In Vitro Hydrolytic Degradation of Hydroxyl-Functionalized Poly(α-hydroxy acid)s

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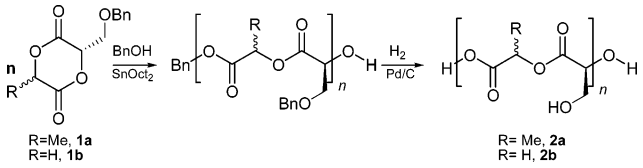
The *in vitro* hydrolytic degradation of hydroxyl-functionalized poly(α-hydroxy acid)s was investigated. Benzyl-ether-protected hydroxyl-functionalized dilactones (*S*)-3-benzyloxymethyl-(*S*)-6-methyl-1,4-dioxane-2,5-dione (**1a**) and (*S*)-3-benzyloxymethyl-1,4-dioxane-2,5-dione (**1b**) were copolymerized in a melt with various amounts of L-lactide using benzyl alcohol and $SnOct_2$ as the initiator and catalyst, respectively. The benzyl groups were removed by hydrogenation to yield polyesters with hydroxyl functional groups, poly(lactic acid-*co*-hydroxymethyl glycolic acid) and poly(lactic acid-*co*-glycolic acid-*co*-hydroxymethyl glycolic acid) (**2a** and **2b**). Degradation of the hydroxyl-functionalized polyesters and poly(lactic-*co*-glycolic acid) (50/50) was studied by incubation of pellets of these polymers in phosphate buffer (174 mM, pH 7.4) at 37 °C. Polymer degradation was monitored by mass-loss measurements and by gel permeation chromatography, differential scanning calorimetry, and ^{1}H NMR analysis. The degradation times ranging from less than 1 day (for the homopolymer of **2a)** to 2 months (copolymer of 25% **2a** and 75% lactide) were found. The degradation rates increased with increasing hydroxyl density of the polymers, which was associated with a switch from bulk to surface erosion. NMR and thermal analysis showed that the moieties with the hydroxyl groups were preferentially removed from the degrading polymer. In conclusion, this study shows that the degradation rate of polyesters containing **2a** and **2b** can be tailored from a few days to 2 months, making them very suitable for biomedical and pharmaceutical applications.

1. Introduction

Biodegradable polymers have been studied and used as controlled drug delivery systems for many years as a means of prolonging the action of drugs, without the need to remove the device after treatment.[1,2] Poly(lactic-*co*-glycolic acid) (PLGA), in the form of implants or injectable micro/nanoparticles has been used for the controlled release of low molecular weight drugs[3] as well as macromolecular therapeutics, such as proteins and plasmid DNA.[4] This polymer undergoes hydrolytic degradation under physiological conditions to form lactic acid and glycolic acid. These degradation products are endogenous compounds and are metabolized via biochemical pathways. The release of entrapped compounds can be controlled by diffusion of the drug through the matrix and/or by degradation of the matrix. Generally, polymer degradation of synthetic polymers can occur via surface erosion or bulk degradation.[5−7] Surface erosion occurs when the hydrolysis of the labile bonds is faster than the diffusion of water into the bulk and has been reported as the main route of degradation for, e.g., poly(anhydrides)[8] and poly(orthoesters).[9] Surface eroding polymers are further characterized by a more or less constant weight loss in time and an unchanged molecular weight of the polymer in the remaining solid. Drugs dissolved or dispersed in the polymer matrix are consequently released at a constant rate during the initial phase of the degradation process because the surface area then remains more or less constant.[8−11]

Scheme 1. Synthesis of the Hydroxylated Poly(α-hydroxy acids) That Were Used in This Study.



In bulk eroding polymers, such as PLGA, the uptake of water is faster than the rate of hydrolysis.[12] Consequently, degradation takes place throughout the entire polymer matrix and proceeds until a critical molecular weight is reached. At this point the degradation products become water-soluble and diffuse out of the degrading material. The hydrolysis rate is influenced by molecular weight and copolymer composition. Since the water-uptake and degradation initially take place in the amorphous phase of the matrix, materials with a high degree of crystallinity generally show a slow degradation. For example, poly(ϵ-caprolactone), which is a highly hydrophobic and semicrystalline polyester, degrades slower than the amorphous, less hydrophobic PLGA. Depending on these variables, the degradation time varies from several weeks up to years and allows the release of drugs over this time period.[13,14] The degradation time of the frequently used PLGA family of polymers ranges from 1 to 2 months for completely amorphous PLGA 50/50 up to 1−2 years for the semicrystalline poly-L-lactide (PLLA).[15] For some applications, however, a shorter degradation time is requested. Aliphatic poly(α-hydroxy acid)s, of which the degradation time can be tailored from a few days up to 2 months, are presently unavailable. A strategy to increase the degradation rate of PLGA is to introduce functional groups such as hydroxyl groups. These

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hydroxyl functionalized polymers will have a stronger water absorption capacity than their non-functionalized counterparts, with, expectedly, increased degradation rates as a result. Until now, several functionalized polyesters have been reported containing functionalities such as hydroxyl, amino, and carboxylic acid groups.[16−21] However, detailed degradation studies on these kinds of polymers have not been reported very often. In this paper, the results of a degradation study of hydroxyl-functionalized poly(α-hydroxy acids) comprised of lactic acid, glycolic acid, and α-glyceric acid are reported. The investigated polymers are poly(α-hydroxy acids) bearing hydroxyl groups along the main chain (Scheme 1).[22] The monomers (*S*)-3-benzyloxymethyl-(*S*)-6-methyl-1,4-dioxane-2,5-dione (**1a**) and (*S*)-3-benzyloxymethyl-1,4-dioxane-2,5-dione (**1b**) in Scheme 1 were homopolymerized (only **1a**) and copolymerized with L-lactide in different ratios. Degradation of the synthesized polymers was studied by the incubation of pellets of these polymers in a phosphate buffer (174 mM, pH 7.4) at 37 °C up to 60 days. Polymer degradation was monitored by mass-loss measurements and by gel permeation chromatography (GPC), differential scanning calorimetry (DSC), and ^{1}H NMR analysis.

2. Experimental Section

2.1. General Information. Reagents and solvents were used without purification, unless stated otherwise. Monomers **1a** and **1b** were prepared as described previously.[22] L-Lactide and PLGA (50/50, M_n = 37 kDa, M_w = 84 kDa) were obtained from Purac (Gorinchem, The Netherlands). Benzyl alcohol (Merck, Darmstadt, Germany) was distilled from CaH_2 prior to use. Tetrahydrofuran (THF, AR grade, Biosolve, Valkenswaard, The Netherlands) was distilled from sodium/benzophenone prior to use as solvent for the deprotection of benzyl ethers, and it was filtered over a 45 μm nylon filter when used as the GPC eluent. Peptide-grade chloroform (Biosolve) was used. Methanol was purchased from Biosolve. Toluene (Acros, Geel, Belgium) was distilled from P_2O_5 and stored over 3 Å molecular sieves under argon. Sodium azide (NaN_3 99%) was obtained from Fluka (Zwijndrecht, The Netherlands). Disodium hydrogen phosphate dihydrate ($Na_2HPO_4 \cdot 2H_2O$) and sodium dihydrogen phosphate dihydrate ($NaH_2PO_4 \cdot 2H_2O$) were purchased from Merck. Other reagents were purchased from Aldrich (Zwijndrecht, The Netherlands). NMR measurements were performed at 298 K on a Varian Gemini-300 NMR machine, operating at 300 MHz (^{1}H) or 75 MHz (^{13}C). Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane (^{1}H) or using the solvent peak as an internal reference (^{13}C). Thermographic analysis was done on a TA Instruments DSC Q1000 machine. Scans were taken from −50 to 190 °C at a heating rate of 10 °C/min. The results of the second run are reported. Inflection points of glass transition temperatures are reported. GPC was carried out on a Waters Alliance system, with a Waters 2695 separating module and a Waters 2414 refractive index detector. Two PL-gel 5 μm mixed-D columns fitted with a guard column (Polymer Labs, M_w range 0.2−400 kDa) were used in this setup. The columns (thermostated at 40 °C) were calibrated with polystyrene standards using THF (Biosolve) as the mobile phase (1 mL/min).

2.2. Homopolymer Synthesis. Ring-opening polymerizations of **1a** and **1b** were carried out in the melt using 1 mol % benzyl alcohol (BnOH) and 0.5 mol % $SnOct_2$ as the initiator and catalyst, respectively. In a typical procedure, monomer (**1a**, 3.30 g, 13.2 mmol) was placed in a dried Schlenk tube equipped with a small stirring bar under a dry nitrogen atmosphere. Initiator (BnOH, 14.0 mg, 0.13 mmol) and catalyst ($SnOct_2$, 28.4 mg, 0.07 mmol) were added, and the tube was evacuated for 1 h. The tube was closed and immersed in an oil bath thermostated at 110 °C for 4 h. The resulting polymer was dissolved in chloroform, precipitated in cold methanol, and dried in vacuo. A homopolymer of **1b** was prepared accordingly. Both polymerizations proceeded in yields of 90+%.

Poly(**1a**): ^{1}H NMR ($CDCl_3$): δ = 1.5−1.7 (m, 3H, −CH_3), 3.8−4.0 (m, 2H, −CH−CH_2−O), 4.4−4.7 (m, 2H, −O−CH_2−C_6H_5), 5.2−5.5 (m, 2H, −CH−CH_3 and −CH−CH_2−O), 7.2−7.4 (m, 5H, −CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ = 16.8 (CH_3); 68.4 (CH); 69.3 (CH_2); 72.5 (CH); 73.4 (CH_2); 127.7 (CH_{Ar}); 127.8 (CH_{Ar}); 128.4 (CH_{Ar}); 137.4 (C_{Ar}); 166.6−166.7 (C═O); 169.1−169.3 (C═O).

Poly(**1b**): ^{1}H NMR ($CDCl_3$): δ = 3.8−4.0 (m, 2H, −CH−CH_2−O), 4.4−4.6 (m, 2H, −O−CH_2−C_6H_5), 4.6−4.9 (m, 2H, −O−CH_2−C(O)O), 5.3−5.5 (m, 1H, −CH−CH_2−O), 7.2−7.4 (m, 5H, −CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ = 60.8 (CH_2); 68.0 (CH_2); 72.5 (CH_2); 73.3 (CH); 127.6 (CH_{Ar}); 127.7 (CH_{Ar}); 128.3 (CH_{Ar}); 137.2 (C_{Ar}); 166.0 (C═O); 166.3 (C═O).

2.3. Synthesis of Random Copolymers of 1a and 1b with L-Lactide. Random copolymers of **1a** and **1b** with 25%, 50%, or 75% (mol/mol) L-lactide were synthesized using the above standard procedure for the preparation of homopolymers. All polymers were obtained in high yields of 90+%.

Poly(lactide-*ran*-**1a**): ^{1}H NMR ($CDCl_3$): δ =1.4−1.7 (m, 9H, −CH_3), 3.8−4.0 (m, 2H, −CH−CH_2−O), 4.5−4.6 (m, 2H, −O−CH_2-C_6H_5), 5.1−5.4 (m, 4H, −CH), 7.2−7.4 (m, 5H, −CH_{Ar}).

Poly(lactide-*ran*-**1b**): ^{1}H NMR ($CDCl_3$): δ = 1.5−1.7 (m, 6H, −CH_3), 3.8−4.0 (m, 2H, −CH−CH_2−O), 4.5−4.6 (m, 2H, −O−CH_2−C_6H_5), 4.6−5.0 (m, 2H, −O−CH_2−C(O)O), 5.1−5.3 (m, 2H, −CH−CH_3), 5.4−5.5 (m, 1H, −CH−CH_2−O), 7.2−7.4 (m, 5H, −CH_{Ar}).

2.4. Deprotection of Poly(1a) to Yield Poly(2a). In a typical procedure, 3.3 g of poly(**1a**) was weighed into a reaction flask. The polymer was dissolved in distilled THF (330 mL) and Pd/C (2.0 g, 10 wt % Palladium (dry basis) on activated carbon, containing 50% w/w water, Degussa type E101 NE/W) (Aldrich) was added. The mixture was placed under a hydrogen atmosphere (balloon) by three consecutive steps of evacuation/refilling with H_2. The reaction took place for 16 h at room temperature. The catalyst was removed by filtration over a fiberglass filter. The filter was washed with an additional 100 mL of distilled THF. Evaporation in vacuo gave the deprotected polymer in a quantitative yield (2.1 g). NMR showed that no signals of the benzyl group were present.

^{1}H NMR ($CDCl_3$): δ = 1.4−1.6 (m, 3H, −CH_3), 3.8−4.1 (m, 2H, −CH_2−OH), 5.0−5.3 (m, 2H, −CH−CH_2−OH amd −CH−CH_3).

2.5. Deprotection of Random Copolymers of 1a and 1b with l-Lactide. Random copolymers of **1a** and **1b** with 25%, 50%, or 75% (mol/mol) L-lactide were deprotected using the procedure described above for the deprotection of poly(**1a**).

Poly(lactide-*ran*-**2a**): ^{1}H NMR ($CDCl_3$): δ =1.4−1.7 (m, 9H, −CH_3), 3.8−4.0 (m, 2H, −CH−CH_2−O), 5.1−5.4 (m, 4H, −CH).

Poly(lactide-*ran*-**2b**): ^{1}H NMR ($CDCl_3$): δ = 1.5−1.7 (m, 6H, −CH_3), 3.8−4.0 (m, 2H, −CH−CH_2−O), 4.6−5.0 (m, 2H, −O−CH_2−C(O)O), 5.1−5.3 (m, 2H, −CH−CH_3), 5.4−5.5 (m, 1H, −CH−CH_2−O).

2.6. Preparation of Polymer Pellets. Polymer pellets were prepared by using a press that is commonly used for the preparation of KBr tablets for infrared spectroscopy. Following a typical procedure, ∼60 mg of polymer was placed in the assembled mould and evacuated for 2 min. Next, pressure was applied (9 bar) for 3 min. The vacuum was removed, the mould was opened, and the pellets were taken out. The pellets had a diameter of 13 mm and a thickness of ∼0.4 mm, corresponding to a weight of 50−70 mg.

2.7. Degradation Study and Analysis. Pellets of the different polymers were transferred into glass containers (one pellet per container) and filled with 10 mL of a phosphate buffer (174 mM, pH 7.4). The buffer also contained 0.05% NaN_3 as a bacterial growth inhibitor. Degradation was done by incubation of the samples at 37 °C. During incubation, the samples were slightly shaken. At regular time intervals, the pH of the solutions was measured, and once the pH dropped below 7, the buffer was refreshed. Pellets were taken out at different time points. After freeze-drying, the weight of the samples was measured,

Table 1. Properties of the Protected (**1a** and **1b**) and Deprotected (**2a** and **2b**) (Co)Polymers Used in This Study

polymer	feed ratio L/M[a]	copolymer ratio NMR	$M_{n\ theoretical}$ (kg/mol)	$M_{n\ measured}$[b] (kg/mol)	M_w/M_n[b]	T_g (°C)
homo(**1a**)			25	10	1.6	24
copolymers **1a**	25/75	28/72	22	nd	nd	40
	50/50	52/48	20	10	1.6	37
	75/25	76/24	17	14	1.5	44
copolymers **1b**	25/75	26/74	21	25	1.8	27
	50/50	51/49	19	18	1.9	33
	75/25	76/24	17	22	1.9	41
homo(**2a**)			16	10	1.4	30
copolymers **2a**	25/75	40/60	16	24	1.9	33
	50/50	54/46	15	8	1.8	36
	75/25	76/24	15	12	1.9	38
copolymers **2b**	25/75	33/67	15	6	1.8	nd
	50/50	56/44	15	11	1.7	26
	75/25	77/23	14	19	1.6	44

[a] L = lactide, M = monomer (**1a**/**1b** and **2a**/**2b**). [b] Determined with GPC in THF using polystyrene as the calibration standard.

and they were analyzed with DSC, NMR, and GPC. At each time point, two pellets were analyzed for each polymer, which gave reproducible results.

3. Results and Discussion

3.1. Polymer Synthesis. Monomers **1a** and **1b** as well as copolymers with L-lactide were polymerized by ring-opening polymerization in the melt at 110 °C using BnOH as the initiator and $SnOct_2$ as the catalyst, with a monomer-to-catalyst-to-initiator ratio of 200/2/1 (Scheme 1). Poly(**1a**/**1b**) as well as their copolymers with lactide were deprotected by catalytic hydrogenation to yield the corresponding hydroxyl-functionalized polyesters.

NMR analysis showed that the copolymer compositions were close to the feed ratio (Table 1), which is expected since the polymers were obtained in high yields (>90%). Table 1 shows that, except for two polymers (homo(**1a**) and 50/50 copolymer of lactide and **1a**), the targeted molecular weights were obtained. It should, however, be mentioned that molecular weight determination of aliphatic polyesters using GPC with polystyrene standards gives an overestimation of the actual molecular weights by a factor of 1.5−2.[23,24] Probably, some chain initiation other than via benzyl alcohol had occurred as well. Quantitative removal (NMR analysis) of the protecting benzyl groups was performed by catalytic hydrogenation in THF using a Degussa type Pd/C catalyst. The deprotection, except for the copolymer of 25% lactide and 75% **1b**, was not associated with chain scission, as evidenced from GPC measurements (Table 1). Poly(**2b**) could not be obtained since, during the deprotection of poly(**1b**), severe catalyst aggregation was observed and no polymer could be isolated from the reaction mixture. Previously, we showed that complete deprotection of this polymer was achieved and poly(**2b**) was isolated from the reaction mixture.[22] However, the polymer in this earlier study had a lower molecular weight than the polymer of the present study. Likely, as deprotection progressed, the (partially) deprotected poly(**1b**) adsorbed irreversibly to the catalyst, causing the reaction to stop, as observed previously for benzylated poly(β-malic acid).[25] The use of acetone or ethyl acetate instead of THF was not successful as well. Therefore, poly(**2b**) was not included in the degradation study.

DSC analysis showed that the T_g of the deprotected polymers increased with increasing lactide content. The measured T_g's of the protected polymers were in good agreement with previously found results.[22]

3.2. Polymer Degradation. Pellets of the different polymers (50−70 mg) were incubated in a phosphate buffer (174 mM, pH 7.4) at 37 °C up to 60 days. Polymer degradation was monitored by weight loss measurements and by GPC, DSC, and ^{1}H NMR analysis. Figure 1 shows the weight loss of the different polymer samples in time. This figure shows that PLGA retained its mass for more than 20 days. At the next sample point (45 days), the material was completely dissolved (point not included in Figure 1). The copolymers of lactide with 25% and 50% of comonomer **2a** showed little to no mass decrease up to 9 and 4 days, respectively, after which the mass gradually dropped. The degradation times shortened with increasing **2a** content in the copolymers and were 70 and 29 days for the copolymers of lactide with 25% and 50% **2a**, respectively. After the indicated times, the polymers were completely degraded in the case of the 50% **2a** copolymer, and only some debris was left in the buffer solution in the case of the 25% **2a** copolymer. Figure 1d shows that the copolymers of lactide with 25% and 50% of comonomer **2b** also started losing weight after 9 and 4 days, respectively. However, after this time, the weight of the solid remains of these copolymers decreased much more rapidly than that of their **2a** counterparts, and they were both completely dissolved in 40 days. The copolymers of 75% **2a**/**2b** and 25% lactide (panels a and b of Figure 1, respectively) showed a rapid degradation, and the pellets were fully dissolved in 4 and 1 days, respectively. The pellets of homopolymer **2a** showed a substantial weight loss during the 4 h of incubation, and they were fully dissolved after 16 h. To distinguish between the degradation and physical dissolution of poly(**2a**), the following control experiment was done. The homopolymer of **2a** was dissolved in THF (10% w/v) and subsequently added dropwise to water. Since polymer precipitation was observed, it is concluded that homo(**2a**) is not water-soluble, and the observed mass loss of the homo(**2a**) is therefore due to degradation. Figure 2a shows that the molecular weight of the remaining solids of homo(**2a**) hardly changed during incubation in buffer. This means that its degradation can be classified as fast surface erosion. The copolymers of lactide with 25% and 50% of **2a** showed a decreasing molecular weight (Figure 2b) and a mass decrease that started after 9 and 4 days, respectively (Figure 1b). The copolymer with 25% **2a** and 75% lactide lost 50% of its starting weight during the next 40−50 days (Figure 1b), whereas, during this time, the M_n of the copolymer decreased to 25% of its original value (Figure 2b). The copolymer with 50% **2a** and 50% lactide showed faster degradation and lost 80% of its weight in around 20 days (Figure 1b), which was associated with a 50% decrease of the M_n (Figure 2b). This demonstrates that, in contrast to the degradation of homo(**2a**), which degrades via a surface erosion process, the copolymers of **2a** and lactide degrade by bulk erosion. Also, the copolymer with 75% **2a** and 25% lactide degraded via a bulk erosion process: this polymer showed a more or less constant weight during 40 h of incubation in buffer (Figure 1a), which was accompanied by a decrease in M_n in time (Figure 2a). In contrast, the copolymer of 25% lactide and 75% **2b** degrades via surface erosion (Figures 1c and 2c), and showed a faster degradation rate than the copolymer with 75% **2a** (6 and 40 h, respectively). The difference in degradation pathways and degradation kinetics between lactide copolymers with 75% **2a** (bulk erosion) and 75% **2b** (surface erosion) can be explained as follows: First, the copolymer with 75% **2b** is slightly more hydrophilic (due to the presence of glycolic acid residues in the copolymer chain) than the corresponding copolymer with **2a**. This higher hydrophilicity results in a higher water absorbing capacity of the polymer, which, in turn, will

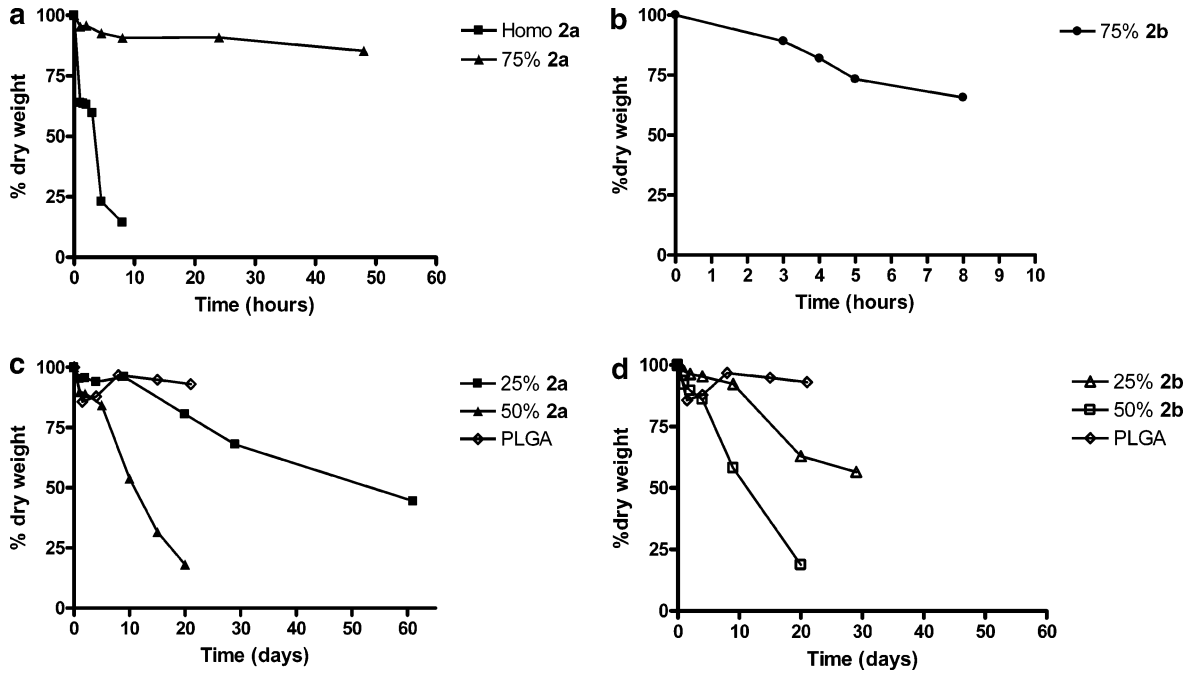

Figure 1. Relative weight decrease of the (co)polymer pellets (averages of two measurements at each time point).

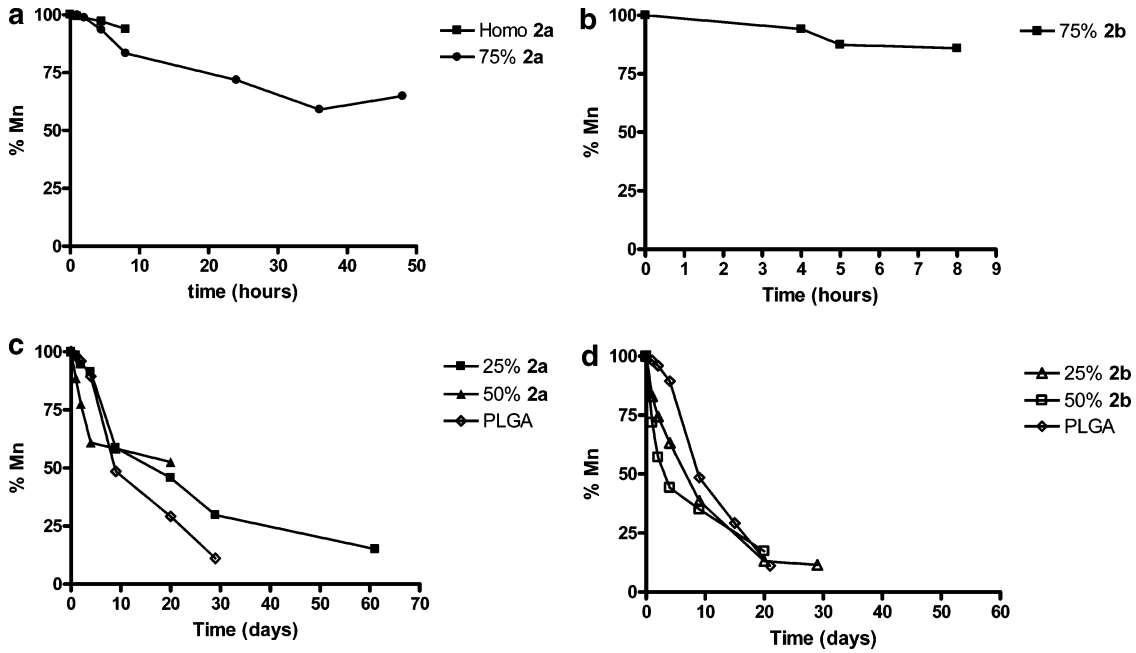

Figure 2. Relative decrease in number average molecular weight (M_n) as a function of time for the co(polymers).

increase the hydrolysis rate of the ester bonds. Second, it has been reported that the ester bond between glycolic acid and lactic acid (and probably also glyceric acid present in the copolymer with **2b**) is more susceptible to hydrolysis than the ester bond between two lactic acid molecules.[3,26] The lactide copolymers with 25% and 50% **2b** showed a decreasing molecular weight (Figure 2d), while the pellets started losing weight after 9 and 4 days (Figure 1d), respectively, indicative of bulk erosion. Again, the copolymers with **2b** degraded faster than their **2a** counterparts. Table 2 summarizes the degradation characteristics of the polymers investigated in this study.

The polymers investigated in this study degrade via hydrolysis of ester bonds. However, the polymers contain two (homo(**2a**) and the copolymers of **2a** and lactide) or three (copolymers of **2b** and lactide) different ester bonds in the polymer chain, which can have different susceptibilities toward hydrolysis. To investigate preferential ester hydrolysis, NMR spectroscopy was used along with thermographic analysis of the solid remains from a selection of samples. Figure 3 shows the change of the **2a**/**2b** contents of the different copolymers, as determined with ^{1}H NMR in time. Only the 25% and 50% **2a**/**2b** copolymers are

Table 2. Summary of the Degradation Characteristics of the Different Hydroxyl-Functionalized Polymers

polymer	degradation time	erosion pathway
homo(**2a**)	<1 day	surface
75% **2a**/25% lactide	~1 week	bulk
50% **2a**/50% lactide	~1 month	bulk
25% **2a**/75% lactide	~2 months	bulk
75% **2b**/25% lactide	<1 day	surface
50% **2b**/50% lactide	~1 month	bulk
25% **2b**/75% lactide	~1.5 month	bulk

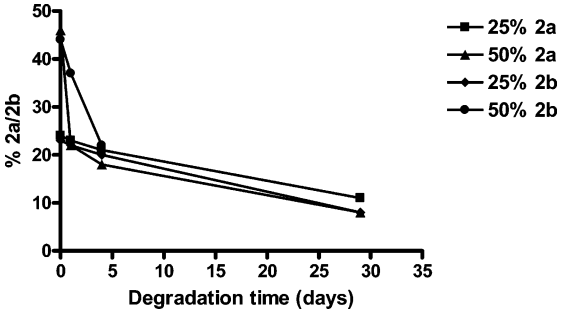

Figure 3. Copolymer compositions of some degradation samples in time determined with ^{1}H NMR.

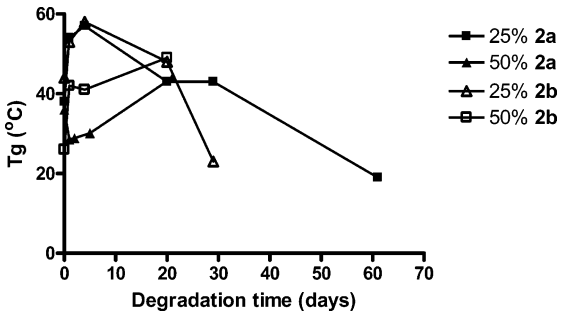

Figure 4. Glass transition temperatures of remaining insoluble polymer after degradation at pH 7.4 and 37 °C. The plotted data points are the means of two independent samples, which differ by <2 °C.

shown, as the 75% **2a**/**2b** copolymers did not give reliable results because of their fast degradation. A clear decrease is observed over time, which means that, during the degradation, the hydrophilic units are preferentially removed, meaning that the remaining insoluble pellets became enriched in lactide content in time. These results demonstrate that hydrolysis preferentially occurs in the hydroxyl-enriched sites in the polymer, likely because of an increased hydration at these sites.[19] Also, the hydroxyl group might stabilize the transition state, thereby accelerating the hydrolysis of the ester bonds.[20]

Figure 4 shows the changes in T_g of the degradation samples in time (values of the second heating cycle are given). Polymers with 75% lactide and 25% **2a**/**2b** initially showed a slight increase in T_g followed by a decrease in T_g in time. NMR analysis (Figure 3) showed the preferential removal of the hydrophilic residues, which caused the non-degraded polymers to become richer in lactide. Since the T_g of homopolymer **2a** is around 30 °C, enrichment of the degrading polymer in lactide will be, as indeed observed (Figure 4), associated with an increase in T_g (the T_g of PLLA is ∼65 °C). The observed decrease in T_g after 4 days is likely due to a reduction in molecular weight of the remaining insoluble material (Figure 2a−d). The polymer with 50% **2a** and 50% lactide showed an increase in T_g from 28 to 42 °C upon degradation at day 21. As pointed out above, preferential removal of the hydrophilic units from the polymer will result in an increase in T_g due to enrichment of the insoluble material in lactide content. No decrease in T_g after 21 days was observed since, at that time, the polymer was fully degraded (Figure 2b).

DSC analysis showed that the copolymer of 25% **2a** and 75% lactide was initially fully amorphous, in both the first and second heating cycles (Figure 5). Obviously, the lactide domains in this copolymer are of insufficient length to allow crystallization. Figure 6 shows that, upon degradation (after 20 days), a T_m (at 91 °C with a ΔH_m of 27.4 J/g) was observed in the remaining solid in the first heating cycle. These values for T_m and ΔH_m indicate a crystallinity of ∼25% (pure PLLA crystals have a ΔH_m^0 of 106 J/g)[27] along with a degree of polymerization for the lactide blocks of ca. 14 lactic acid units.[28] This again demonstrates that, in time, the solids become enriched in lactide content. It should be noticed that, in the second heating cycle, no T_m was detected (Figure 6). Obviously, the crystalline domains were not reformed during the cooling phase. Figure 6 also shows that the T_g of the second heating cycle was lower

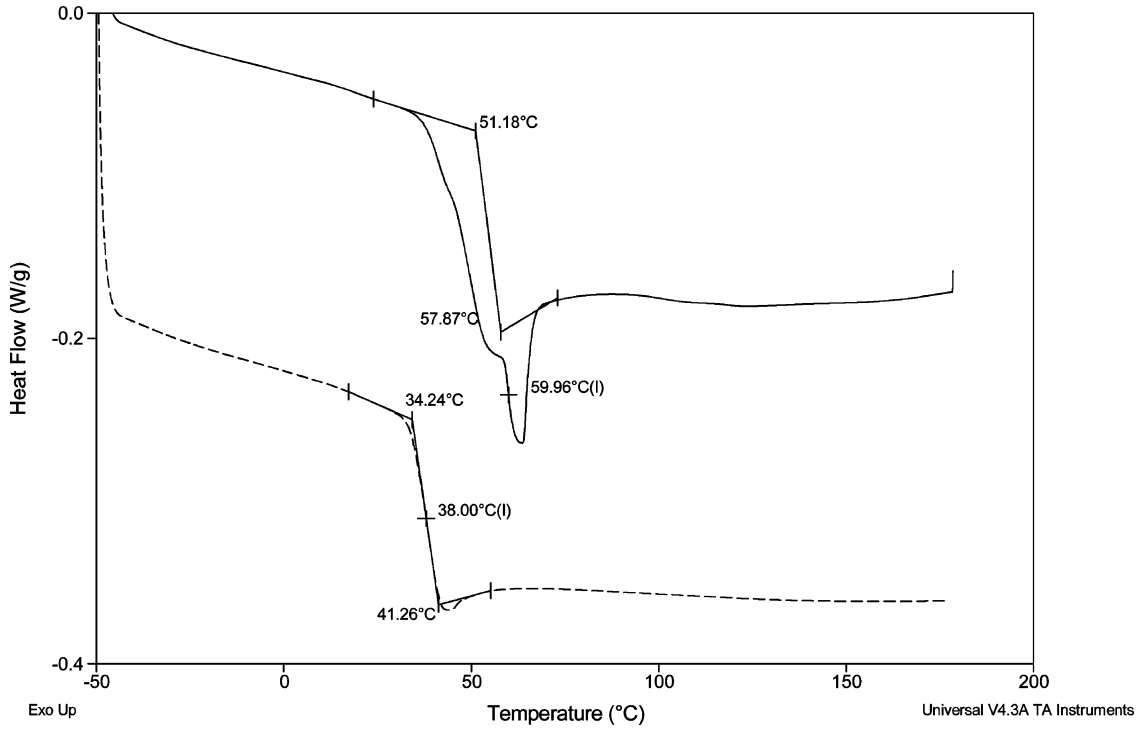

Figure 5. DSC thermograms of the copolymer with 25% **2a** and 75% PLLA in the first heating cycle, showing a very large relaxation (top), and the second heating cycle (bottom).

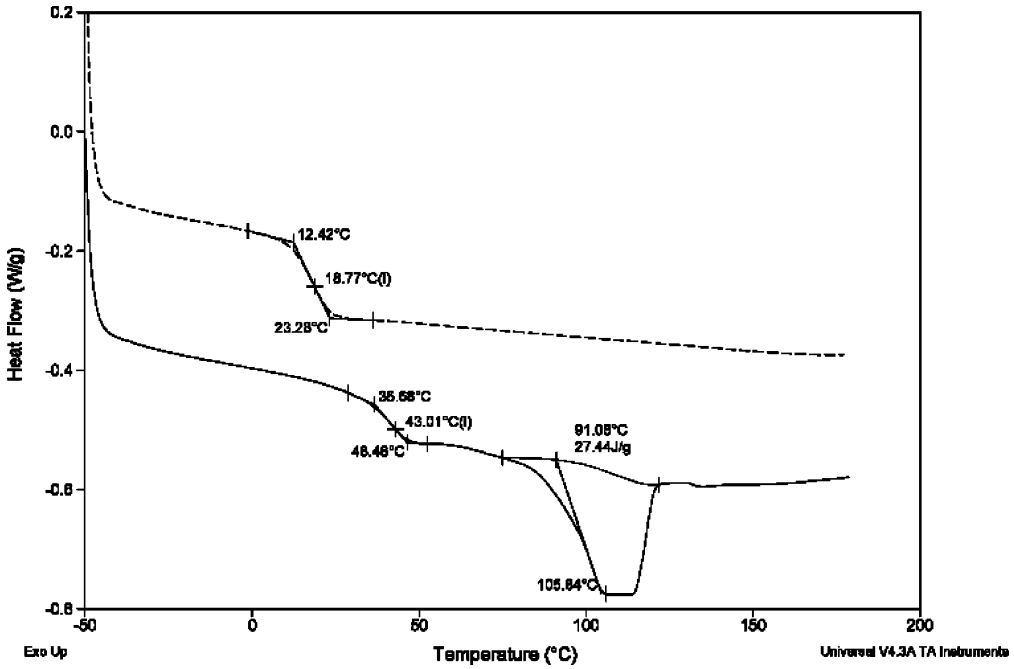

Figure 6. DSC thermogram overlay of a degradation sample (after 20 days) of 25% **2a** and 75% PLLA in the first heating cycle (bottom) and the second heating cycle (top).

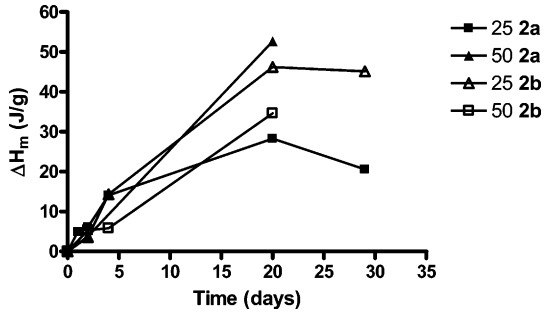

Figure 7. Melting enthalpies of the degrading copolymers in time.

than the T_g of the first heating cycle. The higher T_g observed during the first cycle might be ascribed to the presence of crystallites in the sample. It has been reported previously that the T_g was raised by the presence of crystallites. The inability to recrystallize during the cooling phase then results in a lower T_g (Figure 6).[29−31] In addition to the polymer with 25% **2a**, crystallinity also developed in time in the polymers with 25% **2b** and 50% **2a**/**2b** (Figure 7). After 20 days, the crystallinity started to decrease, because of degradation of the remaining PLLA domains. Upon degradation, the polymers of 75% **2a**/**2b** and 25% lactide did not show the formation of crystalline domains. Obviously, because of the high content of hydrophilic monomers, during degradation, the formed lactide segments are of insufficient length to crystallize.

The monomers that were used in this study consist of either lactic acid or glycolic acid, which are endogenous compounds, and (*S*)-3-(benzyloxy)-2-hydroxypropanoic acid. The latter compound is a derivative of serine. Glyceric acid is formed upon deprotection and hydrolysis, which can be metabolized via the glycolytic pathway.[32] It is therefore expected that the degradation products will not show toxicity, and therefore a good biocompatibility of these polymers is expected. However, to confirm these expectations, studies as described by Albertsson et al. need to be done.[33,34]

4. Conclusions

In this paper, we demonstrate that the degradation rate of poly(**2a**) (the synthesis of poly(**2b**) was not possible) and the copolymers of **2a**/**2b** with lactide can be tailored from a few hours to 2 months by the (co)polymer composition. Given the fact that the frequently studied polymers of the lactic acid/glycolic acid family have degradation times varying from 2 months to 2 years, these new polymers with tailorable degradation times up to 2 months are a very valuable addition to the PLGA type of systems.

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