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Forecasting linear aliphatic copolyester degradation through modular block design

Veluska Arias, Peter Olsén, Karin Odelius, Anders Höglund, Ann-Christine Albertsson*

Department of Fibre and Polymer Technology, KTH Royal Institute of Technology, SE-100 44, Stockholm, Sweden

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ABSTRACT

The development of efficient methods to predict the degradation of renewable polymeric materials is continuously sought in the field of polymer science. Herein, we present a modular build-up approach to create polyester-based materials with forecasted degradation rates based on the hydrolysis of the constituent polymer blocks. This involved the strategic combination of critical factors affecting polyester hydrolysis, *i.e.* hydrophobicity and degree of crystallinity. The starting point of this method was a toolbox of polymers with different hydrophobicities and degrees of crystallinity, as well as an understanding of their inherent differences in hydrolysis rate. Knowledge of the hydrolysis of each polymer block module enabled the prediction of the overall degradation behavior of the constructed copolymers. Taking advantage of the primary factors that affect polymer degradation, block copolymers could be independently designed to incorporate soft or rigid and faster or slower degradation properties. This approach generated a shift for how molecular design can be used to predict the degradation behavior of intended materials for different applications.

1. Introduction

Today's approach to design degradable materials generally proceeds in a "top-down" manner, where the starting point relies on finding a suitable application for a given material. Desired or undesired degradation of the material may also be evaluated, but in most cases, the degradation behavior is regarded as a side-phenomenon. Currently, it is widely recognized that in addition to the importance of the long-term stability of synthetic polymers, there is a need for polymers that break down in a controlled and harmless manner in the environment. The ability to create degradable polymeric materials with forecasted degradation rates and pathways and generate predictable degradation products is still a highly sought-after goal in the area of polymer science. Therefore, we envisioned that the most promising route to achieve the effective material design of degradable polymers was through a bottom-up approach starting from the desired degradation of the material followed by the design of such material.

Among the currently available degradable polymers, aliphatic polyesters are attractive candidates due to their high monomeric structural versatility and large range of hydrolysis rates [1,2]. According to IUPAC terminology, degradable polymers are defined as macromolecules that are able to undergo chain scissions, leading to a decrease in molar mass [3]. When the degradation is caused by the action of water, is then termed hydrolysis. Hydrolysis rates are affected by many factors, with primary factors hydrophobicity, degree of crystallinity and molar mass [4]. Other factors include molar mass dispersity, stereo-configuration, shape of the sample, pH and temperature of the degradation medium, which also influence degradation behaviors. Hydrolytic degradation of aliphatic polyesters has been a key area of interest in our group since the 1980s, especially with regards to controlling degradation by modifying macromolecular designs. The combination of chemically distinct blocks to create different macromolecular architectures offers a wide range of possibilities for designing new materials with enhanced properties [5–8]. Although various macromolecular architectures result in different degradation behaviors for the same polymer constituents, block copolymers exhibit degradation behaviors that strongly correlate to the properties of their pure homopolymers [9–12].

We have a long-standing history of creating different polyester-based block copolymers, and especially triblock structures where the hydrolysis behaviors are selectively tailored depending on the block compositions. Introducing amorphous blocks with controlled

* Corresponding author.
E-mail address: aila@polymer.kth.se (A.-C. Albertsson).

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microstructures allows degradation rates to be tuned by the distribution of weak linkages in a copolymer [10,13]. Triblock copolymers with amorphous side blocks have been shown to have faster hydrolysis rates than copolymers with amorphous central blocks because of the susceptibility of these types of polymer morphologies to hydrolysis [13,14]. There are several examples of how the hydrolysis behavior of triblock copolymers are influenced by the nature of the central block modules, especially for those flanked with poly(L-lactide) (PLLA) [15,16]. Some of the explored systems include central blocks of 1,5-dioxepan-2-one (DXO), ε-caprolactone (CL), poly(but-2-ene-1,4-diyl malonate) (PBM) and ε-decalactone (DL) [13,17–20]. Specifically, fast hydrolyzable block modules of either poly(1,5-dioxepan-2-one) (PDXO) [13] or poly(-but-2-ene-1,4-diyl malonate) (PBM) [20] have shown gradual or rapid hydrolysis profiles, respectively. In contrast, slow degrading blocks of either poly(ε-caprolactone) (PCL) or poly(ε-decalactone) (PDL) have been demonstrated to severely reduce the hydrolysis rates of the triblock materials [19]. It was observed that PLLA-based triblock polymers with different central block modules showed general hydrolysis rates in the following order: PLLA-PBM-PLLA > PLLA-PDXO-PLLA > PLLA-PCL-PLLA > PLLA-PDL-PLLA. Similar results have been obtained for PLLA-based triblock copolymers with the soft polymenthide (PM) as central segment [21]. PLA copolymerized with polyglycolide (PGA) is one of the most attractive combinations for use in biomedical applications, due to the variety in hydrolysis rates and the proven biocompatibility [22–24]. The difference in hydrolysis rates relies on the hydrophilic/hydrophobic balance of the main chains. Similar results have been obtained for PCL-PGA-based copolymer systems [10,25,26]. These results point toward the possibility of using controlled block layout design in different combinations as a means to predict the hydrolysis behaviors of the designed materials. More recently, a wide variety of combinatorial approaches have been proposed to optimize the generation of polymeric structures with specified properties [27–33]. To bypass the problem of designing new materials with unique properties as well as to simultaneously tackle the problem of controlling the degradability of the final polymer structure, a so-called modular approach towards targeted polymer entities may be considered.

By envisioning complex polymeric structures that can be straight-forward designed with meant functionality and forecasted degradability, we aimed to create a polymer hydrolysis prediction protocol based on a modular block design. We hypothesized that aliphatic block copolymers would exhibit predictable hydrolysis behaviors depending on the inherent hydrolysis behaviors of the block components. The approach proceeded in a bottom-up manner contrary to traditional top-down designs, suggesting that the constituent polymer blocks could be chosen and carefully combined to create materials with desired properties and hydrolysis rates during use (Fig. 1). The experimental dissemination started with investigating the hydrolysis behaviors of a toolbox of homopolymers with different hydrophobicities and degrees of crystallinity based on PLLA, PCL, PDXO, PDL; these properties were then related to the hydrolysis rates of different modular combinations. This modular approach meets the expectations of a polymer chemist designing degradable materials in terms of efficiency, versatility and simplicity. Our vision is that this will provide an overview on how to tune the hydrolysis behaviors of copolymer structures for future applicability.

2. Materials and methods

2.1. Materials

The monomer L-lactide (LA, Boehringer Ingelheim, France) was purified by recrystallization three times in dry toluene; ε-decalactone (DL, 99%, Sigma-Aldrich, Sweden) and D,L-lactide (99%, Sigma-Aldrich, Sweden) were used as received; and ε-caprolactone (CL, 97%, Sigma-Aldrich, Sweden) was dried over calcium hydride (CaH_2) and distilled under reduced pressure prior to usage. The monomer 1,5-dioxepan-2-one (DXO) was synthesized via Bayer-Villiger oxidation process according to an earlier described procedure [34]. The DXO monomer was purified by recrystallization two times in dry ether and subsequently drying under reduced pressure.

1,6-hexanediol (Sigma-Aldrich, Sweden) and benzyl alcohol (Sigma-Aldrich, Sweden) were used as initiators, and stannous 2-ethylhexanoate ($Sn(Oct)_2$; 95%, Sigma-Aldrich, Sweden) dried over molecular sieves was used as catalyst. The solvents methanol (Fisher Scientific, Sweden), ethanol (Fisher Scientific, Sweden) and chloroform (Fisher Scientific, Sweden) were used as received.

2.2. Polymer synthesis

The synthesis of the polymers was performed in bulk where the monomer, initiator and catalysts were added into the reaction vessels under an inert atmosphere. $Sn(Oct)_2$ was used as catalyst ($[M]/[Sn(Oct)_2] \approx 100$) and benzyl alcohol was used as initiator in the synthesis of poly(L-lactide) (PLLA), poly(ε-decalactone) (PDL) and poly(ε-caprolactone) (PCL) homopolymers. The synthesis of PLLA and PCL was executed in a thermostatically controlled oil bath at 110 °C and the reaction time was 3 h. In the synthesis of PDL the reaction conditions were 150 °C for 6 h.

The synthesis of the block copolymers was carried out in two-steps, were the middle-block segment was polymerized first and after complete conversion was achieved, the second component was added to form the side-blocks. $Sn(Oct)_2$ was used as catalyst ($[M]/[Sn(Oct)_2] \approx 100$) and 1,6-hexanediol was used as initiator for the triblock copolymers. Thereafter, the reaction products were cooled down to room temperature, dissolved in chloroform and finally precipitated three times in cold methanol. The precipitates were dried under reduced pressure for one week.

2.3. Film preparation

The materials were dissolved in chloroform (~6% (w/w)) and further casted in glass Petri dishes. The solvent was let to evaporate and finally the films were dried under reduced pressure for one week before hydrolysis.

2.4. Hydrolysis

The copolymers and respective homopolymers were subjected to hydrolytic degradation in deionized water at 37 °C for a period of approximately 600 days. Each hydrolyzed sample had an approximate weight of 30 ± 1 mg and a square shape with dimensions of 1 cm × 1 cm and 0.200–0.300 mm thickness. The samples were placed in a vial containing 10 mL of water sealed with a butyl/PTFE septa and aluminum lid, and finally placed in a thermostatically controlled oven. Triplicate samples of each material were withdrawn from degradation milieu at predetermined time intervals, dried under vacuum for a week and subjected to various analyses.

2.5. Mass loss

The progress of the degradation was followed by determining the remaining mass of the samples after each hydrolysis time. After withdrawing the materials from the degradation medium, the samples were dried under reduced pressure. The mass loss was determined by comparing the dry mass of the specimen (md) at the