Polymer Degradation and Stability 130 (2016) 58–67

Contents lists available at ScienceDirect

Polymer Degradation and Stability

journal homepage: www.elsevier.com/locate/polydegstab

Forecasting linear aliphatic copolyester degradation through modular block design

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A R T I C L E I N F O

Article history:
Received 30 March 2016
Received in revised form
16 May 2016
Accepted 23 May 2016
Available online 27 May 2016

Keywords:
Polyesters
Hydrolysis
Hydrophobicity
Crystallinity
Macromolecular engineering

A B S T R A C T

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

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http://dx.doi.org/10.1016/j.polymdegradstab.2016.05.021
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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

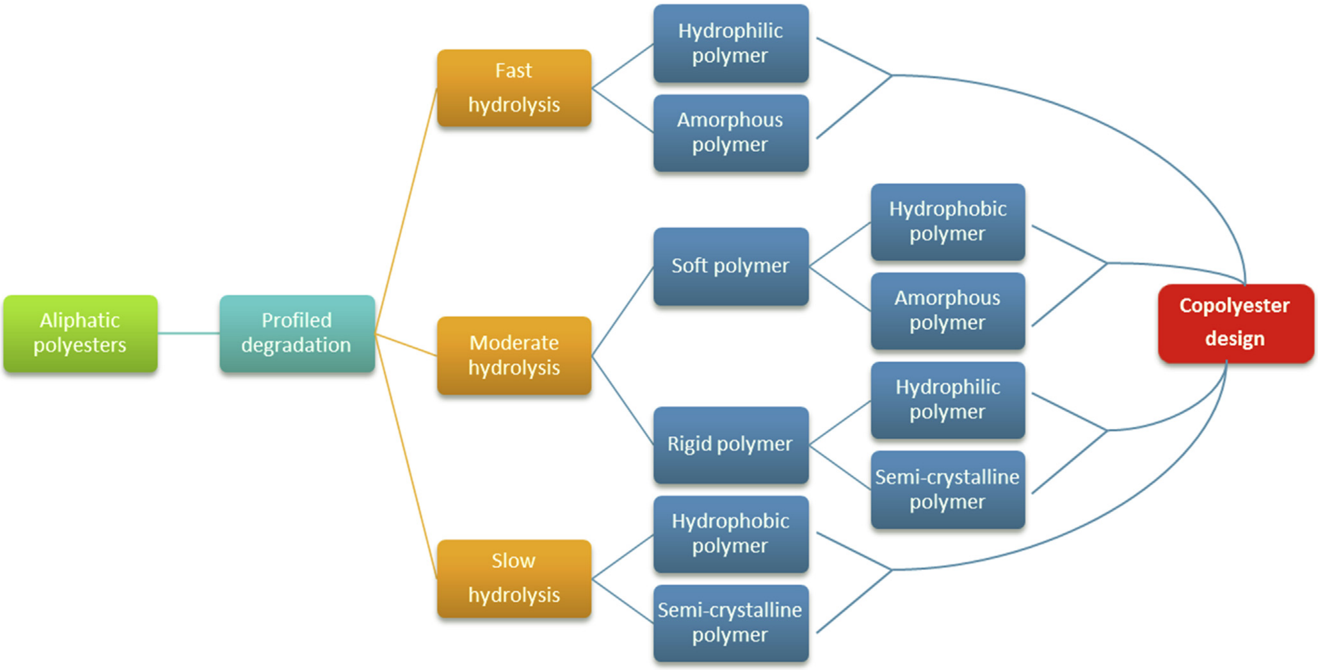

Fig. 1. Outline of the modular strategy applied for designing polyester-based materials with predictable hydrolysis profiles. Based on this hydrolysis chart, we have created a library of polymer building blocks with distinctive hydrophobicities and degrees of crystallinity. By combining these blocks in various configurations, it is possible to forecast and fine-tune hydrolysis rates with respect to time and polymer properties.

specific time with the initial mass of the specimen (m0), according to Equation (1).

$$\Delta m_d = (m_{o-}m_d)/m_0 \times 100 \tag{1}$$

2.6. Size exclusion chromatography (SEC)

The number average molar mass (M_n) and dispersity (Đ) of the starting materials and after each hydrolysis time were evaluated using a Verotech PL-GPC 50 Plus system with a PL-RI Detector and two Mixed-D (300 × 7.5 mm) columns from Varian. The samples were injected with a PL-AS RT autosampler for PLGPC 50 Plus using chloroform as the mobile phase (1 mL/min, 30 °C). Polystyrene standards with a molar mass in the range of 580–400 000 g/mol were used for calibration. Corrections for flow rate fluctuations were made using toluene as an internal standard. CirrusTM GPC Software was used to process the data. The kinetics of the degradation was followed assuming an exponential decrease of the M_n according to Equation (2) [35].

$$ln\, Mn(t2) \;=\; ln\, Mn(t1) - kt \tag{2}$$

2.7. Nuclear magnetic resonance (NMR)

^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker Advance DPX-400 Nuclear Magnetic Resonance spectrometer operating at 400 MHz and 100 MHz correspondingly. Approximately 10 and 100 mg samples were dissolved in 1 mL of deuteronchloroform ($CDCL_3$) in a 5 mm diameter sample tube for ^{1}H NMR and ^{13}C NMR, respectively. The composition of the materials was determined using ^{1}H NMR by comparison of the peaks intensities of the homopolymers δ_{PLLA} 5.13 ppm, δ_{PCL} 4.05, δ_{PDXO} 3.75 ppm and δ_{PDL} 4.83 ppm. ^{13}C NMR was used to qualitative determine the block sequences in the carbonyl region. The residual chloroform was used an internal standard ($\delta = 7.26$ ppm and $\delta = 77.0$ ppm for ^{1}H NMR and ^{13}C NMR, respectively).

2.8. Differential scanning calorimetry (DSC)

The degree of crystallinity of the materials was determined by means of DSC (Mettler Toledo DSC 820 module). Approximately 5 mg of polymer was encapsulated in 40 μL aluminum crucibles without pin. The temperature program used was: (I) heat from −70 °C to 200 °C, (II) cooling down to −70 °C, and (III) heating for a second time to 200 °C. The heating and cooling rate was 10 °C/min under nitrogen atmosphere (nitrogen flow rate 50 mL/min). From the first heating scan, the approximate crystallinity of the materials was calculated according to Equation (3).

$$w_c = \frac{1}{wt}\frac{\Delta H_f}{\Delta H_f^0} \times 100 \tag{3}$$

where w_c is the degree of crystallinity, ΔH_f is the heat of fusion of the sample, ΔH_f^0 is the heat of fusion of 100% crystalline polymer and wt is the weight fraction of the crystalline polymer in the sample. For PLLA and PCL, ΔH_f^0 is 93 J/g [36] and 139.5 J/g [37] respectively.

2.9. pH

pH measurements of the degradation medium were performed after each hydrolysis time using a VWR symphony pH-meter SB70P equipped with an Ag/AgCl or a Biotrode (Hamilton, USA) electrode.

3. Results and discussion

There are many factors that need to be considered to be able to forecast the hydrolysis behavior of aliphatic polyester-based block copolymers. These factors include the hydrophobic/hydrophilic balance and morphology of a polymeric structure, as well as other chemical and physical features. In light of this, we designed a box of modules composed of various polyester building blocks with clear structural differences (Fig. 2) including: two rigid semicrystalline modules of poly(L-lactide) (PLLA) and poly(ε-caprolactone) (PCL) and three soft amorphous modules composed of poly(ε-decalactone) (PDL), poly(1,5-dioxepan-2-one) (PDXO) and poly(D,L-lactide) (PDLLA). The classification of soft and rigid polymers is based on the physical properties of the polymer blocks used at room temperature. Rigid polymers are herein described as semicrystalline polymers with usage temperature below the glass transition and melting temperatures, and soft describes the amorphous polymers with usage temperature over their glass transition [38]. Each building block has a characteristic hydrophilic/hydrophobic balance in the polymer backbone that is defined as the carbon/oxygen (C/O) ratio. The polyesters were synthesized by sequential ring-opening polymerization (ROP) of the corresponding lactones and lactides according to previously described procedures [34,39,40]. Using these modules, a series of triblock copolymers with clear differences in properties was generated and subjected to hydrolysis.

The characteristics of the materials before hydrolysis are presented in Table 1. The notation of the materials is represented by the polymer compositions in the initial feed. The compositions of the copolymers were close to the theoretical (feed) values. The polymers presented molar masses in a narrow range with relatively low dispersity values. The differences in molar masses measured by ^{1}H NMR and by size-exclusion chromatography (SEC) were attributed to differences in hydrodynamic volume of the modules. These differences affect the molar masses measured by SEC; over or underestimation of molar masses of linear polyesters is common when using polystyrene standards [40,41]. Furthermore, the presence of zero, one or two semicrystalline components was determined, depending on the nature of the compositional blocks in the copolymers. The theoretical C/O ratios, which gives an indication of the hydrophobic character of the material, correlated in most cases with the experimental values determined from the water contact angles of the materials surfaces (See Supporting Information). Variations were observed in the pure homopolymers, where PLLA has the lowest C/O ratio showed a high water contact angle value in the range of the homolog semicrystalline PCL. This is caused by the surface energy of polymers, which is in direct correlation with their contact angles, and is strongly related to their crystalline character [42]. Thus, it is expected that highly crystalline polymers exhibit high surface energies due to an increase in their surface density.

3.1. Evaluation of the hydrolysis behavior of the individual modules

Knowledge of the hydrolytic behavior of each individual module opens the possibility of predicting the hydrolytic path of a constructed material. Hence, a strategic combination of different modules can be used to achieve a specific hydrolysis behavior for use in different applications. The hydrolysis behavior of the pure modules (in water at 37 °C) revealed a close linear relation between C/O ratios and the remaining molar masses with time (Fig. 3a). Thus, each module had clear differences in hydrolysis behaviors that were mainly affected by the C/O ratios of the polymeric structures. Lower C/O ratio resulted in faster hydrolysis, as indicated by PLLA (C/O = 1.5) and PDXO (C/O = 1.7) in comparison to PCL (C/O = 3) and PDL (C/O = 5).

The molar mass changes for a period of approximately 600 days were used to calculate the hydrolytic degradation rate constants (k) according to Equation (2). The k values were estimated from the logarithm of the remaining M_n relative to the degradation time (See Supporting Information). The homopolymers, PDL and PCL with higher C/O ratio, have the slowest degradation rate values of $4.7 \times 10^{-4}(days^{-1})$ and $2.0 \times 10^{-3}(days^{-1})$, respectively. PLLA and PDXO, which have lower C/O ratios, had faster degradation rates of $2.2 \times 10^{-2}(days^{-1})$ and $8.2 \times 10^{-3}(days^{-1})$, respectively. The fast degradation of PLLA was comparable to our previous results on hydrolysis of PLLA-based polymers in the first stage of degradation [43,44].

However, it was observed that mass loss was not linked to the C/O ratio of a polymer but rather to the material morphology (Fig. 3b). Comparing PDL to PCL (C/O ratios >3), PDL demonstrated a slightly faster mass loss over the hydrolysis period, probably because amorphous polymers have higher chain mobility in the degradation medium. In the same manner, comparing PDXO to PLLA (C/O ratios <3), amorphous PDXO exhibited a much faster decrease in mass than the semicrystalline PLLA module. Thus, different solubility behaviors in the degradation medium were expected depending on the polymer morphology. The amorphous nature of DXO oligomers leads to an increase in water solubility compared to LLA oligomers [45,46]. In contrast to the amorphous blocks, the semicrystalline PLLA and PCL modules have mass loss that is quite slow during the hydrolysis period, due to the relatively low water solubility of the oligomeric degradation products [45,46].

Changes in the pH of the degradation medium are a good indicator of the release of water-soluble products into the medium and hence of the mass loss suffered by the specimens [45]. Upon

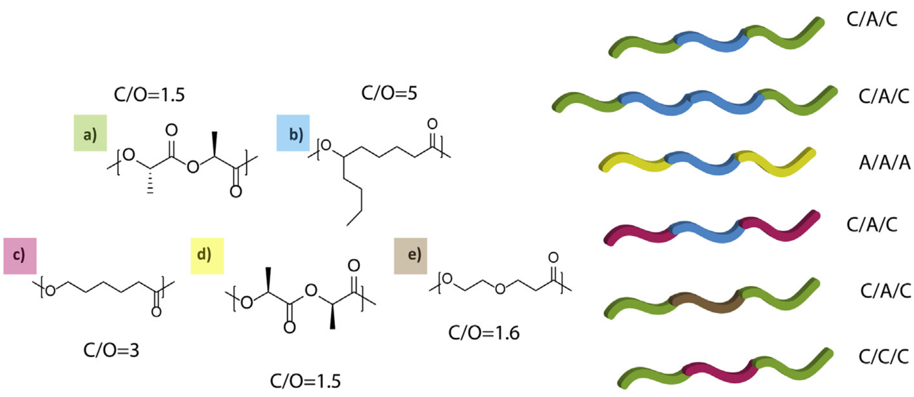

Fig. 2. Building blocks used to exemplify the modular approach for the design of hydrolyzable materials: a) poly(L-lactide) (PLLA) with C/O ratio = 1.5; b) poly(ε-decalactone) (PDL) with C/O = 5; c) poly(ε-caprolactone) (PCL) with C/O = 3; d) poly(D,L-lactide) (PDLLA) with C/O = 1.5; e) poly(1,5-dioxepan-2-one) (PDXO) with C/O = 1.6. A schematic representation of the copolymers built through the modular design with the selected blocks, where "C" and "A" stand for semicrystalline and amorphous polymer blocks, respectively.

Table 1
Materials molar mass, dispersity, crystallinity and composition before hydrolysis.

Material ID	Copolymer block composition[a]	Copolymer block composition[b]	C/O[c] ratio	M_n[b] (g/mol)	M_n[d] (g/mol)	Đ[d]	w_c[e] (%)
PLLA-PDL-PLLA	1:1:1	1:1.1:1	2.7	51,000	45,000	1.2	66 ± 1
PCL-PDL-PCL	1:1:1	1:1.1:1	3.7	44,100	47,500	1.3	61 ± 0
PLLA-2PDL-PLLA	1:2:1	1:1.8:1	4	48,500	41,000	1.2	49 ± 0
PDLLA-PDL-PDLLA	1:1:1	1:0.8:1	2.7	30,400	51,800	1.2	–
PLLA-PCL-PLLA	1:1:1	1:1.2:1	2	43,700	78,300	1.2	59 ± 0[f]; 35 ± 0
PLLA-PDXO-PLLA	1:1:1	1:0.8:1	1.5	61,700	52,200	1.1	65 ± 1
PDL	1	1	5	–	30,300	1.2	–
PCL	1	1	3	–	63,900	1.2	61 ± 1
PLLA	1	1	1.5	–	86,000	1.3	45 ± 0
PDXO	1	1	1.7	–	83,800	1.3	–

[a] Theoretical composition.

[b] Determined from ^{1}H NMR spectra by comparing the integrals of the monomers and initiator.

[c] Theoretical values.

[d] Determined by SEC using $CHCl_3$ as the eluent and polystyrene standards.

[e] Determined by DSC from the first heating scan. Values normalized to their weight fraction. See Supplementary material for the w_c values from the second heating scan (Table S2).

[f] $w_{c\ (PLLA)} = 59 \pm 0\%$; $w_{c\ (PCL)} = 35 \pm 0\%$.

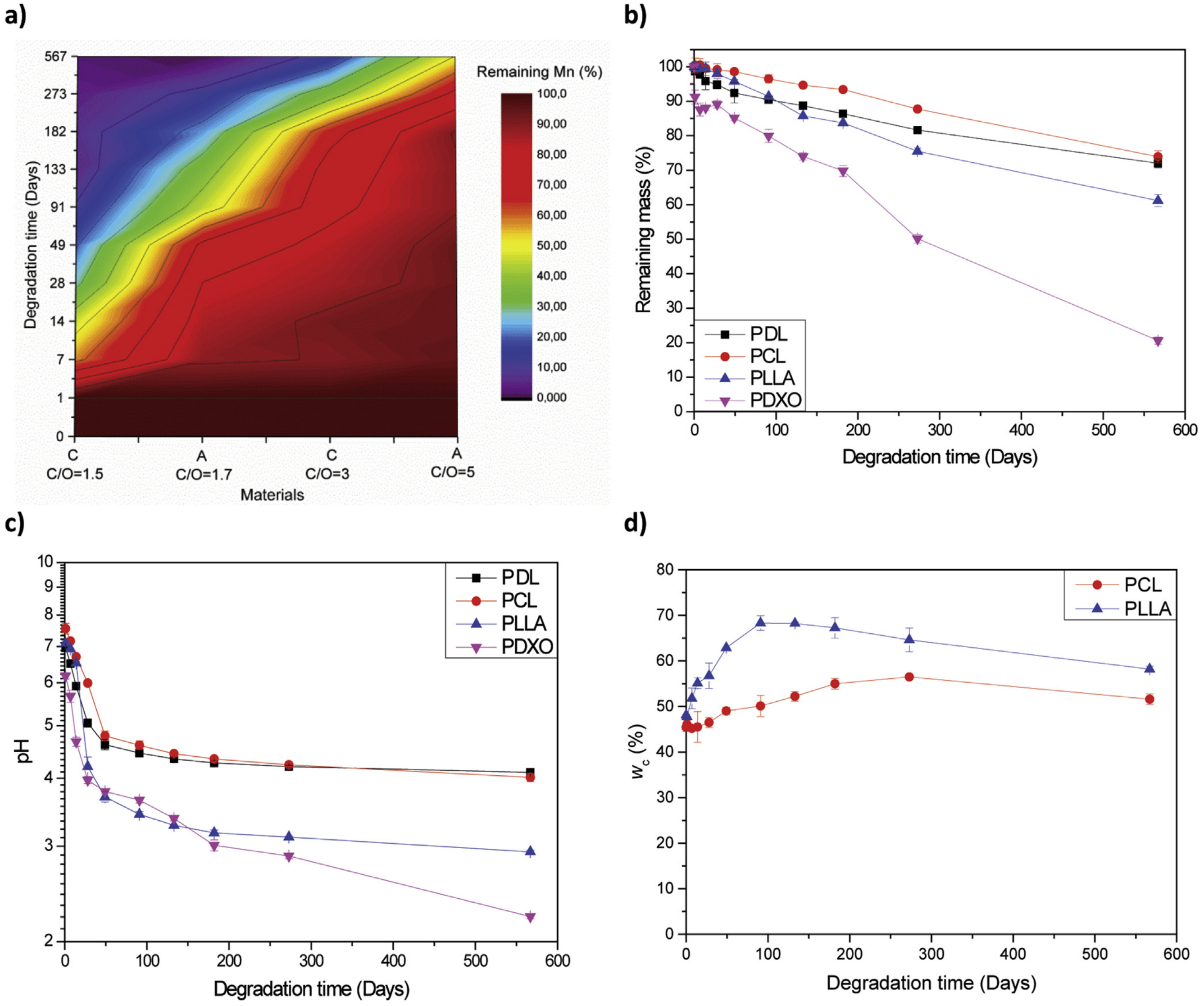

Fig. 3. Hydrolysis process for formulations with one building block: PLLA, PCL, PDL, and PDXO were subjected to hydrolysis in water at 37 °C for a period of approximately 600 days. a) Remaining molar mass; b) remaining mass; c) pH and d) degree of crystallinity during hydrolysis of the semicrystalline modules.

hydrolysis, a slight decrease in the pH of the degradation medium was observed for the PCL and PDL modules (Fig. 3c). In contrast, the pH of the degradation milieu decreased considerably for the PLLA and PDXO modules. These observations were a result of the degradation products generated from the hydrolysis of each of the modules. The degradation products for PLLA and PDXO are their oligomers, which eventually can degrade further to lactic acid and hydroxyethoxic propanoic acid, respectively. The latter has a lower acid dissociation constant (pK_a) than 6-hydroxyhexanoic acid and 6-hydroxydecanoic acid for PCL and PDL, respectively. Differences in starting pH were observed for the materials along with a decrease of pH at early degradation stages; this is most probably due to the known error associated to the measurement of the pH of deionized water, that was used as the degradation medium. Deionized water has quasi-absence of ions, which are the responsible for enabling the electron transport, and in the absence of dissolved polymer chains in the milieu it could generate a non-precise reading of the pH of the water [47].

The degrees of crystallinity for the semicrystalline PLLA and PCL modules increased during the early stages of hydrolysis with subsequent decreases during a later hydrolysis period (Fig. 3d). The hydrolysis of semicrystalline polymers starts in the less organized amorphous regions, which enhances the motion of the smaller degraded chains and allows for reorganization. This contributes to an increase in the degree of crystallinity. In a second step, when most of the amorphous parts are degraded, the hydrolysis continues in the crystalline domains [36,48].

In summary, the synthesized modules or blocks with clear differences in molecular structures (i.e., crystallinity) and in their physical properties (i.e., hydrophilic/hydrophobic balance), which led to different hydrolytic degradation behaviors. Taking this to the next level, we attempted to use the knowledge on the different hydrolysis behaviors of each of the modules as a means to predict the lifetimes of the constructed polymers. To this end, we constructed different triblock formulations composed of an amorphous central-block flanked with semicrystalline side-blocks with different C/O balances: PLLA-PDXO-PLLA ($C/O = 1.5$), PLLA-PDL-PLLA ($C/O = 2.7$) and PCL-PDL-PCL ($C/O = 3.7$). Additionally, variations in the length of the amorphous middle blocks, represented by PLLA-2PDL-PLLA ($C/O = 4$), were also included. Thus, the question was which hydrolysis path these combinations followed. From the perspective of C/O ratios, the forecasted hydrolysis rates were expected to proceed in the following order:

PLLA-PDXO-PLLA > PLLA-PDL-PLLA > PCL-PDL-PCL > PLLA-2PDL-PLLA.

3.2. Block copolymers with forecasted hydrolysis

After approximately 600 days of hydrolysis, it was found that the hydrolysis rates of the copolymers followed the predicted order. The hydrolysis rates were governed by the hydrophilic/hydrophobic balance of the polymers, which resulted from the compositional modules used as center- and side-blocks that had different C/O balances as observed in Fig. 3. The hydrolytic behaviors of the selected combinations are displayed in Fig. 4. The contour graph makes it possible to foresee how long the hydrolysis process will take to reach a specific molar mass for a known C/O ratio (Fig. 4a).

The formulations with higher C/O ratios such as PCL-PDL-PCL and PLLA-2PDL-PLLA, displayed relatively slow and similar hydrolysis rates of $1.0 \times 10^{-3}(days^{-1})$ and $9.3 \times 10^{-4}(days^{-1})$, respectively. This was because the individual C/O ratios of each of the modules, which was higher for PCL-PDL-PCL than for PLLA-2PDL-PLLA, contributed to a higher hydrolytic endurance of the material. PLLA-PDL-PLLA and PLLA-PDXO-PLLA, which had lower C/O ratios, displayed degradation rates of $3.0 \times 10^{-3}(days^{-1})$ and $1.7 \times 10^{-2}(days^{-1})$, respectively. The hydrolytic behavior obtained for a similar copolymer systems based on PLLA-PBM ($C/O = 1.6$) was compared to our prediction contour plot and was confirmed to undergo a 50% decrease in molar mass over a period of approximately 30 days [49], which confirmed the effectiveness of our prediction model for assessing the hydrolysis rates of block copolymer systems. Material properties and degradation products affected during hydrolysis such as molar mass loss, mass loss, block compositional changes, pH of the degradation milieu and the degrees of crystallinity of the semicrystalline side-blocks were then analyzed.

The molar mass loss during hydrolysis decreased with increasing C/O ratios of the polymer structures (Fig. 4a). Polymer with PCL and PDL had the highest C/O ratios, which resulted in polymers with higher hydrolytic endurance than that of polymers formulated with PLLA and PDXO modules. The addition of PDL as a central-block increased the hydrolytic stability of the materials. This was confirmed by doubling the length of the most hydrophobic central block in the formulations, which increased the C/O ratio and hence the stability of the copolymers, as in the case of PLLA-PDL-PLLA compared to PLLA-2PDL-PLLA.

The mass loss of the copolymers with a central hydrophilic module (i.e., PDXO) and thereby a lower C/O-ratio occurred at a much faster rate than the other formulations. PLLA and PCL building blocks have been shown to be bulk-eroding polymers, where mass loss occurs at a much slower rate than molar mass loss (Fig. 4b) [50,51]. PDXO is a polyester-ether which undergoes both bulk and surface erosion, where the loss of material also occurs from the exterior surface [39]. The slowest mass loss rate was observed for the copolymers with two hydrophobic modules; the PCL-PDL-PCL construction had the highest C/O ratio of 4 units.

As the hydrolysis proceeded, the pH of the degradation medium decreased with increasing mass loss (Fig. 4c). For the polymer with the two most hydrophobic modules, PCL-PDL-PCL, a higher pH was retained than for the formulations containing a PLLA module. The pK_a of oligomeric PLLA degradation products (i.e., hydroxy acids) was 3.1 compared to the other hydroxy acid derivatives (e.g., hydroxyhexanoic acids for PCL, which had a pK_a of 5) [52]; thus, the dissociation of the acid end-groups occurred faster in an acidic environment, which contributed to the acid-catalyzed hydrolysis.

The composition of the copolymers during hydrolysis was directly affected by the hydrophobic ratios of the modules (Fig. 4d). The PLLA and PDXO copolymer demonstrated a decrease in the PDXO content at early stages of hydrolysis (approximately 100 days). In contrast, the PLLA content decreased slowly with time for the copolymers that had PLLA side-blocks and a PDL central-block; the PDL module was much more hydrolytically stable than the PLLA block. For the construction of a polymer with PCL and PDL blocks, the composition showed very little variation until approximately 600 days of hydrolysis, where a slight decrease in the PCL content was observed. Both components, PCL and PDL, have high C/O ratios and thus have higher hydrolytic endurance than the PLLA and PDXO blocks. Previous studies have shown that by combining PCL with PDXO, the hydrolysis rate of the material can be increased as a result of an increase in surface hydrophilicity [13]. The degrees of crystallinity of the copolymers increased until 300 days of hydrolysis. Thereafter, a decrease in crystallinity was observed in later stages of hydrolysis, at approximately 600 days, for all the formulations (See Supporting Information).

In summary, it was confirmed that the formulations discussed above with different C/O ratios had their hydrolysis paths ruled by the hydrophilic/hydrophobic balance of the modules, as predicted. Thus, when using polymer modules of the same kind the hydrolysis path is directly affected by the hydrophilic/hydrophobic balance of the modules. However, other factors such as the degree of

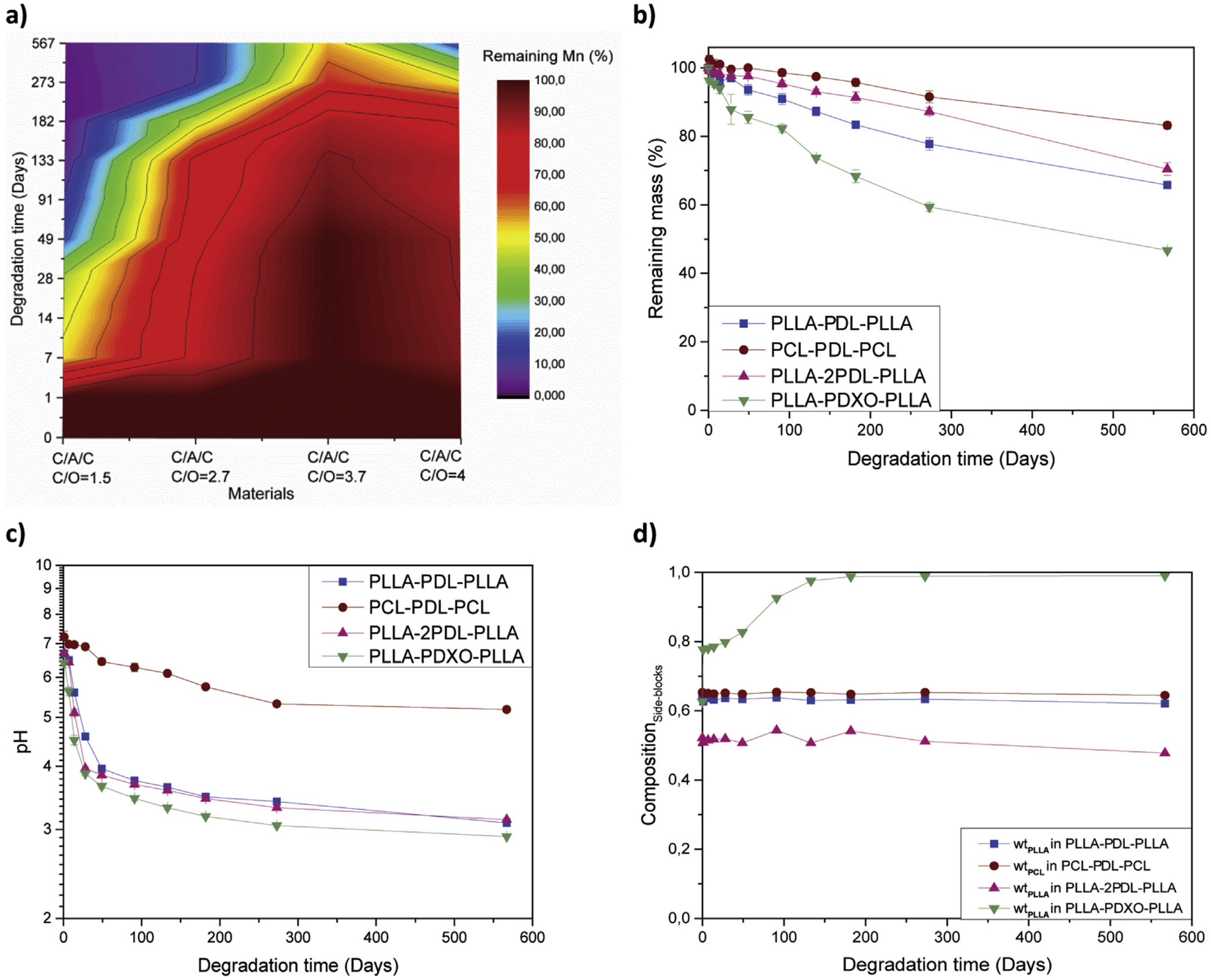

Fig. 4. Hydrolysis process for the PLLA, PDL, PCL and PDXO modules with flanking semicrystalline blocks in water at 37 °C for a period of approximately 600 days. a) Remaining molar mass; b) remaining mass; c) pH and d) side-block compositional variations during hydrolysis for the selected combinations. The designed triblocks with different C/O ratios had an amorphous central-block, PDL or PDXO, and semicrystalline side-blocks, PLLA and PCL.

crystallinity of the modules highly influence the degradation process, and therefore this is thoroughly described in the next section.

3.3. Deviations from the prediction model

There is occasionally the need to construct fully amorphous or fully crystalline polymers to fulfill specific application requirements. By building triblock structures with only semicrystalline or amorphous blocks, similarities in C/O ratios between the structures were obtained. The question was what happens when combined formulations have the same or similar C/O ratios but have different polymer morphologies. Using selected modules, two triblock copolymers with fully amorphous or fully crystalline side- and central-blocks were constructed: PDLLA-PDL-PDLLA (C/O = 2.7) and PLLA-PCL-PLLA (C/O = 2). Additionally, due to the similarities in C/O ratios but differences in the morphologies of the modules with PDLLA-PDL-PDLLA, PLLA-PDL-PLLA (C/O = 2.7) was included for comparison. Considering only the C/O ratios, it was assumed that the hydrolysis rates would proceed in the following order: PLLA-PCL-PLLA > PLLA-PDL-PLLA ≥ PDLLA-PDL-PDLLA. However, after approximately 600 days of hydrolysis, the hydrolysis rates of these formulations proceeded differently than predicted, and the hydrolysis profiles were governed primarily by the degrees of crystallinity of the modules. The amorphous side-blocks seemed to contribute to faster hydrolysis rates of the structures (Fig. 5).

The contour graph allows to foresee the length of the hydrolysis process to reach a specific molar mass with similar C/O ratios for materials that do not follow the prediction model (Fig. 5a). The material properties under hydrolysis conditions and the pH of the degradation medium were also evaluated. These findings will serve as a platform to achieve the effective construction of degradable, fully semicrystalline or amorphous materials with different hydrolysis rates for use in different applications.

Molar mass loss occurred much faster for the PDLLA-PDL-PDLLA polymer at a rate of $9.4 \times 10^{-3}(days^{-1})$, where only approximately 10% molar mass remained after approximately 600 days of hydrolysis, than for PLLA-PDL-PLLA, which had approximately 3 times the amount of molar mass remaining at the same hydrolysis stage and displayed a degradation rate of $3.0 \times 10^{-3}(days^{-1})$ (Fig. 5a). This observation was attributed to the differences in crystallinity of the flanking blocks, i.e., semicrystalline PLLA and fully amorphous PDLLA. The difference in hydrolysis rates for polylactides with

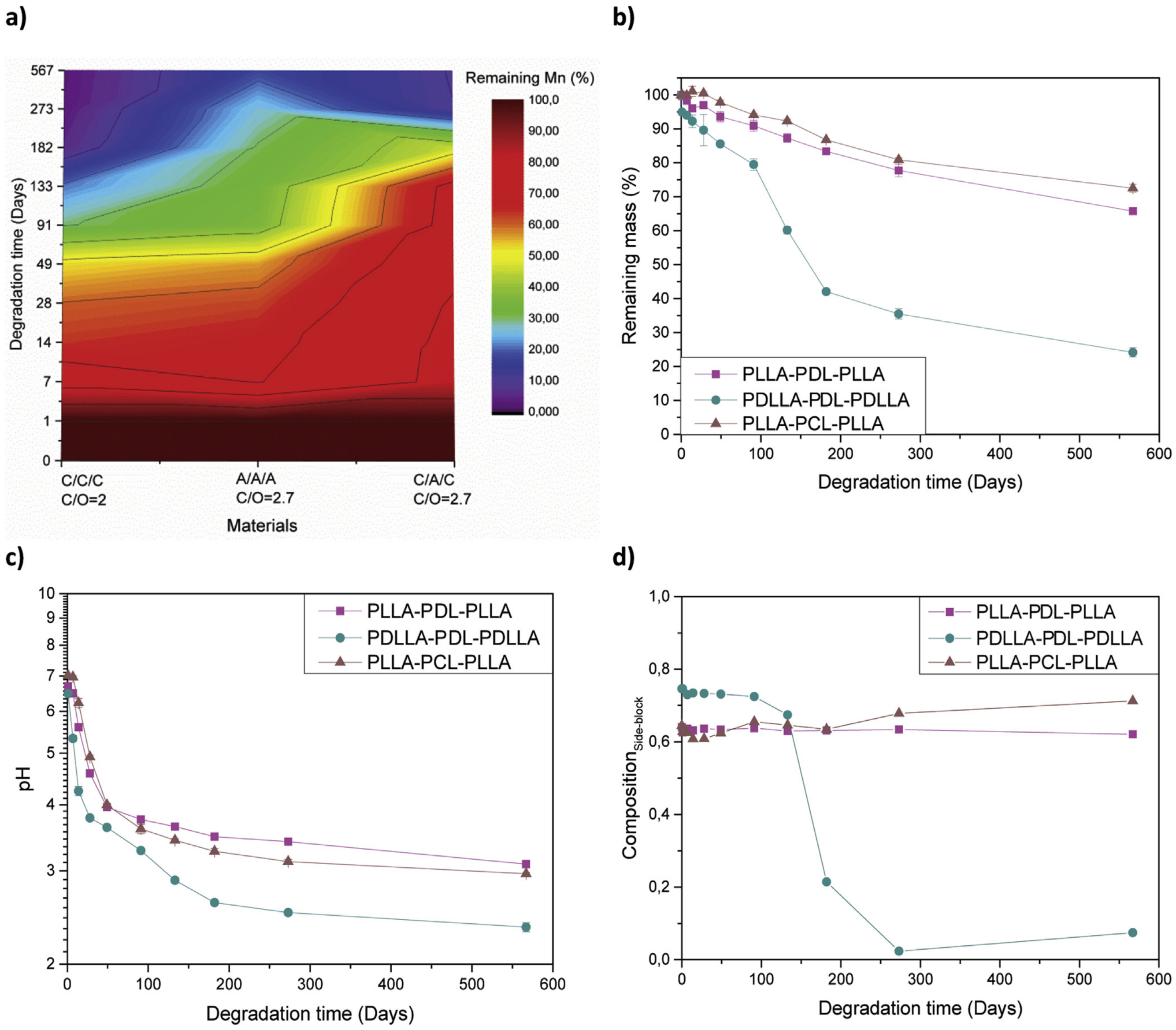

Fig. 5. Hydrolysis process for the PLLA, PDL, PCL and PDLLA modules with flanking semicrystalline and amorphous blocks in water at 37 °C for a period of approximately 600 days. a) Remaining molar mass; b) remaining mas; c) pH; and d) Side-block compositional variations during hydrolysis for the selected combinations. The designed triblocks with similar C/O ratios had semicrystalline (C) or amorphous (A) central-blocks, PCL and PDL, and semicrystalline or amorphous side-blocks, PLLA and PDLLA.

different isomeric compositions, and hence degrees of crystallinity, have been extensively studied and have been shown to have faster hydrolysis rates with decreasing polymer crystallinity [53]. In the case of the material with semicrystalline components, PLLA-PCL-PLLA, the molar mass loss occurred faster at a rate of $1.6 \times 10^{-2}(days^{-1})$ than for the PLLA-PDL-PLLA formulation due to the higher hydrolytic endurance of the most hydrophobic PDL components than when PCL was used in the central-blocks.

Mass loss occurred faster for PDLLA-PDL-PDLLA than for PLLA-PDL-PLLA and PLLA-PCL-PLLA, where at approximately 600 days of hydrolysis 20, 70 and 80% of mass remained in the formulations, respectively (Fig. 5b). The pH of the degradation medium decreased along with the observed mass loss (Fig. 5c). The block compositions under hydrolysis conditions demonstrated large variations across the formulations (Fig. 5d). The design containing PDLLA as side-blocks revealed a sharp decrease in the PDLLA content at early stages of hydrolysis (approximately 200 days). In contrast, the formulations containing PLLA as side-blocks showed a variation in composition after approximately 300 days of hydrolysis. The PLLA content decreased for the PLLA-PDL-PLLA copolymer and surprisingly, an increase in PLLA content was observed for the PLLA-PCL-PLLA copolymer. The latter occurrence can be explained by the increase in the hydrolysis rate of PCL in acidic environments [52]. The pH of the degradation medium decreased dramatically when the more acidic PLLA degradation products were released from the bulk material. Finally, the degrees of crystallinity increased for up to 300 days of hydrolysis and then subsequently started to decrease at later stages of hydrolysis (See Supporting Information).

It was confirmed that the morphology of the modules had a significant effect on the degradability of the materials. The morphology of the modules refers to the special arrangement of the polymer phases, i.e. semicrystallinity or amorphousness of the polymer [38]. Furthermore, we have previously shown that the heterogeneity of the amorphous phase plays a significant role in copolyesters degradation, leading to a more selective chain scission when having a more homogeneous amorphous phase [19]. Based on the previous results, it could even be said that the morphology of the modules had a bigger effect on the hydrolysis behavior of the copolymers than the C/O ratios of the polymer structures when having similar hydrophobicities. Thus, the hydrolysis rates were modified to the following order: PLLA-PCL-PLLA > PDLLA-PDL-PDLLA > PLLA-PDL-PLLA.

Herein, the known degradation characteristics of the individual modules were used to create block copolymers with forecasted hydrolysis pathways. The hydrolysis pathways of the designed copolymers were predicted and further verified in terms of physical structure, represented by the hydrophilic/hydrophobic balance in the polymer backbones, and morphology, represented by the degree of crystallinity of the polymeric structures. Despite the fact that these polyesters underwent hydrolysis as a degradation mechanism, the obtained pathways are complex processes that depend on many factors such as morphology, chain orientation, chemical composition as well as on the configurational structure.

4. Conclusions

We successfully developed a modular platform based on polymer blocks that allows for the design of polyester-based materials with forecasted hydrolysis rates. Herein, we summarized our findings through an outlined decision-making tree, where combining selected building blocks with known features made it possible to foresee and fine-tune hydrolysis rates with respect to time and polymer properties (Fig. 1). Several combinational tactics based on polymer structures and polymer morphologies were designed, which covered a wide range of different degradable polymeric structures with projected hydrolysis rates for different applications. Both of the effects discussed (i.e., polymer structure and polymer morphology) greatly affected the hydrolysis process of the formulations. The hydrophilic/hydrophobic balance of the main chains had greater effects on the hydrolysis behavior of the copolymers than the degrees of crystallinity. Combining polymer blocks with amorphous morphologies and hydrophilic structures was preferred for fast hydrolysis. On the contrary, blocks with semicrystalline morphologies and hydrophobic structures resulted in slow hydrolysis. For moderate hydrolysis rate, several block combinations were used, depending on the desired polymer properties. Amorphous, soft blocks with more hydrophobic structures behaved relatively similar to semicrystalline, rigid blocks with more hydrophilic structures. Fast hydrolysis rates were then obtained when structures had lower C/O ratios (i.e., more hydrophilic) and amorphous morphologies. A moderate hydrolysis rate was achieved for both soft and rigid polymer structures. The soft polymers had high C/O ratios (i.e., more hydrophobic) and amorphous structures. The rigid polymers hydrolyzed at a moderate rate either when they had low C/O ratios or when they had semicrystalline structures that degraded heterogeneously. Finally, slow hydrolysis was obtained when the structures had high C/O ratios and semicrystalline morphologies. When developing a hydrolysis strategy for a designed polymeric material, it is important to take into consideration the intricacy of the final hydrolysis process, which is an outcome of the structural transformations that the elaborated molecules were subjected to in terms of morphology and structure. The degradation-design criteria and improved structure-morphology relationships provided by these results will engender new approaches to synthetic material design that can generate degradation properties with greater predictability.

Acknowledgements

The authors acknowledge the ERC Advance Grant, PARADIGM (Grant agreement no.: 246776) and the Swedish Research Council, VR (Grant ID: D0408101) for their financial support of this work.

Appendix A. Supplementary material

Supplementary material related to this article can be found at http://dx.doi.org/10.1016/j.polymdegradstab.2016.05.021.

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