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Degradable Polymers: Design, Synthesis and Testing

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Summary: The object for our research is to mimic Nature´s perfectly designed resorbable materials to obtain important materials, which are biocompatible and degradable. We have therefore synthesized different architectures and copolymers of aliphatic polyesters with ring-opening polymerization. The first studies of these materials properties show that properties like hydrophilicity and tensile properties can be controlled.

Keywords: functionalization of polymers; polyesters; ring-opening polymerization; structure-property relations; tin initiators

Introduction

Synthetic polymers are relatively simple compared to the sophisticated materials built by nature. Learning from the microstructure of natural polymers, it is possible to design and synthesize new specialized polymers with superior functionalities and properties compared to the polymers of today. Biological materials, such as tendon, bone, wood, and many others, are characterized by hierarchial architectural designs in which organization is controlled with striking precision on many descrete length scales, which range from the molecular to the macroscopic. The goal is to to develop new materials with inherent environmental interaction by biomimicking the environmental interaction of biopolymers. Using ring-opening polymerization (ROP) we have achieved well-designed block copolymers. These block copolymers, triblock as well as multiblock, are used as tools for tailoring the mechanical properties, hydrophilicity, and degradation processes for specific applications. Functionalized macromonomers as well as star-shaped polymers have also been synthesized and their properties will be investigated. This will increase the understanding about the important structure-property relationships and how molecular structure and function can impact improved materials performance.

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Experimental

Materials. L-lactide (L-LA) (Serva Feinbiochemica, Germany) was purified by recrystallization in dry toluene, and subsequently dried under reduced pressure (10^{-2} mbar) at room temperature for at least 48 h prior to polymerization. 1,5-dioxepan-2-one (DXO) was synthesized according to our earlier published work[1]. Succinyl chloride (95%, Acros Organics, Belgium) was used as received. Chloroform (Labora Chemicon, Sweden), was dried over calcium hydride for at least 24h and distilled under reduced pressure in an inert atmosphere just before use.

Initiators. A five membered cyclic tin initiator were synthesized according to the literature[2]. Two spirocyclic tin initiators were synthesized and have been described elsewhere[3]. Kricheldorf provided the six membered and seven membered cyclic functionalized tin initiators.

Triblock copolymer. DXO and the five membered cyclic tin initiator were weighed into a silanized round-bottomed flask under inert atmosphere in a glovebox. Chloroform was added through a syringe. During the polymerization the flask was immersed in a thermostated oil bath at 60°C. L-LA was dissolved in chloroform following the same procedure as for DXO and transferred to the reaction vessel with a syringe. The polymer was precipitated in a hexane-methanol mixture.

Functionalized macromonomer. L-LA macromonomers were synthesized using functionalized initiators, six- or seven membered cyclic tin initiators with a double bond within the structure. L-LA and the initiator were weighed into a silanized round-bottomed flask under inert atmosphere in a glovebox. Chloroform was added through a syringe. The polymerization flask was immersed in a thermostated oil bath at 60°C and the polymer was precipitated in cold hexane.

Star-shaped polymer. New spirocyclic tin initiators were synthesized and used for the polymerization of star shaped L-LA, the procedure have been described earlier[3].

Results and Discussion

Much effort goes into the design, synthesis and fabrication of new biomaterials to ensure that they have the appropriate mechanical properties, durability, and functionality. During the last years we have used ROP to achieve polymers with different designs and we have also started the characterization of these materials. We have successfully synthesized poly(L-LA-*b*-DXO-*b*-L-LA) triblock and poly(L-LA-*b*-DXO) multiblock copolymers[4,5]. ROP was used for the synthesis of the triblock while ROP together with polycondensation techniques were used to create high molecular weight L-LA/DXO multiblock copolymers. In Figure 1 and 2 are the structures of the different designed polymers presented. A five membered cyclic tin initiator, which we have earlier been investigated was used as initiator[2]. Polymers with different LLA and DXO proportions were synthesized and the effect of the polymer composition on the polymer properties were evaluated.

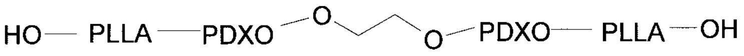

Figure 1. Structure of the triblock copolymer.

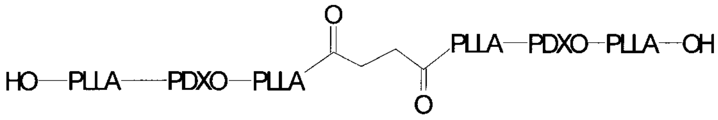

Figure 2. Structure of the multiblock copolymer.

The properties of the triblock copolymers have been investigated and in some cases been compared with the properties of the multiblock copolymers. Contact angle measurements were used to investigate the hydrophilicity of the triblock copolymer films. The materials hydrophilicity increased with higher DXO content. The estimated receding angle was 44±3° when the DXO content was 65% while it decreased to 27±1° when the DXO content increased to 88%. These are all very hydrophilic surfaces compared to PLLA and PCL, which have been reported to have contact angles of 74° and 64° respectively[7,8]. Since a hydrophilic material generally has a better biocompatibility than a hydrophobic material[9] are these values very interesting. From these results it was concluded that just changing the composition of the copolymer could control the hydrophilicity of the surface.

The elasticity was high for all polymers compared to other hydrolyzable polyesters and they had very high elongations-at-break, Table 1.

Table 1. Tensile properties of tri- and multiblock copolymers.

Name[a)]	Elongation [%]	Stress-at-break [MPa]
PLLA[10,11]	30	
PCL[10,11]	200-300	
triblock 400:200	560±40	23±2
triblock 300:150	830±70	42±3
triblock 200:100	620±30	20±1
triblock 300:100	910±70	33±7
triblock 400:100	460±20	4±1
multiblock 120:60	830±70	26±2

[a)] A triblock copolymer consisting of a middle block of 200 DXO units and two side blocks of 50 lactide units each is named "triblock 200:100". Themultiblock has 60 lactide units long segments within the structure, whereasthe end blocks consist of 30 lactide units. The DXO segments consists of 120 units.

From the results in Table 1 it can be established that the composition have a significant influence on the tensile properties. Triblock 300:150 had the highest stress-at-break and a very high elongation-at-break. The films of triblock 400:100 had the highest DXO content and were therefore the weakest. The morphology of these polymers was examined. Generally, polymers built of different segments exhibit a pronounced tendency for phase separation, which results in different morphologies depending on the copolymer composition and structure. Polarized optical microscopy was used and it was seen that the PLLA blocks of the triblock copolymer were able to phase separate into spherulites. Large amorphous domains of DXO separated the PLLA blocks. The multiblock did not contain these large amorphous domains of DXO and could not phase separate in the same manner. The presence of phase-separated semi-crystalline PLLA blocks made the films strong while the relatively long and flexible PDXO blocks made the film elastic.

The polymers have also been subjected to in vitro degradation and their tensile properties were tested at a regular time intervals during degradation. As expected, the mechanical properties of both the triblock and multiblock copolymers decreased during hydrolysis. It is though very interesting to note that both the triblock and multiblock copolymers still showed a high stress-at-break as well as a high elongation-at-break after 59 days of in vitro degradation.

Apart from copolymerization, another way to achieve materials with unique, controlled and well-defined properties is to promote architectural diversity. One interesting approach is to synthesize star-shaped PLLA in a controlled way. Variations in the macromolecular architecture from linear to multiarm can have considerable effects on the morphological and physical-mechanical properties. New spirocyclic tin initiators have therefore been synthesized and their usefulness have been thoroughly evaluated[3]. The structure of the star-shaped PLLA is presented in Figure 3.

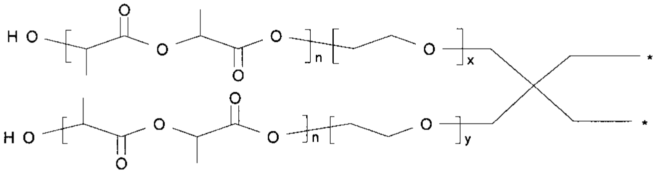

Figure 3. Star-shaped PLLA synthesized with new spirocyclic tin initiators.

Polymers of L-LA were polymerized at monomer-to-initiator ([M]/[I]) ratios between 20 and 500. The initiation was instantaneous and the molecular weight distribution was very narrow. The number average molecular weight could be controlled by the [M]/[I] ratio and the yield was very high. ^{1}H NMR, SEC and DSC were used to clarify the architecture. All four arms were polymerized, the star-shaped polymers had a smaller hydrodynamic volume and the melting point was lower than for the corresponding linear PLLA.

Another way to construct new architecture is to functionalize the initiator and incorporate the functionalization into the polymer. We have used new cyclic tin alkoxides with one doublebond[6] as initiators. L-LA macromonomers with an incorporated double bond, Figure 4, was thereby successfully synthesized by controlled ROP. NMR verified the incorporation of the doublebond within the structure.

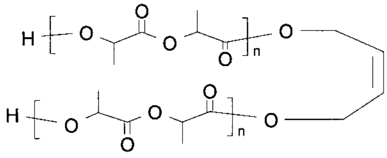

Figure 4. L-LA macromonomer with an incorporated double bond.

Adjusting the monomer-to-initiator ratio could effectively control the molecular weight and the molecular weight distribution was very narrow. A plot of the number-average molecular weight versus conversion was linear up to a conversion of 98%, which indicate that the system is propagating in a living manner. The kinetic investigation showed that all the polymerizations were first order in monomer, and that no termination reactions occurred during polymerization.

Conclusion

New polymers with different architectures and functionality were synthesized. One object was to inquire if it was possible to control the properties of the polymers. The first measurements were performed on L-LA/DXO triblock and multiblock copolymers. It was possible to control the material properties by changing the proportions of the monomers in the polymer. The surface became more hydrophilic when the proportion of DXO was increased and the elasticity of the polymers increased. New tin initiators were synthesized which made it possible to obtain star-shaped as well as functionalized polymers. The reactions and the polymers were thoroughly investigated. The molecular weight dispersity was very narrow and the molecular weight could be controlled by the monomer-to-initiator ratio in all reactions. The significant smaller hydrodynamic radius of the star-shaped polymer compared to that of the corresponding linear polymer together with NMR results confirmed the star-shaped architecture. The functionalization of linear PLLA by the incorporation of a double bond into the backbone was also confimed by NMR.

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