, both as films and microspheres.19)

A more advanced molecular structure as a triblock copolymer with pDXO as the amorphous middle block and pL-LA as crystalline side-blocks exhibited even better mechanical properties than the random copolymer, Tab. 1. The triblock copolymers had the advantage of controllable block lengths and controllable compositions, and this had a great influence on the elastic properties. A triblock copolymer with a very high DXO ratio (12/88 L-LA/DXO) was very soft and sticky. The elongation at break was 463±21 % and the stress at break was 4.4±0.6 MPa. An increase in L-LA content made the polymer stronger and more elastic. A triblock copolymer with an L-LA/DXO ratio of 27/73 had a stress at break of 42±4.5 MPa and an elongation at break of 828±72 %. At even higher L-LA contents, the polymer became stiff and less elastic. For example, a triblock copolymer with an L-LA/DXO ratio of 35/65 had an elongation at break of 555±41 % and a stress at break of 23±1.4 MPa, Tab. 1.20)

The thermal properties did not change significantly with changing composition. The glass temperature was almost constant at –33°C for triblock copolymers with 75-95% DXO. The melting temperature increased from 139°C to 163°C with increasing L-LA block length. An interesting feature of the triblock copolymers is that they are semi-crystalline down to an L-LA/DXO ratio of 11/89, whereas random copolymers lose their crystallinity at 60/40 L-LA/DXO.

The triblock copolymer was hydrolytically degraded in a buffered salt solution at 37°C and pH 7.4. 3-(2-hydroxyethyl)-propanoic acid and L-lactic acid were released from the films during the degradation.21) The films were completely degraded after 100-200 days, the actual time depending on the molecular weight and the composition of the copolymer. A copolymer with a L-LA/DXO ratio of 25/75 had a weight loss of 50% after 70 days, while a copolymer with a L-LA/DXO ratio of 7/93 had the same weight loss after 120 days, both with a molecular weight of 65 000g/mol. Many different factors such as molecular weight, hydrophilicity and sensitivity towards hydrolysis affect the degradation time. A polymer with a high pDXO content has a longer degradation time because hydrolysis of pDXO is slower than hydrolysis of L-LA.

Triblock copolymers of DXO and ε-CL have been synthesized by adding the monomers sequentially in a three-step process. This triblock copolymer had very good elasticity with an elongation at break of 1210±67 % and a stress at break of 53±3 MPa, Tab. 1. This is explained by the difference between the L-LA and ε-CL homopolymers, where pCL has a more flexible backbone than pL-LA. The thermal properties were constant for the synthesized compositions. The melting temperature of poly(ε-CL-b-L-LA-b-ε-CL) was 51°C and the glass transition temperature was –38°C.

The advanced molecular architecture in triblock poly (L-LA-co-DXO) and in triblock poly(ε-CL-b-L-LA-b-ε-CL) results in excellent but expensive materials for temporary tissue replacement. These materials exhibit good strength and elasticity in combination with a slow degradation process, which makes them valuble for use as tendons or for nerve guidance.

Conclusion

The synthesized polymers have very different characteristics and consequently different areas of application. The crosslinked pDXO matrix has an exceptionally long degradation time, being completely degraded after 360 days. This, in combination with the absence of crystallinity, makes it suitable for cell seeding applications. Increasing the crosslinking density of the matrix could to some extent improve the mechanical properties.

Random copolymerization of L-LA and DXO gave a polymer with significantly better strength and elasticity. The random poly(L-LA-co-DXO) degraded slowly (50% weight loss after 230-300 days) and can be useful as films or microspheres for controlled drug delivery.

More sophisticated molecular architecture as in triblock poly(L-LA-b-DXO-b-L-LA) and in triblock poly(ε-CL-b-DXO-b-ε-CL) gave very strong elastic materials. These triblock copolymers can be used for temporary tissue replacement, for example as artificial tendons or as nerve guides. The drawback is that the synthetic pathway is much more complicated than that required for random copolymerization. Consequently the random copolymer will be preferred when it is a suitable material.

References

1. H. R. Kricheldorf, S. R. Lee, *Macromolecules* **29**, 8689, (1996)
2. Y. R. Choi, Y. H. Bae, S. W. Kim, *Macromolecules* **31**, 8766 (1998)
3. A. Breitenbach, T. Kissel, *Polymer* **39**, 3261 (1998)
4. H. R. Kricheldorf, D. Langanke, *Macromol. Chem. Phys.* **200**, 1183 (1999)
5. H. R. Kricheldorf, J. Meierhaack, *Makromol. Chem.* **194**, 715 (1993)
6. P. Veld, E. M. Velner, P. VanDeWitte, J. Hamhuis, P. J. Dijkstra, J. Feijen, *J. Polym. Sci. Polym. Chem. Ed.* **35**, 219 (1997)
7. A. Löfgren, A.-C. Albertsson, *Polymer* **36**, 3753 (1995)
8. R. Palmgren, S. Karlsson, A.-C. Albertsson, *J. Polym. Sci. Polym. Chem. Ed.* **35**, 1635 (1997)
9. A.-C. Albertsson, A. Löfgren, *Makromol. Chem., Macromol. Symp.* **53**, 221 (1992)
10. K. Stridsberg, A.-C. Albertsson, *J. Polym. Sci. Polym. Chem. Ed.* **38**, 1774 (2000)
11. A. Löfgren, R. Renstad, A.-C. Albertsson, *J. Appl. Polym. Sci.* **55**, 1589 (1995)
12. T. Mathisen, K. Masus, A.-C. Albertsson, *Macromolecules* **22**, 3842 (1989)
13. R. Palmgren, Ph. D. thesis, *"Degradable elastomers"*, KTH, 1997
14. J. Bornstein, B. R. La Liberte, T. M. Andrews, J. C. Montermoso, *J. Org. Chem.* **24**, 886 (1959)
15. K. Stridsberg, A.-C. Albertsson, *J. Polym. Sci. Polym. Chem. Ed.* **37**, 3407 (1999)
16. A. Löfgren, A.-C. Albertsson, *J. Appl. Polym. Sci.* **52**, 1327 (1994)
17. J.-R. Sarasua, R. E. Prud'homme, M. Wisniewski, A. L. Borgne, N. Spassky, *Macromolecules* **31**, 3895 (1998)
18. A. Löfgren, A.-C. Albertsson, Y. Zhang, L.-M. Bjursten, *J. Biomat. Sci., Polym. Ed.* **6**, 411 (1994)
19. U. Edlund, A.-C. Albertsson, *J. Polym. Sci. Polym. Chem. Ed.* **37**, 1877 (1999)
20. M. Ryner, A.-C. Albertsson, manuscript
21. K. Stridsberg, A.-C. Albertsson, *Polymer* **41**, 7321 (2000)