In Vitro Degradation Characteristics of Poly(anhydride–imides) Containing Trimellitylimidoglycine

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ABSTRACT: The *in vitro* degradation characteristics of poly(anhydride–imides) containing trimellitylimidoglycine, with either 1,6-bis(carboxyphenoxy)hexane or sebacic acid, were assessed. The copolymers contained 10, 30, or 50 mol % of the imide monomer, trimellitylimidoglycine. Degradation was pH-sensitive, being enhanced under basic conditions. Control of degradation times from 1 day to 2 months was achieved by the selection of appropriate monomer units in the polymer backbone. Monomers were chosen based on their solubility in aqueous media, as well as how they influenced the hydrophobicity of the polymer matrices. Increasing the amount of imide monomer, trimellitylimidoglycine, and the use of sebacic acid rather than 1,6-bis(carboxyphenoxy)-hexane as the comonomer increased the degradation rate of the polymer matrices. © 1997 John Wiley & Sons, Inc. J Appl Polym Sci **63:** 1401–1411, 1997

Key words: biodegradable; poly(anhydride–imides); polyanhydrides; *in vitro* degradation

INTRODUCTION

Metallic orthopedic devices are commonly used as they offer the advantages of strength and corrosion resistance. However, the high modulus of elasticity can result in bone atrophy due to stress shielding,[1] which is caused by the stiffness mismatch between the metal implant and the surrounding bone. Therefore, the use of orthopedic implants composed of biodegradable materials with mechanical properties similar to bone are considered to be a good alternative to metallic orthopedic devices. The main advantage to degradable orthopedic implants is that the mechanical properties of the implant are gradually transferred to the bone, preventing stress-shielding, as the degradation occurs. The required degradation characteristics may best be achieved by polymers that undergo a heterogeneous degradation in which degradation on the surface of the polymer matrix is faster than water penetration into the bulk.

Polyanhydrides are biocompatible,[2] have well-defined degradation characteristics,[3] and have been successfully utilized clinically as drug-delivery systems.[4] These polymers have hydrophobic backbones with hydrolytically labile anhydride linkages such that hydrolytic degradation can be controlled by manipulation of the polymer composition. However, polyanhydrides have limited mechanical properties that restrict their usefulness in load-bearing applications. For example, poly[1,6-bis(carboxyphenoxy)hexane] has a

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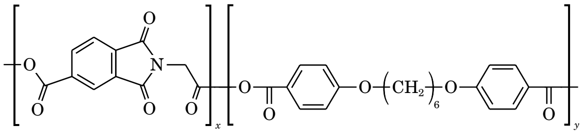
Young's modulus of 1.3 MPa,[3] which is well below the modulus of human bone (40–60 MPa).[5]

We have developed several biocompatible, high-strength polymers[6] that do not generate toxic by-products[7] upon degradation. These polymers are poly(anhydride–imides), combining the desirable properties from both polyanhydrides and polyimides. Polyimides are high-performance polymers with high strength and temperature stabilities.[8] The combination of polyimides with the readily biodegradable polyanhydrides yielded copolymers with higher mechanical strengths[5] than those of the anhydride homopolymers.

We are evaluating several poly(anhydride–imides) as potential orthopedic implant materials. In this study, the degradation profiles of copolymers of trimellitylimidoglycine (TMA-gly) with either 1,6-bis(carboxyphenoxy)hexane (CPH) (**1**) or sebacic acid (SA) (**2**) were examined:



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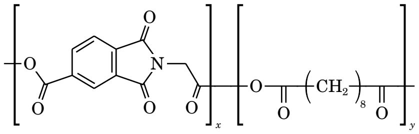

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The copolymers were composed of the imide monomer, TMA-gly, in 10, 30, and 50 mol % ratios. An understanding of polymer degradation is essential for proper utilization as orthopedic devices. For this study, degradation was defined as the appearance of monomers in the buffered media. Degradation of the polymer depends on several factors: the types of chemical bonds between polymer mer units,[9] mobility of water within the polymer,[10] polymer crystallinity,[11] and pH of the polymer solution.[3] The pH of the solution can catalyze the hydrolysis of some chemical bonds, as well as affect the dissolution rates of the degradation products.

In this study, the effect of media pH on the degradation of various polymer compositions was investigated to assess the mechanism of polymer degradation. To examine the role of hydrophobicity, the degradation characteristics of poly(anhydride–imides) containing either CPH, a hydrophobic monomer, or SA, a less hydrophobic monomer, were examined. The degraded polymer matrices were characterized by gel permeation chromatography, differential scanning calorimetry, and infrared and proton magnetic resonance spectroscopy.

EXPERIMENTAL

Materials

Monobasic and dibasic potassium sulfate were used as received from Fisher. Sebacic acid was used as received from Aldrich. Trimellitic anhydride (Aldrich) was hydrolyzed at room temperature for 12 h and evaporated to dryness to give trimellitic acid. Trimellitylimidoglycine, 1,6-bis-(carboxyphenoxy)hexane, and the poly(anhydride–imides) were synthesized as described elsewhere.[6] The poly(anhydride–imides) are denoted as, e.g., TMA-gly : SA (10 : 90), which indicates that TMA-gly composed 10 mol % of the polymer.

Instrumentation

Infrared spectroscopy was obtained on a Nicolet Magna 550 FTIR spectrometer and Nicolet data station with OMNIC 1.20 software. Samples were either film-cast in chloroform onto NaCl plates or pressed into KBr pellets. The molecular weights were determined on a Perkin-Elmer system consisting of the isocratic LC pump 250, oven 101, and LC-30 RI detector at 254 nm. Turbochom3 software was used on a DECpc 433 data station. Samples dissolved in chloroform were eluted through two columns in series (Polymer Laboratories, PL-Gel, linear and 100 Å). Molecular weights of the polymers were determined relative to narrow molecular weight polystyrene standards (Polysciences). Thermal analyses were determined on a Perkin-Elmer system consisting of TGA7 and DSC7 analyzers, with TAC7/7 instrument controllers. UNIX software was used on a DECpc 433 data station. For DSC, an average sample weight of 5–10 mg was heated at either 10 or 20°C/min under a flow of N_2 (30 psi). For TGA, an average sample weight of 10 mg was heated at 20°C/min under a flow of N_2 (8 psi). ^{1}H-NMR spectra were obtained on a Nicolet 360 MHz spectrometer on solutions in DMF-d_6, with the solvent used as the internal reference.

Methods

For determination of monomer solubility, an excess of each monomer was suspended in 10 mL of

0.1*M* phosphate buffer at pH 5, 7.4, or 10. The solutions were stored at 37°C for 60 min, then at room temperature for at least 48 h. Heating over longer periods of times hydrolyzed the imide bonds of TMA-gly. Prior to analysis, the samples were filtered though 0.25 μm pore-size filters. The solutions were assayed with a Shimadzu UV-1201 UV-vis spectrophotometer at 210 nm for sebacic acid and 253 nm for the other monomers. A calibration curve was generated for each monomer.

For the degradation studies, samples were compressed in dies (Fred S. Carver, Inc., Wabash, IN) using a Carver press (Fred S. Carver, Inc.). The samples were compressed into polymer discs (average weight of 0.200 ± 0.009 g) for 10 min with a 10,000 lb load at room temperature. On average, discs were 14 mm in diameter and 1 ± 0.05 mm thick. The degradation studies were carried out in triplicate at each pH. Discs had a glossy appearance with homogeneous coloration. The polymer discs were placed in 10 mL of 0.1*M* phosphate buffer solution at either pH 5, 7.4, or 10 and incubated at 37°C for the duration of the experiment. At regular time intervals, the buffer solution was decanted and assayed with a Shimadzu UV-1201 UV-vis spectrophotometer. The data had a maximum standard deviation of 5% from the average value for the assayed samples. After decanting the buffer solution, the polymer discs were placed in fresh buffer solution and maintained at 37°C. The experiment was continued until severe cracking or disintegration of the polymer was observed. Degradation curves for the polymer matrices were normalized by the cumulative experimental change in absorption of the buffer solution at 253 nm. A plot of these data showed the percent of aromatic monomers released with time, which was related to the rate of polymer degradation. Based on our monomer solubility studies, the monomer concentration is less than 1000-fold below their maximum solubility in the media.

At the end of the degradation experiment, the polymer remains were frozen and lyophilized. Standard deviation for weights of the polymer samples was 0.04 g. For infrared analyses, the peak intensities of the anhydride carbonyl stretches (near 1800 cm^{-1}) were calculated relative to the C—H bends (820 cm^{-1}) characteristic of aromatic rings.

RESULTS AND DISCUSSION

The polymers examined were based on the imide, TMA-gly, with either CPH or SA as the comonomer. The use of several monomer units enabled us to tailor the polymer properties by changing the monomer ratios. For example, increasing the hydrophobicity of a polymer may have reduced the entrance of water into the core, protecting the water-labile chemical bonds from further hydrolysis.[12] One of our goals was to determine how the incorporation of TMA-gly in varying degrees affected the degradation properties of the polymers. In addition, we determined how the pH of the degradation media affected polymer degradation.

Table I Monomer Solubilities (mol/L)

TMA	8.8×10^{-2}	3.4×10^{-1}	1.3×10^{-1}
TMA-gly	3.3×10^{-3}	6.5×10^{-2}	6.4×10^{-2}
SA	1.7×10^{-3}	1.6×10^{-2}	2.3×10^{-2}

Monomer Solubilities

Previous studies have shown that poly(anhydride–imides) degraded upon exposure to aqueous media.[13] Analysis of the buffer solution by ^{1}H-NMR spectroscopy indicated that only monomer units are solubilized in aqueous media and not the polymers or their oligomers.[14] As only monomers were present in the buffered solution, spectrophotometric analysis was a viable method of analysis for degradation studies. The solubilities of trimellitic acid (TMA), TMA-gly, CPH, and SA were determined to ensure that the monomer concentrations in the degradation media were sufficiently low, such that the presence of monomer in the media did not affect degradation rates.

The maximum absorbances for both TMA-gly and CPH monomers occurred at approximately 253 nm with molar extinction coefficients of 5740 and 89,500, respectively. TMA-gly had an additional peak at 304 nm. SA had a low-intensity absorbance at 253 nm with an extinction coefficient of 0.26. Therefore, the degradation solutions were analyzed at 253 nm for the presence of the aromatic monomers in the degradation products to determine the total monomer content in the buffer solutions.

All the compounds were most soluble in basic media (Table I), as expected for carboxylic acids. TMA-gly was slightly more soluble than was SA at the three pH's examined. As CPH was not completely solubilized at concentrations greater than 1.0×10^{-7}, it was not sufficiently soluble in water

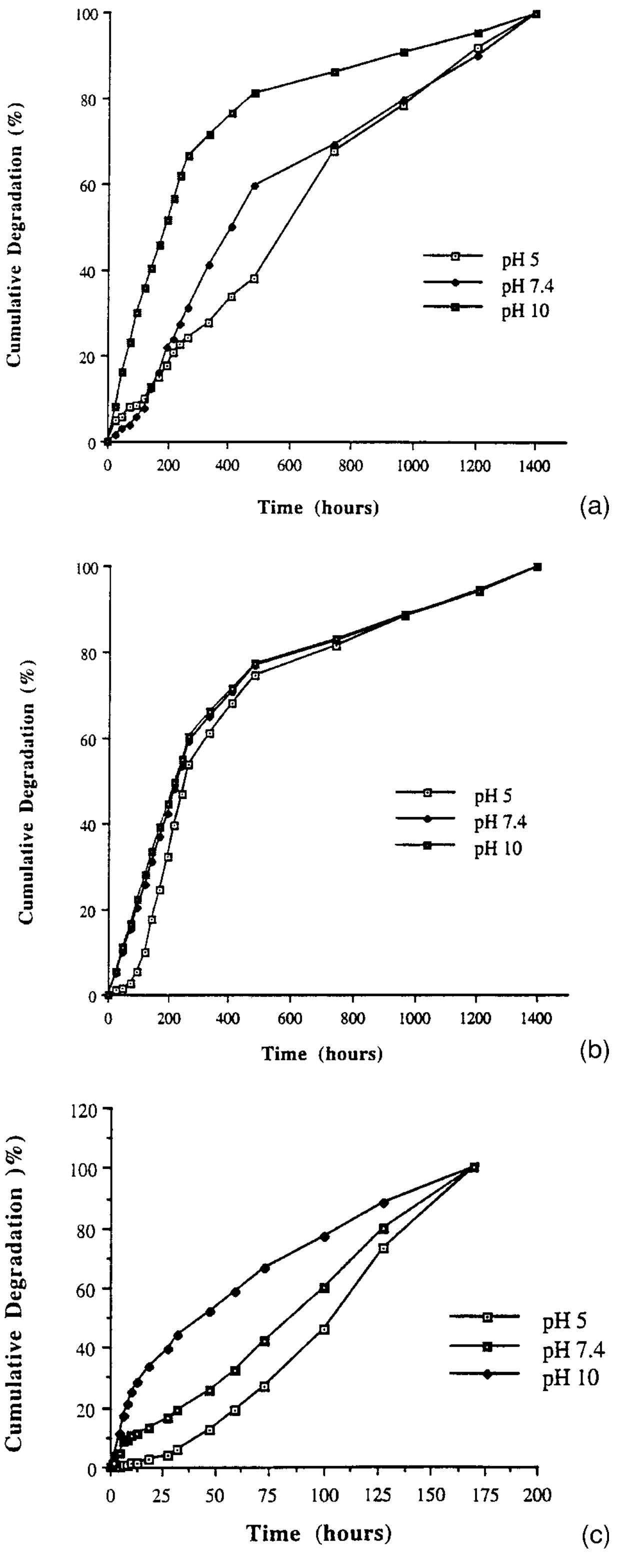

Figure 1 Degradation profiles of TMA-gly : CPH in buffer solution at pH 5, 7.4, and 10 at compositions of (a) 10 : 90, (b) 30 : 70, and (c) 50 : 50.

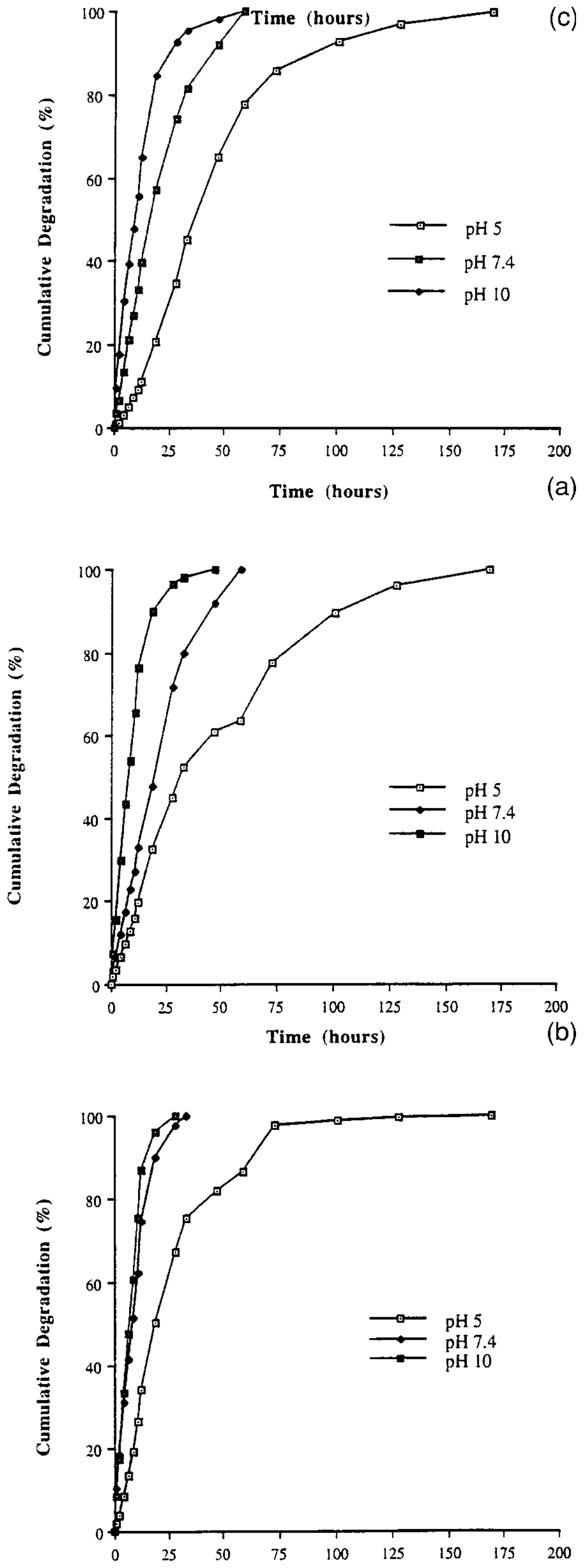

Figure 2 Degradation profiles of TMA-gly : SA in buffer solution at pH 5, 7.4, and 10 at compositions of (a) 10 : 90, (b) 30 : 70, and (c) 50 : 50.

to accurately measure its concentration by UV spectroscopy.

Polymer Degradation Characteristics

The effect of the media pH on the degradation of the poly(anhydride–imides) was investigated to assess the mechanism of polymer degradation, as the degradation process may be accelerated by the carboxylic acids generated by hydrolysis of the anhydride bonds. Figure 1(a) shows the degradation profiles of the TMA-gly : CPH (10 : 90) under acidic (pH 5), physiological (pH 7.4), and basic (pH 10) conditions. As the pH of the phosphate buffer increased, the degradation of the polymer matrices increased. At pH 5, matrix erosion proceeded in a fairly linear fashion throughout the entire experiment. At pH 7.4, the degradation profile was sigmoidal. The polymer had a 150 h period of induction during which degradation was slow without substantial erosion. After this initial induction period, there was a surge in the polymer degradation rate that subsided between 400 and 600 h. Degradation occurred most rapidly at pH 10. Up to 300 h, there was a rapid, linear increase in degradation that subsides after 400 h.

Figure 1(b) shows the degradation profiles of TMA-gly : CPH (30 : 70) in media at pH 5, 7.4, and 10. At pH 5, the polymer underwent a period of induction for 100 h. After this time, the polymer displayed a sigmoidal profile until approximately

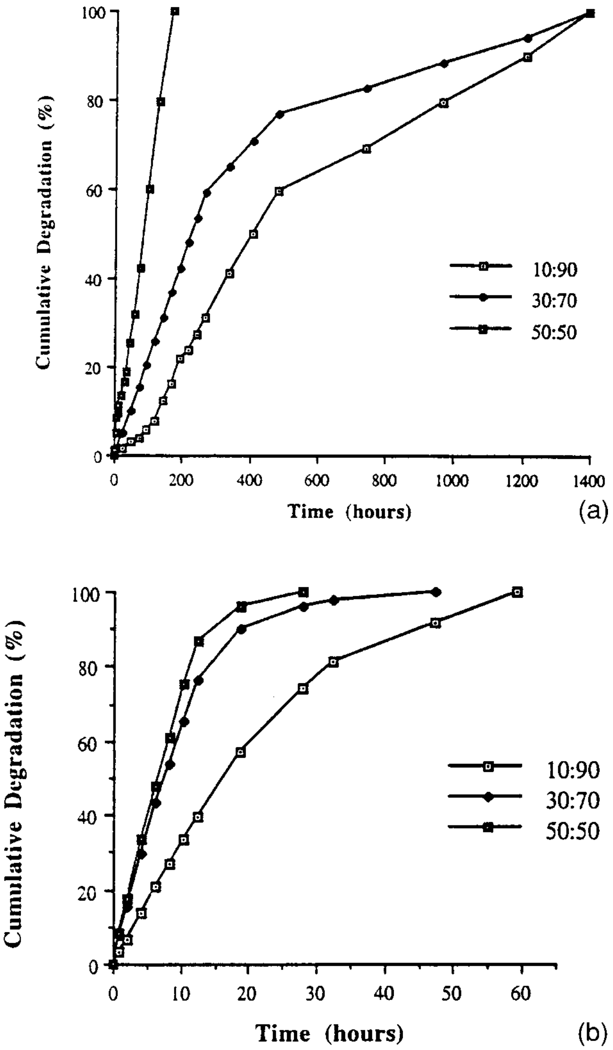

Figure 3 Degradation profiles of polymer matrices in media at pH 7.4 for (a) TMA-gly : CPH and (b) TMA-gly : SA.

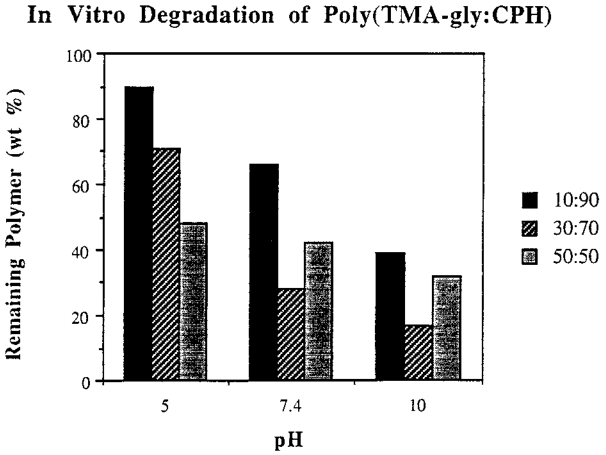

Figure 4 Relative change in weight of TMA-gly : CPH copolymers after degradation.

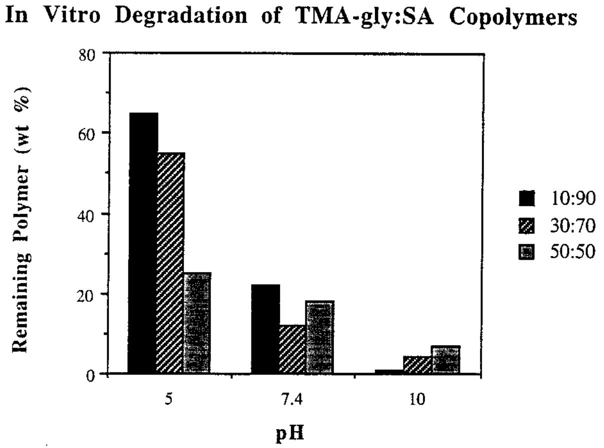

Figure 5 Relative change in weight of TMA-gly : SA copolymers after degradation.

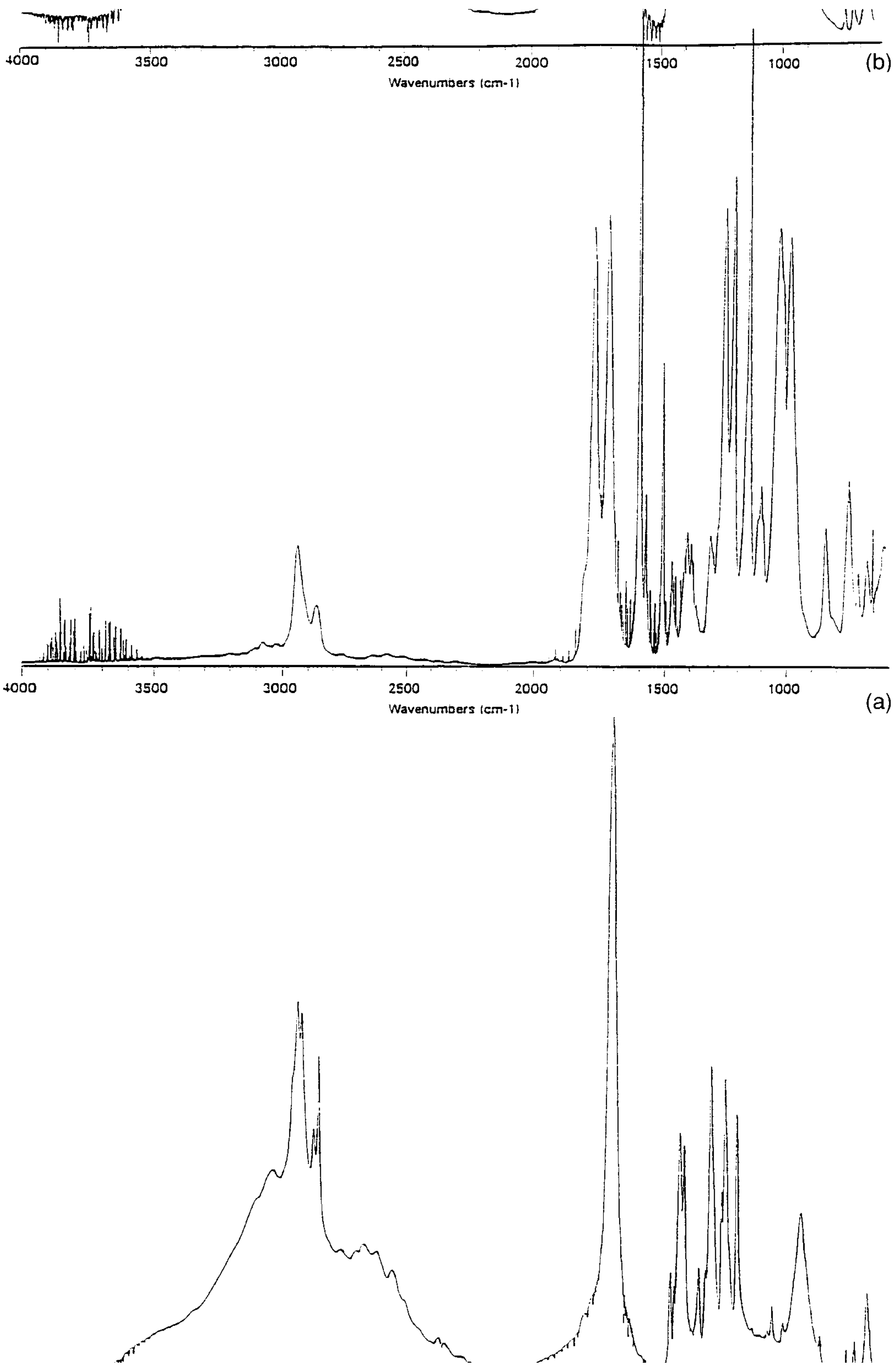

Figure 6 Infrared spectra of TMA-gly : SA (30 : 70) (a) before and (b) after degradation.

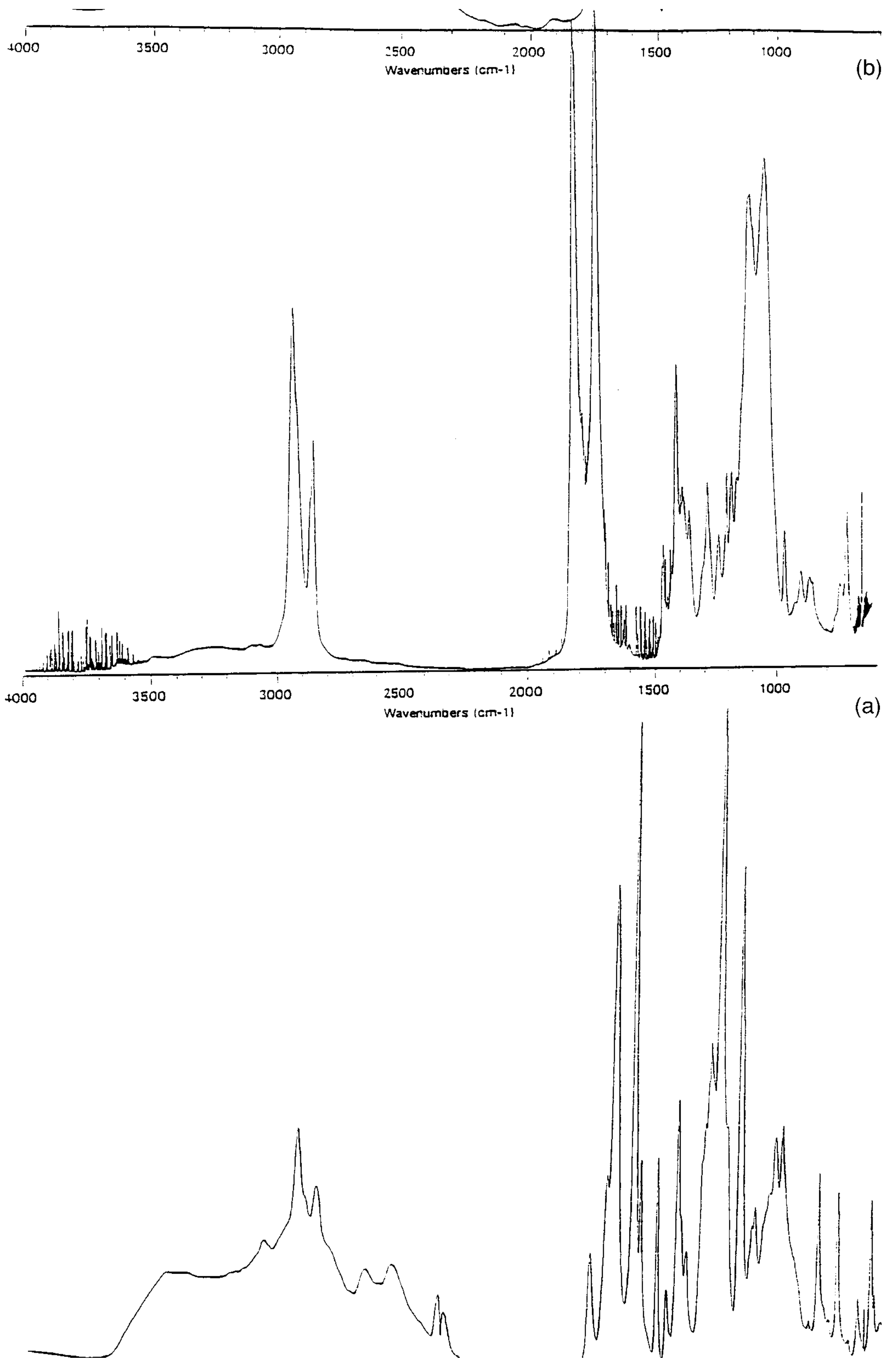

Figure 7 Infrared spectra of TMA-gly : CPH (30 : 70) (a) before and (b) after degradation.

Table II Characteristics of TMA-gly : CPH and TMA-gly : SA Copolymers Before Degradation

Polymer	% TMA-gly (feed)	M_w	PDI	T_g (°C)	T_m (°C)	T_d (°C)
TMA-gly : CPH	10	21,600	2.51	46	—	406
TMA-gly : CPH	30	7500	2.23	62	—	356
TMA-gly : CPH	50	4600	2.45	71	—	310
TMA-gly : SA	10	36,400	2.93	−25	65, 77	326
TMA-gly : SA	30	8500	2.46	11	55, 61	311
TMA-gly : SA	50	4800	2.95	36	45	312

400 h at which time the degradation subsided. In media at both pH 7.4 and 10, the polymer demonstrated linear degradation to 250 h, at which time the degradation subsided. Overall, polymer degradation rates increased with increasing pH of the media and degradation of the TMA-gly : CPH (30 : 70) occurred at a rate similar to the 10 : 90 composition at pH 10 [Fig. 1(a)].

Figure 1(c) illustrates the degradation profiles of TMA-gly : CPH (50 : 50) under pH conditions of 5, 7.4, and 10. There was an induction period of approximately 30 h in media at pH 5, with degradation increasing up to 175 h. At pH 7.4, there was a rapid, linear increase in polymer degradation for approximately 12 h, followed by constant degradation to 175 h. At pH 10, the degradation occurred in a linear manner up to 12 h, after which time the degradation slowed.

Visually, the TMA-gly : CPH (50 : 50) discs appeared to degrade more readily than did the other TMA-gly : CPH compositions. The degradation experiments were halted after only 200 h due to severe cracking of the polymer discs. By comparison, the degradation studies with the 10 : 90 and 30 : 70 TMA-gly : CPH compositions continued to 1400 h. These results can be correlated to contact angle data in which the 50 : 50 ratio of TMA-gly : CPH was found to be the most hydrophilic copolymer composition.[6] The increase in hydrophilicity increased water sorption into the polymer matrix, leading to enhanced degradation.

To further examine the role of hydrophilicity in degradation, copolymers containing SA, a more hydrophilic monomer than CPH, were also examined. Copolymers of TMA-gly : SA degraded much faster than did copolymers of TMA-gly : CPH.

Figure 2(a) shows the degradation profiles of the TMA-gly : SA (10 : 90) in media at pH 5, 7.4, and 10. At pH 5, the degradation profile was sigmoidal to 75 h; then, it is constant to nearly 175 h. At pH 7.4, the degradation was linear to 25 h, then subsided. At pH 10, degradation was linear to 20 h and completed by 50 h.

Figure 2(b) shows the degradation profiles of TMA-gly : SA (30 : 70) in media at pH 5, 7.4, and 10. At pH 5, the degradation was linear to 35 h; then, degradation decreased. For pH 7.4, the degradation was nearly linear to 30 h, decreasing slightly to 60 h. At pH 10, the degradation was rapid and linear to 20 h with the matrices completely degraded by 50 h.

Figure 2(c) shows the degradation profiles of TMA-gly : SA (50 : 50) in media at pH 5, 7.4, and 10. Degradation of these matrices was the most rapid of all the polymers. At pH 5, the degradation curve was linear to 30 h, and by 75 h, the degradation subsided. At pH 7.4 and 10, the degradation profiles were very similar, both increasing linearly to 20 h. By 25 h, the studies were concluded due to disintegration of the matrices.

For all the copolymers examined, degradation of the polymer matrices increased with increasing pH of the buffer solution. This indicates that the degradation process is not accelerated, or catalyzed, by the carboxylic acids generated by hydrolysis of the anhydride bonds. Previous studies of polyanhydrides have shown that differences in erosion rates with changes in media pH can be dependent on the solubility of the degradation products (i.e., monomers) in the medium.[15] Solubility studies with SA, 1,3-bis(carboxyphenoxy)-propane, and their corresponding homopolymers in 0.1*M* phosphate buffer indicated that monomer solubility was highest under basic conditions.[15] Based on our present study, the degradation mechanism of poly(anhydride–imides) is similar to that of the polyanhydrides.

The degradation profiles of TMA-gly : CPH and TMA-gly : SA in buffer solution at pH 7.4 are compared in Figure 3. Increasing the mol % of TMA-gly in the polymers increased polymer degradation. Thus, addition of TMA-gly to the poly-

Table III Decomposition Temperatures (°C) for TMA-gly : CPH and TMA-gly : SA Copolymers after Degradation

Copolymer	Molar Ratio	pH = 5	pH = 7.4	pH = 10
TMA-gly : SA	10 : 90	247	227	232
	30 : 70	242	266	249
	50 : 50	231	239	236
TMA-gly : CPH	10 : 90	401	405	405
	30 : 70	387	357	415
	50 : 50	365	376	361

mer backbone had a twofold effect. First, incorporation of the imide monomer, TMA-gly, increased the hydrophilicity of the polymer matrices, enabling water to penetrate more easily. Second, as the polymer backbone was hydrolyzed, the TMA-gly monomer was released and solubilized in the degradation media.

Properties of Degraded Polymer Matrices

The degradation studies were halted when the polymer matrices became severely cracked. After drying, the polymer fragments were then characterized by weight loss, infrared, and ^{1}H-NMR spectroscopy, thermal gravimetric analysis, and differential scanning calorimetry. The polymer remnants were not completely soluble in solvents such as chloroform, so that the molecular weights were not determined by gel permeation chromatography.

The weight of the polymer discs after degradation were compared to the weight of the original samples. The relative weight changes for TMA-gly : CPH and TMA-gly : SA matrices are shown in Figures 4 and 5. For both classes of polymers, the largest weight change occurred under basic conditions, indicating that degradation was most rapid in media at pH 10. Another factor that greatly influenced degradation was polymer compositions: Polymers containing SA lost more weight relative to polymers containing CPH, and increasing the level of TMA-gly in the polymer backbone enhanced weight loss of the matrices.

Several changes occurred in the polymer discs during the degradation process: The most prominent feature was the appearance of carboxylic acids as indicated by the intense O—H stretch near 3400 cm^{-1} [Figs. 6(b) and 7(b)] as degradation proceeded. In addition, a decrease in the intensity of the anhydride carbonyl bonds, relative to the other carbonyl bonds, was observed: The C=O stretch of the anhydride bond resonated near 1800 cm^{-1}; carbonyl stretches for the imide, amide, and acid bonds overlapped in the region from 1740 to 1640 cm^{-1}. For copolymers of TMA-gly : SA, essentially no anhydride carbonyl stretches were observed in all the samples [Fig. 6(b)] compared to the polymer before degradation [Fig. 6(a)]. By the end of the degradation study (200 h), no anhydride bonds were present. Alternately, copolymers of TMA-gly : CPH showed a significant amount of anhydride carbonyl bonds remaining after degradation [Fig. 7(b)] compared to the polymer before degradation [Fig. 7(a)].

The concentration of the imide monomer, TMA-gly, relative to the comonomer (SA or CPH) concentration was determined by ^{1}H-NMR spectroscopy. The relative concentration of TMA-gly to the

Table IV Transition Temperatures (°C) for TMA-gly : SA after Degradation

Molar Ratio	T_m (°C) pH = 5	T_m (°C) pH = 7.4	T_m (°C) pH = 10
10 : 90	136	123, 143	124, 149, 156
30 : 70	135, 144	125, 143	104, 144
50 : 50	123, 143	122, 130, 143	121, 143, 174

Table V Transition Temperatures (°C) for TMA-gly : CPH after Degradation

Molar Ratio	T_g (°C) pH = 5	T_g (°C) pH = 7.4	T_g (°C) pH = 10	T_m (°C) pH = 10
10 : 90	47	−18, 52	4.6, 81	175, 239
30 : 70	2.1, 49	4.6	22	175, 246
50 : 50	−1.6, 53	−2.6	—	243, 283

CPH monomer was determined by integrating the methylene protons of TMA-gly (near 4.6 ppm) relative to the methylene protons of SA (near 3.7 ppm) or CPH (near 4.3 ppm). For copolymers of TMA-gly : SA, the TMA-gly monomer was absent in the discs after the degradation study—only SA remained. This phenomenon was due to the higher solubility of TMA-gly relative to SA. For the copolymers of TMA-gly : CPH, the TMA-gly monomer was present in low concentrations in the discs degraded in acidic media. For the 10 : 90, 30 : 70, and 50 : 50 TMA-gly : CPH copolymers in the buffer solution at pH 5, the concentration of TMA-gly in the matrices after degradation was calculated to be 7, 8, and 15%, respectively. The TMA-gly monomer was absent from the polymer matrices degraded in media at pH 7.4 and 10, with only CPH remaining in the polymer fragments. As discussed previously, the solubility of TMA-gly increased under basic conditions (Table I), thus increasing polymer degradation in media at pH 10.

The thermal transition temperatures changed as the polymer discs underwent degradation. Table II shows the initial characteristic of the polymer disc before the degradation study. The decomposition temperatures decreased by approximately 80°C in the TMA-gly : SA copolymers and 50°C in the TMA-gly : CPH copolymers (Table III), relative to the undegraded polymer discs (Table II). Glass transition and melting temperatures changed quite significantly in both types of copolymers. The melting temperatures for TMA-gly : SA after the degradation study are shown in Table IV. After degradation, no glass transitions were observed in any of the discs, and several new melting transitions appeared ranging from 104 to 174°C. As the degradation proceeded, many new oligomers were formed, each accounting for additional melting transitions. The glass transition and melting temperatures for TMA-gly : CPH after degradation are shown in Table V. Many more glass transitions were observed after degradation (Table V), as many new oligomers were formed. The glass transition temperatures were generally lower than the initial glass transition temperature (Table II). Only under basic conditions were melting transitions observed; no melting transitions were present in these polymers before degradation.

CONCLUSION

This study showed that there are three significant factors that affected polymer degradation: pH of the degradation media; monomer solubility; and polymer hydrophobicity. We have shown that the degradation characteristics were manipulated by synthesizing a polymer with the desired properties. For most orthopedic applications, polymers must maintain their mechanical integrity over a few months. Matrices of TMA-gly : CPH may be good candidates for orthopedic devices as they show promising mechanical properties[6] and degrade over a period of several months.

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