Degradation Behavior of Hydrogels from Poly(vinyl Alcohol)-*graft*-[poly(*rac*-lactide)/ Poly(*rac*-lactide-*co*-glycolide)]: Influence of the Structure and Composition on the Material's Stability

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ABSTRACT: The swellability and mass loss of poly(vinyl alcohol)-*graft*-[poly(*rac*-lactide)/poly(*rac*-lactide-*co*-glycolide)] hydrogels upon hydrolysis are strongly affected by the composition of the hydrogels. Hydrophobic hydrogels remain at a relatively constant mass for a couple of weeks, and the mass decreases dramatically thereafter, whereas more hydrophilic hydrogels lose mass right from the beginning. All hydrogels display water uptake values between 90 and 280% within 8 weeks. For longer periods of degradation, the water uptake increases up to a maximum of about 900%. Studies of the thermal properties of samples upon degradation and their IR measurements have shown that the degradation rate is related to the physical and chemical structure of the hydrogels and hence to the hydrophobic/hydrophilic balance; that is, the degradation increases with the increasing hydrophilicity of the material. As a result, degradation can be engineered through the variation of the composition and structure of the material. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 112: 1538–1545, 2009

Key words: degradation; hydrogels; polyesters

INTRODUCTION

Aliphatic polyesters such as polylactide (PLA), polyglycolide (PGA), and polylactide–polyglycolide (PLGA) copolymers are the most widely investigated synthetic polymers to be applied as biomaterials because of their biocompatibility and degradation properties.[1,2] They are successfully used as bioerodible materials because naturally occurring metabolites are immanent as degradation products. Ester bonds in the homopolymers and copolymers are hydrolytically unstable, inducing random chain cleavage.[3] Carboxylic acid end groups that appear as a result of ester hydrolysis reactions further catalyze the hydrolysis reaction. The resulting lactic and glycolic acids enter the tricarboxylic acid cycle and are metabolized and subsequently eliminated from the body as carbon dioxide and water.[3,4] Upon copolymerization with trimethylene carbonate[5] or ε-caprolactone,[6–8] the degradation of amorphous D,L-PLA is slowed down or degradation is enhanced by the incorporation of the faster degrading glycolide (GA).[7,9,10]

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Generally, the degradation behavior of linear aliphatic polyesters depends on the molecular weight (MW), polydispersity, composition, and degree of crystallinity. Thus, PGA is highly crystalline, whereas PLA exists in two stereoisomeric forms (D-PLA and L-PLA) of a semicrystalline structure, and D,L-PLA is always amorphous.[1,2] The thermal properties, indicators of a material's susceptibility to degradation, show some interdependence with MW; low-MW polymers have lower glass-transition temperatures (T_g's) and degrade faster than polymers with higher MWs. Concerning crystallinity, L-PLA displays a higher T_g value than D,L-PLA, whereas PGA has a lower T_g value than both L-PLA and D,L-PLA.[1,2,11,12] The synthesis of block copolymers of the type A–B–A allows a modification of aliphatic polyester A with hydrophilic block B [e.g., poly(ethylene oxide)[13,14]], which leads to faster degradation of the material in comparison with the homopolyester. Linear PLA, PGA, and PLGA show a slower rate of degradation than branched polymers of the same composition and MW.[11,12] Moreover, grafted structures offer an additional way to modify the hydrophilic/hydrophobic balance.[11,12,15]

To accelerate the degradation of the matrix and to promote the water uptake, polyelectrolytes such as charged dextrans have been used as backbones.[12]

PLA or PLGA grafted onto poly(vinyl alcohol) (PVA) and polyols[11,15–18] have been synthesized to control the properties of copolymers used for drug delivery. It has been shown that, through the variation of the lactide (LA) to GA molar ratio in the copolymers and their ratio with the third comonomer in different copolymers, the degradation rate and other properties such as thermal and mechanical properties can be modulated. Short hydrophobic PLGA chains grafted onto a hydrophilic backbone lead to both faster water uptake and a higher rate of degradation of the copolymers, whereas long grafted L-PLA chains result in properties comparable to those of the linear polyester.[15]

The aim of this study was to investigate in the presence of a phosphate-buffered solution (PBS) the degradation of hydrogels that were prepared through the grafting of PVA with D,L-PLA or poly (D,L-lactide-*co*-glycolide).[19] The degradation of the hydrogels was followed by mass loss measurements and by IR and thermal analysis.

EXPERIMENTAL

Polymers

The synthesis of the polymers has been described previously in detail.[19] D,L-PLA and poly(D,L-lactide-*co*-glycolide) with various compositions and with one methacrylate end group and one carboxylate end group were synthesized and grafted onto PVA via the carboxylate group. The graft copolymers were crosslinked via the methacrylate groups with a free-radical initiator.

Hydrolytic degradation experiment

For degradation experiments, samples were prepared by the punch cutting of circular disks 15 mm in diameter and approximately 0.3 mm thick. All dimensions were measured in the swollen state. The discs were placed in 20-mL glass vials, and the vials were filled with 10 mL of pH 7.4 PBS. The degradation was followed at room temperature for various periods of time. To prevent the growth of microorganisms, sodium azide was added (40 mg/kg). The pH value was measured after 4–7 days, and when the value was below 7.2, the buffer solution was exchanged. During the degradation, at a given point of time, samples were taken (three discs at each point), and the mass loss of the samples was determined. The mass loss (%) was calculated according to eq. (1):

$$\text{Mass loss}(\%) = 100(m_0 - m_d)/m_0 \qquad (1)$$

where m_0 is the initial mass of the dry specimen and m_d is the mass of the dry sample after a given period of degradation. The water uptake (%) as an indicator of the accessibility of the hydrogels to degradation was determined according to eq. (2):

$$\text{Water uptake}(\%) = 100(m_s - m_d)/m_d \qquad (2)$$

where m_s is the mass of the swollen sample at a given time of degradation, corresponding to m_d.

Analytical methods

Differential scanning calorimetry (DSC) measurements were carried out with a DSC 204 calorimeter (Netzch, Selb, Germany). The range of investigation was 20–150°C with a heating and cooling rate of 10°C/min. A nitrogen flow of 20 mL/min was used for rinsing the cells. The sample chamber was cooled with liquid nitrogen. The thermal effects were evaluated from the second heating run.

Thermogravimetric analysis (TGA) measurements were performed with a Netzsch TG 209 instrument in a nitrogen atmosphere. Thermograms were taken in the range of 30–600°C. The mass loss of the samples as a function of temperature was followed at a heating rate of 10°C/min.

IR spectra were recorded with a Nexus Fourier transform infrared spectrometer with the photoacoustic method. For each sample, scans were recorded between 4000 and 400 cm^{-1} with a resolution of 8 cm^{-1}.

RESULTS AND DISCUSSION

The various poly(vinyl alcohol)-*g*-poly(aliphatic ester) hydrogels investigated are named PVA–PLAx or PVA–PLGAx_y, where x is the total number of ester units in the grafts and y is the molar percentage of the GA content (Table I).

The degradation was followed by the measurement of the mass loss and the water uptake over a period of 8–21 weeks. IR, TGA, and DSC analyses were also performed on the samples in the dry state at given points of the degradation.

Mass loss

Figure 1 shows the dependence of the mass loss on the degradation time of samples A, B, D, and E (Table I). The degradation-induced mass loss displays a noticeable difference depending on the structure and composition of the hydrogels. Degradation proceeds at a lower rate in hydrogels A and B with pure PLA grafts. There seems to be a kind of induction period in sample A: up to 60 days of degradation, the mass loss does not increase significantly. Sample B, with shorter PLA grafts than those in hydrogel A, shows

TABLE I
Theoretical and Experimental Compositions and Degree of Substitution (DS) of Poly(vinyl alcohol)-*graft*-[Poly(D,L-lactide)/Poly(D,L-lactide-*co*-glycolide)] Hydrogels[19]

		N[a]		LA : GA		DS (%)		
Symbol	Polymer	Theoretical	Experimental	Theoretical	Experimental	Theoretical	Experimental	T_g (°C)
A	PVA–PLA16	16	16	100 : 0	100 : 0	15		59
B	PVA–PLA8	8	8	100 : 0	100 : 0	15	7.6	65
C	PVA–PLA4	4	4	100 : 0	100 : 0	15	7.3	69
D	PVA–PLGA18$_{50}$	16	18	50 : 50	50 : 50	15	11	51
E	PVA–PLGA9$_{50}$	8	9	50 : 50	50 : 50	15	14	57
F	PVA–PLGA4$_{50}$	4	4	50 : 50	50 : 50	15	8	68
G	PVA–PLGA8$_{25}$	8	8	75 : 25	75 : 25	15		

[a] Number of repeating ester units.

a more rapid mass loss because of its higher hydrophilicity. Networks D and E display faster mass loss than networks A and B, and this indicates that, because of higher hydrophilicity, water diffusion into the polymer network proceeds more readily. Besides, sample D with longer polyester grafts than those in sample E degrades more slowly, particularly initially, than sample E. When hydrogels A and D, which have similar graft lengths but different compositions, are examined more closely, they both show a small mass loss initially, but as degradation proceeds, the rate of mass loss of sample D increases faster than that of sample A; these hydrogels show a mass loss of 10% after 35 and 110 days, respectively. The results suggest that the influence of the hydrophobicity is stronger than that of the number of ester groups for degradation upon hydrolysis.

In Figure 2, hydrogels B, E, and G are presented; they have about the same number of repeating ester units but different compositions. Samples B and G show similar mass losses up to 60 days, but sample G shows much faster mass loss beyond that time. Hydrogel E, with the highest portion of GA, shows the most rapid mass loss from the onset because of its high hydrophilicity, despite its slightly longer polyester grafts. Thus, network B shows 10% mass loss after 70 days, and network G shows it after 60 days, whereas network E requires only 10 days for a mass loss of 10%. This is in agreement with the finding that PLGA films with an LA/GA molar ratio of 50 : 50 degrade faster than films of similar MWs but with an LA/GA molar ratio of 75 : 25.[20] The diffusion of eroded products from the network is a function of the crosslinking density, which changes with degradation. In crosslinked systems with long grafts and dense network structures, the mass loss profile has an induction period because of the higher hydrophobicity and less accessible ester bonds, whereas in more hydrophilic systems, mass loss proceeds in a straightforward fashion. The literature[20–22] clearly shows the dependence between the rate of mass loss (erosion) and the cleavage of ester bonds in polyester networks.

Water absorption

Figure 3 illustrates the water uptake of hydrogels A, B, D, and E in the course of degradation. The water

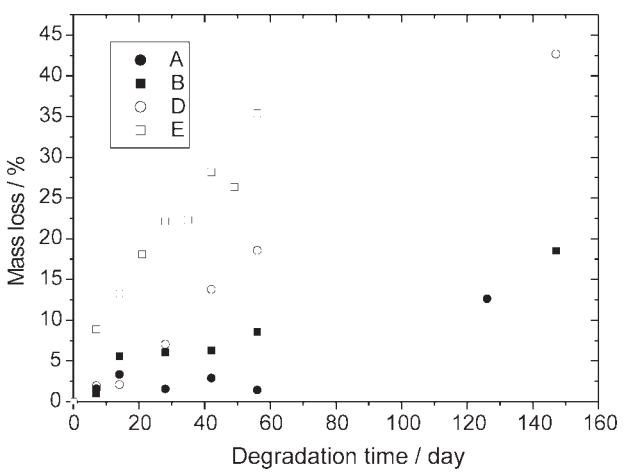

Figure 1 Mass loss of networks A, B, D, and E in the hydrolytic degradation experiments at pH 7.4 and room temperature.

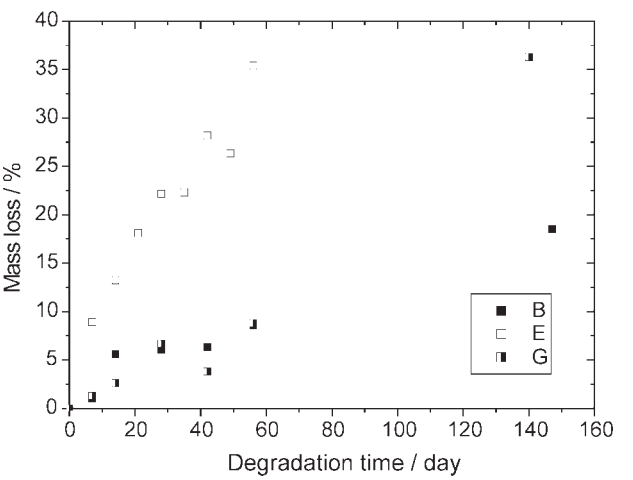

Figure 2 Mass loss of networks B, E, and G in the hydrolytic degradation experiments at pH 7.4 and room temperature.

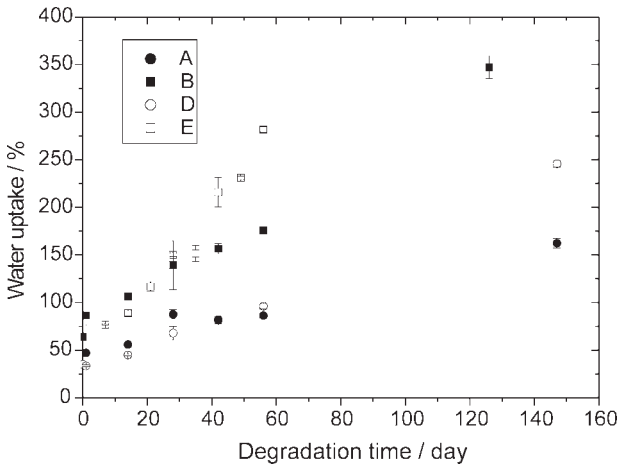

Figure 3 Water uptake of hydrogels A, B, D, and E during hydrolytic degradation at pH 7.4 and room temperature.

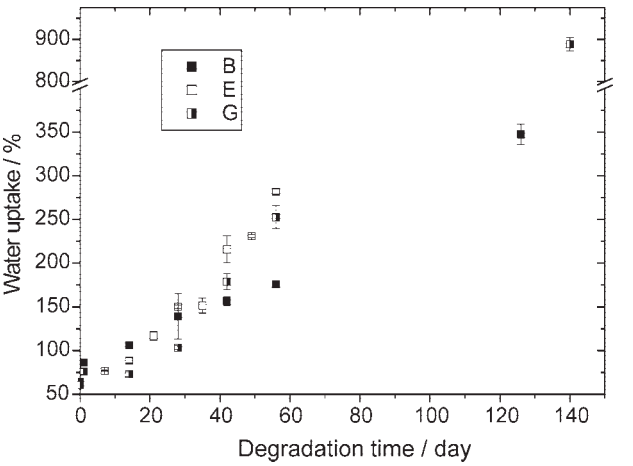

Figure 4 Water uptake of hydrogels B, E, and G during hydrolytic degradation at pH 7.4 and room temperature.

uptake continues to increase strongly during the whole time of degradation, and this indicates the loosening of the network structure. Hydrogels A and D, with a higher polyester content, show lower water uptake and a lower rate of water uptake upon degradation, whereas hydrogels B and E, with a lower polyester content, show higher water uptake and a higher rate.

This proves the strong influence of the polyester content on the swelling behavior of the hydrogel. Even though the hydrogel with longer polyester grafts has more ester bonds capable of hydrolysis, it is their hydrophobicity that slows down the process of swelling. Further comparing hydrogel A with hydrogel D and hydrogel B with hydrogel E, we find that besides the influence of the composition, there is an influence of the length of the polyester grafts. Thus, hydrogel A, with pure LA polyester grafts, and hydrogel D, with 50 mol % LA in the grafts, do not show a significant difference in swelling up to 50 days. It seems that the higher hydrophilicity of hydrogel D, due to the presence of GA units, initially is compensated by the longer polyester grafts. Hydrogels B and E, with shorter polyester chains, show a significant influence of the composition on the water uptake. The water uptake of hydrogels B, G, and E during degradation has been examined more closely (Fig. 4). Initially, all samples show similar swelling; after about 35 days of degradation, the influence of the GA present in samples E and G results in a significantly higher water uptake than that of sample B.

IR analysis

An attempt was made to follow the status of the degraded materials by IR analysis. The characteristic peaks around 3380 (OH), 2940 (C—H), and 1750 cm^{-1} (C=O), as well as the fingerprint region, were regarded (Table II). The IR spectrum of network C,

TABLE II
Characteristic Bands Around 3380, 2940, and 1750 cm^{-1}, Band Areas, and Their Ratios for Hydrogels A–F After Hydrolytic Degradation

		Characteristic signal						Area ratio	
Sample	Week	O—H stretching (cm^{-1})	A_{O-H}	C—H stretching (cm^{-1})	A_{C-H}	C=O stretching (cm^{-1})	$A_{C=O}$	A_{O-H}/A_{C-H}	$A_{O-H}/A_{C=O}$
A	4	3413	1813	2939	577	1755	1176	3.142	1.539
	8	3375	3308	2943	983	1755	2193	3.351	1.508
B	4	3379	3946	2939	1047	1743	2061	3.769	1.915
	8	3359	4319	2939	1150	1739	2293	3.756	1.883
C	4	3379	3823	2939	810	1739	1476	4.720	2.590
	8	3375	6362	2939	1284	1736	2190	4.955	2.905
D	4	3383	2729	2943	1049	1756	2554	2.600	1.069
	8	3370	2096	2940	755	1760	2108	2.776	0.994
E	4	3370	4613	2939	1186	1740	2571	3.889	1.794
F	4	3360	3092	2940	752	1736	1664	4.110	1.858

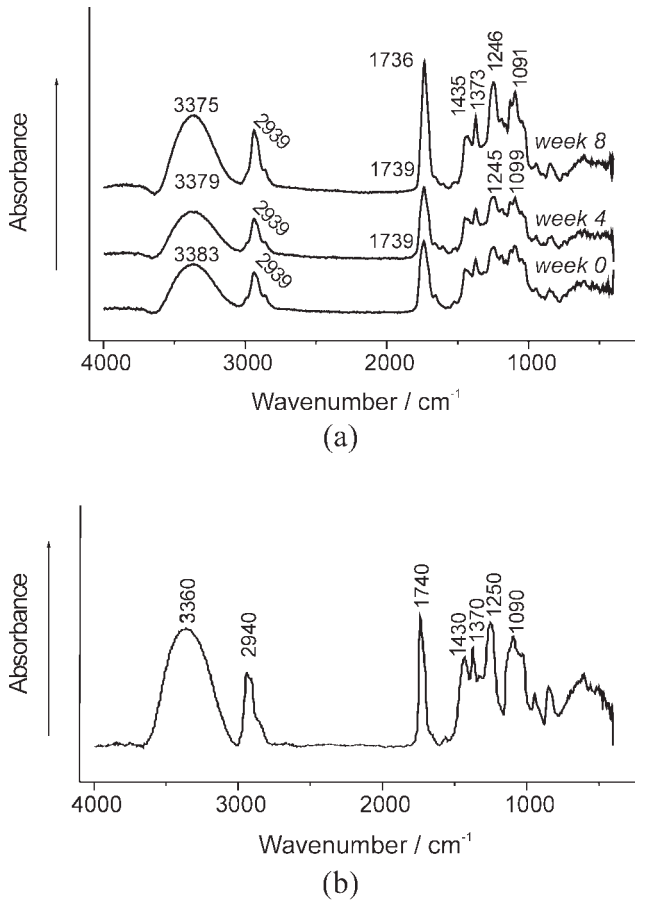

Figure 5 IR spectra of (a) sample C before and after 4 and 8 weeks of degradation and (b) PVA.

before and after hydrolytic degradation for 4 and 8 weeks in PBS at room temperature, is presented in Figure 5(a). The IR spectrum of PVA is shown in Figure 5(b). Figure 6 presents IR spectra of samples A, B, D, E, and F after 4 and 8 weeks of degradation.

The wave number of the OH band in the hydrogels is between that of PVA (3360 cm^{-1}) and that of polyester copolymers (3465–3500 cm^{-1})[23–27] and is slightly downward shifted during degradation. On the other hand, the band around 2940 cm^{-1} remains constant over the course of degradation. The increasing polyester content in the hydrogels moves the C=O band toward higher wave numbers. Besides, the OH/C—H and OH/C=O ratios of the band areas decrease with an increasing portion of the polyester in hydrogels A–F.[19] As the degradation proceeds, the C=O band moves toward lower wave numbers pronouncedly in hydrogels with short polyester chains, and this confirms their faster degradation due to the lower hydrophobicity. This indicates a reduction of ester bonds in the hydrogel. At the same time, hydrogels with long polyester chains show an insignificant shift of the C=O band (Table II; cf. ref. 19). However, the general observation is that hydrolysis of the ester bonds leads to an increase in the intensity of the absorption band of the OH groups over that of the C=O groups.

On the basis of IR spectroscopy of the samples before and after hydrolytic degradation, certain conclusions can be drawn from the fingerprint region despite the poorly separated bands. In sample C, already after 4 weeks of degradation, the band at 1245 cm^{-1} is stronger than that at 1099 cm^{-1}, and this is the opposite of their ratio before degradation [Fig. 5(a)]. After 8 weeks of degradation, the difference becomes even larger, and the spectrum resembles that of PVA [Fig. 5(b)]. At the same time, the band at 1190 cm^{-1}, characteristic of the polyester, gradually disappears. The spectra of networks A and B (Fig. 6) have similar shapes. After 8 weeks of degradation, there is a decrease of the band at 1190 cm^{-1} in comparison with the bands at 1250 and 1080–1090 cm^{-1}, and this proves the loss of ester units. The increase of the band at 1250 cm^{-1} with respect to the band at 1080 or 1090 cm^{-1} during degradation occurs faster in hydrogel B than in hydrogel A, whereas the ratio becomes more similar to that in PVA, and this shows its faster degradation as a result of the shorter polyester grafts and lower hydrophobicity. Sample F displays similar behavior already after 4 weeks of degradation (Fig. 6). This demonstrates a rapid degradation of the samples with high hydrophilicity due to the short polyester chains with four repeating ester groups and 50 mol % GA units. Sample E, in the fingerprint region, has bands of equal intensity at 1180, 1100, and 1250 cm^{-1} [the band strongly expressed in the PVA spectrum results from the presence of acetate groups; Fig. 5(b)]. The ratio of these three bands confirms the lower portion of the polyester in comparison

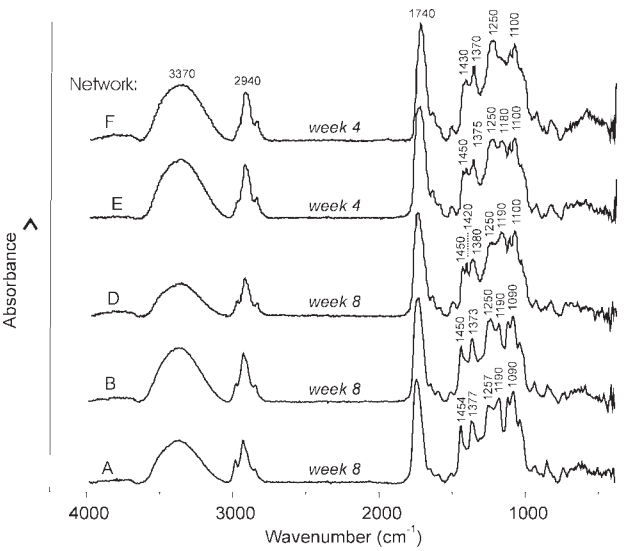

Figure 6 IR spectra of samples A, B, D, E, and F after 4 or 8 weeks of degradation.

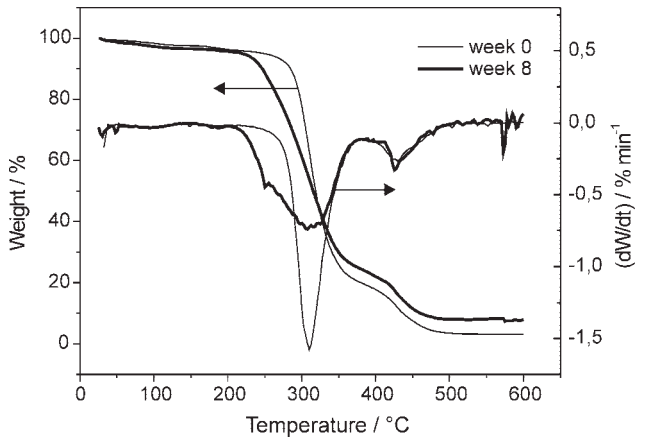

Figure 7 TGA and DTGA plots of network A before and after hydrolytic degradation measured at a heating rate of 10°C/min. dw/dt, change of weight of the sample with time in % min.

with hydrogel D, which contains 18 repeating ester units per graft and has a much weaker band at 1250 cm^{-1} than samples E and F (Fig. 6). Furthermore, in sample D, the band at 1190 cm^{-1}, assigned to the polyester content, has decreased with respect to the band at 1250 cm^{-1} in comparison with the position before degradation,[19] and this confirms the slow degradation of the polyester. Both samples D and E have a split band around 1450 cm^{-1} as a result of the GA content in the copolyester chain.[24,28] Generally, with a decreasing polyester portion in the hydrogels (A–C and D–F), there is an increase in the OH/C—H and OH/C=O area ratios (cf. Table II). For each sample after degradation, there is an increase in the OH/C—H ratio, which indicates an increase in the number of OH groups resulting from the hydrolysis of the polyester chains.

Thermal properties of the degraded networks

The thermal properties of PVA-*g*-PL/GA hydrogels were analyzed by means of TGA/differential thermogravimetric analysis (DTGA) and DSC during their hydrolytic degradation to observe the influence of degradation (destruction of the crosslinked structure) as well as the mass loss. The samples were freeze-dried before the measurements. There was no significant change, however, in the appearance of TGA and DTGA curves of the networks before and after degradation, except for the degradation onset, as shown in Figure 7 for hydrogel A. After an initial small weight loss caused by water evaporation, there is a two-stage decomposition process. In Table III, thermal analysis data for networks A (Fig. 7), B, C, and E are given. The structure and composition of the networks (A, B, and C) have some influence on the onset of the thermal decomposition process before and after hydrolytic degradation. The onset is shifted to lower temperatures in networks with long polyester chains. When we compare the temperature values at a 10% weight loss before and after the degradation of networks A, B, C, and E (Table III), a shift toward lower values becomes evident: 38°C for network A, 27°C for network B, and 21°C for network C after degradation for 8 weeks. Network E displays a maximum shift of 45°C after a period of 8 weeks because of the presence of GA units, which cause the acceleration of the degradation. Other characteristic values [e.g., the temperature at the maximum rate of weight loss (T_{max})] do not change considerably, except for those of network C with the shortest grafts, which make it the least stable, and those of network E because of the previously mentioned GA units.

DSC measurements were performed from 20 to 150°C. The second run was taken because the thermal history was erased by the first run. All samples show a single T_g. There is no sign of crystallization or melting at all, and this indicates the absence of the formation of a crystalline phase during hydrolytic degradation. This is the advantage of these materials in applications as degradable implant materials because crystalline particles may cause the formation of fibrous capsules *in vivo*.[29,30] In Table IV, the values of T_g and the heat capacity change (ΔC_p) of the networks over the course of hydrolytic

TABLE III
Thermal Characterization of Networks A–C and E After Hydrolytic Degradation

	A		B		C		E	
	Week 0	Week 8	Week 0	Week 8	Week 0	Week 8	Week 0	Week 8
$T_{10\%}$ (°C)	285	247	281	254	266	245	266	221
T_{max1} (°C)	310	309	312	315	318	305	312	322
ΔW_1 (%)	76	72	64	63	62	62	68	61
T_{max2} (°C)	429	427	429	427	436	444	433	426
ΔW_2 (%)	16	15	23	25	27	21	21	27
$Y_{600°C}$ (%)	4	8	7	7	5	11	8	3

Data were obtained by TGA at a heating rate of 10°C/min. $T_{10\%}$ = temperature at 10% weight loss; ΔW_1, ΔW_2 = weight losses at T_{max1} and T_{max2}, respectively; $Y_{600°C}$ = residue at 600°C.

TABLE IV
Changes in T_g and ΔC_p During the Degradation of the Hydrogels

	Sample											
	A		B		C		D		E		F	
Week	T_g (°C)	ΔC_p (J g^{-1} K^{-1})	T_g (°C)	ΔC_p (J g^{-1} K^{-1})	T_g (°C)	ΔC_p (J g^{-1} K^{-1})	T_g (°C)	ΔC_p (J g^{-1} K^{-1})	T_g (°C)	ΔC_p (J g^{-1} K^{-1})	T_g (°C)	ΔC_p (J g^{-1} K^{-1})
0	59	0.551	65	0.596	69	0.581	51	0.549	57	0.612	68	0.618
4	60	0.597	65	0.628	72	0.628	52	0.614	64	0.660	73	0.585
8	61	0.540	68	0.657			53	0.641	66	0.698		

degradation are given. All the networks display similar values of ΔC_p, and this means that there is no significant difference in the short-range order of the amorphous samples. The increase in T_g is small. It amounts to 2–3°C in networks A, B, and C. Like network A, network D with 18 repeating ester units in the grafts shows an increase of 2°C, whereas network E, with 9 ester repeating units, shows a T_g increase of 9°C after 8 weeks of degradation.

The T_g values of the samples containing GA units in the grafts are lower than those of the samples containing pure LA and stay lower during the whole degradation period, but they exhibit a greater increase in T_g during degradation. The GA content results in a lower T_g value and faster degradation as a result of its higher hydrophilicity.

The increase in the T_g values upon degradation might be due to the loss of ester units and, correspondingly, to the increase in the PVA fraction of the molecules.

CONCLUSIONS

Networks based on poly(vinyl alcohol)-*g*-[poly(*rac*-lactide)/poly(*rac*-lactide-*co*-glycolide)] combine the advantages of both PVA and polyesters, that is, hydrophilicity and degradability, respectively. Studies of amorphous PVA-*g*-PL/GA networks have shown that the mass loss and water uptake depend on the structure and composition of the hydrogels with a broad variety of features. The degradation of the graft copolymers with pure LA grafts representing a relatively high degree of hydrophobicity is retarded; the longer the grafts are, the more this occurs. In contrast, the graft copolymers with LA/GA grafts representing a higher degree of hydrophilicity show a faster mass loss upon hydrolysis; the shorter the grafts are, the faster this is. Moreover, the composition of the grafts, that is, their hydrophilicity/hydrophobicity, has a stronger influence on the hydrolytic degradation behavior than the length of the grafts.

IR analysis confirms the different resistivities against degradation depending on the structure and composition or hydrophobicity of the hydrogels. The thermal properties show the dependence of the rate of weight loss on the networks' characteristics as well. Moreover, the T_g shift is caused by the structure and composition of the network. All this indicates a higher stability of hydrogels with a higher polyester portion and, furthermore, a higher stability of hydrogels with pure PLA grafts versus hydrogels containing PGA in the grafts, which increases the hydrophilicity of the material and accelerates the rate of degradation.

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