Miscibility of Bioerodible Polyphosphazene/ Poly(lactide-*co*-glycolide) Blends

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We have previously demonstrated the feasibility of blending bioerodible polyphosphazenes with poly(lactide-*co*-glycolide) (PLGA) to form versatile polymeric materials with altered bioerosion properties. These studies demonstrated the effective neutralization of the acidic degradation products of PLGA by the polyphosphazene hydrolysis products. In the present study, five new polymers of dipeptide polyphosphazenes poly[(ethyl glycinato)$_x$-(glycyl-ethyl glycinato)$_y$phosphazene] and novel blends of these polyphosphazenes with poly(lactide-*co*-glycolide) (PLGA) were synthesized and fabricated. The miscibility was analyzed using differential scanning calorimetry and scanning electron microscopy. Hydrogen bonding within the blends was assessed by attenuated total reflectance infrared spectroscopy. The phosphazene component of the blend contained varying ratios of the glycyl-glycine ethyl ester to the glycine ethyl ester. Poly[(ethyl glycinato)$_{0.5}$(glycine ethyl glycinato)$_{1.5}$phosphazene formed completely miscible blends with PLGA (50:50) and PLGA (85:15). This is ascribed to the multiple hydrogen-bonding sites within the side groups of the polyphosphazene. The components of the blend act as plasticizers for each other because a glass transition temperature for each blend was detected at a lower temperature than for each individual polymer. A hydrolysis study showed that unblended solid poly[(ethyl glycinato)$_{0.5}$(glycyl ethyl glycinato)$_{1.5}$phosphazene] hydrolyzed in less than 1 week. However, the blends degraded at a slower rate than both parent polymers. This is attributed to the buffering capacity of the polyphosphazene hydrolysis products, which increases the pH of the degradation media from 2.5 to 4, thereby slowing the degradation rate of PLGA.

Introduction

Synthetic biodegradable polymers have generated extensive interest for applications that range from drug delivery to tissue engineering.[1−4] A biodegradable polymer must yield nontoxic degradation products and, depending on the application, the polymer must degrade at a specified rate. Classical polymers that have been examined as biodegradable matrices include polyesters,[5,6] polyethers,[7] polyamides,[8] polyanhydrides,[9] and polycarbonates.[10]

Poly(lactide-*co*-glycolide) (PLGA) polymers have been studied in the greatest detail partly because of their FDA approved status for some biomedical applications.[1−5] PLGA has many useful characteristics for medical applications such as the biocompatibility of the hydrolysis products.[11] Moreover, the degradation rate is controllable via the ratio of the comonomer residues,[12] the degradation products are metabolized by the body,[11,13] and PLGA has good structural integrity.[14] However, the use of PLGA is hindered by the acidity of the hydrolysis products and by its bulk erosion characteristics,[12] which lead to catastrophic failure of structural devices derived from this polymer. One method for circumventing these problems is to incorporate PLGA into polymer blends with other macromolecules that might control the hydrolysis rate, as well as reduce the acidity of the hydrolysis products. Polyphosphazenes are potentially the best candidates to achieve this objective.[15]

Polyphosphazenes are inorganic−organic hybrid polymers that are highly tailorable via the macromolecular substitution method used for their synthesis. More than 250 different side groups have been linked to phosphazene chains.[15] Different side groups generate widely differing properties.[15,16] Specific polyphosphazenes have received much attention as potential biomaterials.[17,18] A few polyphosphazenes are hydrolytically sensitive. Amino acid esters,[17] glucosyl,[19] glyceryl,[20] and lactide[21] and glycolide[21] ester side groups sensitize the polymers to hydrolysis. The amino acid ester derivatives hydrolyze to biocompatible products such as the amino acid, ethanol, phosphate, and ammonia.[15,17,22] This creates a pH buffer effect that has been shown by Ibim et al. to control the pH of a well-known polyphosphazene blended with PLGA.[23]

Previous blend studies of PLGA with polyphosphazenes that bear glycine ethyl ester side groups showed miscibility with PLGA at a ratio of 50:50 lactide to glycolide.[23] However, only semi-miscible blends were obtained when the lactide to glycolide ratio was changed to 85:15.[24] Miscibility was attributed to the hydrogen bonding that occurs between the protons attached to the nitrogens of the glycine substituents and the carbonyl units of PLGA.[23]

The work described here uses polyphosphazenes that contain the dipeptide glycyl-glycine ethyl ester units as side groups linked to a polyphosphazene chain, together with varying ratios of glycine ethyl ester side groups. Glycyl-glycine ethyl ester

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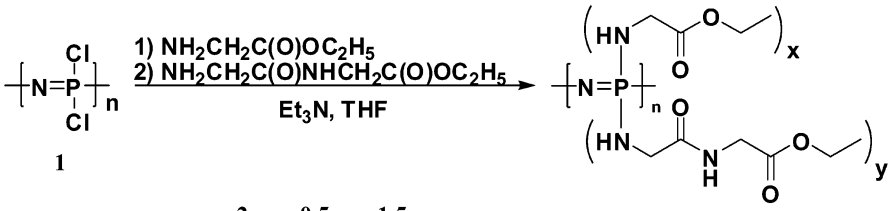
Scheme 1. Synthesis of Polymers **2**−**6** via Macromolecular Substitution of Polymer **1**



2: x = 0.5 y = 1.5
3: x = 1.0 y = 1.0
4: x = 1.5 y = 0.5
5: x = 0 y = 2.0
6: x = 2.0 y = 0

units contain both amide and amine protons that can participate in hydrogen bonding. This increased hydrogen-bonding capacity could increase the ability of these polymers to form miscible blends with PLGA. Thus, these novel polyphosphazenes were blended with PLGA [(50:50) and (85:15)], and the miscibility was studied with the use of differential scanning calorimetry (DSC). Scanning electron microscopy (SEM) was used to determine if phase separation was detectable. A qualitative analysis of the hydrogen bonding was obtained using attenuated total reflectance infrared spectroscopy (ATRIR). The most miscible blends contained poly[(ethyl glycinato)$_{0.5}$(glycyl-ethyl glycinato)$_{1.5}$phosphazene] with PLGA (50:50) and (85:15). These miscible blends were then immersed in aqueous media for 12 weeks, and hydrolysis of the solid films was monitored using gel permeation chromatography and SEM, together with pH measurements of the aqueous media.

Experimental Procedures

Reagents and Equipment. All reactions were carried out under a dry argon atmosphere using standard Schlenk line techniques. Tetrahydrofuran (EMD) and triethylamine (EMD) were dried using solvent purification columns.[25] Glycyl-glycine ethyl ester hydrochloride (MP-Bio), glycine ethyl ester hydrochloride (Aldrich), and poly(lactic-*co*-glycolic acid) (50:50 − M_w = 75 000 g/mol and 85:15 − M_w = 80 000 g/mol) (Aldrich) were used as received. Poly(dichlorophosphazene), reactive intermediate **1**, was prepared by the thermal ring-opening polymerization of recrystallized and sublimed hexachlorocyclotriphosphazene in evacuated Pyrex tubes at 250 °C. All ^{31}P and ^{1}H NMR spectra were obtained with a Bruker 360 WM instrument operated at 145 and 360 MHz, respectively. Glass transition temperatures were determined with a TA Instruments Q10 differential scanning calorimetry apparatus with a heating rate of 10 °C/min and a sample size of ca. 10 mg. The second scan of each sample was used to identify the glass transition temperature. Gel permeation chromatograms were obtained using a Hewlett-Packard HP 1090 gel permeation chromatograph equipped with two Phenomenex Phenogel linear 10 columns and a Hewlett-Packard 1047A refractive index detector. The samples were eluted at 1.0 mL/min with a 10 mM solution of tetra-*n*-butyl ammonium nitrate in THF. The elution times were calibrated with polystyrene standards. ATRIR scans of the films were analyzed using a Digilab FTS 7000 spectrometer with a zinc selenide ATR crystal, with 32 scans per sample. A conventional dual-stage scanning electron microscope (SEM) (FEI-Phillips XL-20) was used to study the surface morphology of the degrading films. All samples were gold coated, and an accelerating voltage of 20 kV was used with an 8 mm working distance. Water contact angle measurements were obtained using a Ramé-Hart contact goniometer. Ultrapure water (Millipore System, 18 MΩ) was dispensed from a needle, with a droplet size of 12 μL. pH measurements were obtained using a Beckman Φ 31 pH meter.

Synthesis of Polymers 2−**4.** The syntheses of all the polymers were carried out in a similar manner (Scheme 1). The procedure for polymer **2** is given as a representative example. Poly(dichlorophosphazene) (**1**) (1.0 g, 8.6 × 10^{-3} mol) was dissolved in dry THF (100 mL). Glycine ethyl ester hydrochloride (0.60 g, 0.0043 mol) was suspended in THF (25 mL) with triethylamine (1.3 mL, 0.0095 mol). This suspension was refluxed for 24 h. It was then cooled, filtered, and added to the stirred poly(dichlorophosphazene) solution. Glycyl-glycine ethyl ester hydrochloride (3.4 g, 0.017 mol) was suspended in THF (75 mL) with triethylamine (5.1 mL, 0.036 mol). This suspension was also refluxed for 24 h. It was then cooled, filtered, and added to the polymer solution. The resultant solution was stirred at room temperature for 48 h. The reaction mixture was then filtered, concentrated, and precipitated into hexanes. Polymer **2** was purified by dialysis versus methanol (3 times) and ethanol (twice) and was then isolated by precipitation into hexanes. The product was a tough, pale yellow solid.

Synthesis of Polymer 5. Poly(dichlorophosphazene) (**1**) (1.0 g, 8.6 × 10^{-3} mol) was dissolved in THF (100 mL). Glycyl-glycine ethyl ester hydrochloride (6.8 g, 0.035 mol) was suspended in THF (100 mL) with triethylamine (10.8 mL, 0.077 mol). This suspension was refluxed for 24 h. It was then cooled, filtered, and added dropwise to the poly(dichlorophosphazene) solution. A noted increase in viscosity was observed as the glycyl-glycine ethyl ester solution was being added to the polymer solution. The mixture turned yellow and was stirred for 120 h at room temperature. The polymer solution was then filtered, concentrated, and precipitated into hexanes. Purification utilized dialysis versus methanol (3×) followed by isolation by precipitation into hexanes. A brittle, yellow polymer was isolated.

Synthesis of Polymer 6. The synthesis of polymer **6** followed previous procedures.[17]

Formation of Blended Matrices. Blends of polymers **2**−**6** with PLGA (50:50) and PLGA (85:15) were produced with the following weight ratios of polymers **2**−**6** to PLGA: 25:75, 50:50, and 75:25. Polymers **2**−**6** and PLGA, total weight 400 mg, were dissolved separately in 1 mL of chloroform for 24 h. The polymer solutions were combined and stirred for another 4 h. Films were then cast in Teflon trays and allowed to air dry for 24 h and were vacuum-dried for 96 h.

Static Water Contact Angle Measurements. Solutions containing a total of 400 mg of polymer in 2 mL of chloroform were spun cast (1000 rpm, 1 min) onto glass slides. Each sample was analyzed using ImageJ software.

Hydrolysis Study of Blended Matrices. Films were fabricated as described using polymer **2** with PLGA (50:50) or PLGA (85:15). Each blend consisted of polyphosphazene/PLGA ratios of 25:75, 50:50, and 75:25, and each was compared with the pristine polymers. The films were cut into 1 cm × 1 cm squares of 500 μm thickness. The solid samples were placed in 10 mL of deionized water (pH 6) maintained at 37 °C in a constant shaker bath. Three samples were removed at weeks 1, 4, 7, 10, and 12. The solid samples were dried under vacuum for 2 weeks and were characterized by GPC in THF solvent and SEM techniques. The pH of each aqueous medium was analyzed using a pH meter.

Results and Discussion

Synthesis and Characterization of Polymers 2−**6.** Synthesis of the polymers was achieved via macromolecular substitution

Table 1. Physical Characteristics of Polymers **2**−**6** and PLGA

polymer	T_g (°C)	M_W (g/mol)	PDI	^{31}P NMR (ppm)	^{1}H NMR (ppm)
2	47.7	56 900	2.1	3.4	4.1, 3.6, 1.7, 1.4, 1.2
3	26.3	52 300	2.4	3.2	4.1, 3.7, 1.7, 1.5, 1.1
4	−8.5	44 700	2.2	2.8	4.0, 3.6, 1.7, 1.6, 1.2
5	56.4	45 800	2.2	3.6	4.1, 2.6, 1.1
6	−15.7	52 600	2.1	1.5	4.2, 3.7, 1.3
PLGA (50:50)	52.3	75 300			
PLGA (85:15)	55.6	80 000			

Table 2. Glass Transition Data of Polymers **2**−**6** When Blended with PLGA (50:50)

blend	% PPhos	T_g blend (°C)	T_g PPhos (°C)	T_g PLGA (°C)
PLGA (50:50)	25	19.4		
2	50	21.2		
	75	23.9		
PLGA (50:50)	25	14.3		
3	50	26.9		
	75	27.4		
PLGA (50:50)	25	17.7		
4	50	22.3	−5.6	
	75	20.3	−7.4	
PLGA (50:50)	25	17.2		
5	50	24.8		43.4
	75	19.9	59.2	38.3
PLGA (50:50)	25	13.9		
6	50	13.4		
	75	14.9		

Table 3. Glass Transition Data of Polymers **2**−**6** When Blended with PLGA (85:15)

blend	% PPhos	T_g blend (°C)	T_g PPhos (°C)	T_g PLGA (°C)
PLGA (85:15)	25	26.2		
2	50	39.6		
	75	46.28		
PLGA (85:15)	25	20.6		43.0
3	50	26.1		48.7
	75	22.7		50.5
PLGA (85:15)	25	25.0		
4	50	26.2	−4.7	48.5
	75	22.9	−8.4	43.2
PLGA (85:15)	25	23.9		38.5
5	50	31.2	62.3	48.8
	75	25.5	63.4	41.3
PLGA (85:15)	25	17.5		
6	50	20.5		36.2
	75	21.7		43.7

with the use of a two-step process. Thus, the thermal ring opening of hexachlorocyclotriphosphazene to the reactive intermediate, polymer **1**, was followed by sequential replacement of the chlorine atoms in the polymer by the amino acid substituents, as shown in Scheme 1. For polymers **2**−**4**, glycine ethyl ester was used in stoichiometric amounts, and the substitution was completed using an excess of the glycyl-glycine ethyl ester. Structural characterization was accomplished by ^{31}P and ^{1}H NMR spectroscopy and by GPC, as shown in Table 1. Side group ratios were estimated using ^{1}H NMR spectroscopy by comparing the α-carbon atoms on the glycine ethyl ester units to the α-carbons on the glycyl-glycine ethyl ester. The actual substitution ratios were within 3% of the calculated substitution amounts.

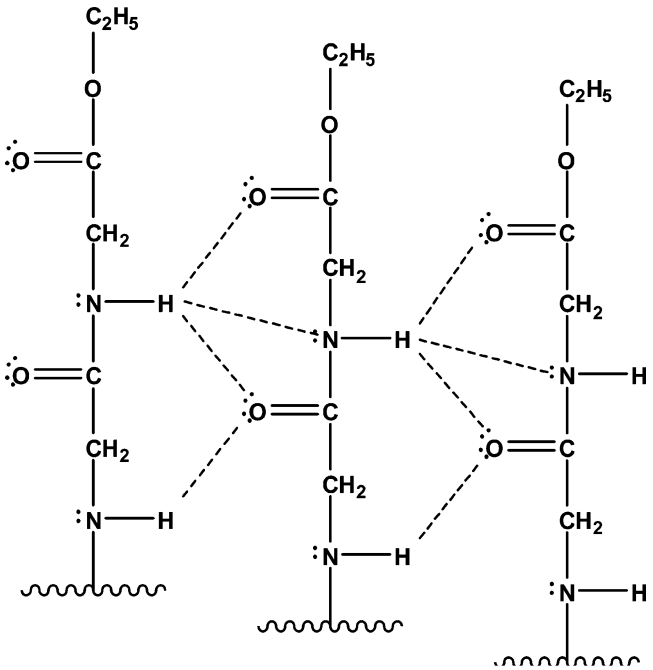


Figure 1. Potential hydrogen-bonding network that is generated within polymers **2**−**5** from the glycyl-glycine ethyl ester substituent. This creates a network of tightly bound protons that restrict the backbone motion. A similar hydrogen-bonding system occurs with the glycine ethyl ester substituent.

The glass transition temperatures of the component polymers, determined by DSC, are shown in Table 1. The glass transition temperature increased as the amount of glycyl-glycine ethyl ester in the polyphosphazene increased. This is attributed to a substantial hydrogen-bonding network that is formed from the amide linkage in glycyl-glycine ethyl ester and the amine proton located adjacent to the backbone on both substituents. These protons are accessible to both intra- and intermolecular hydrogen bond formation with the adjacent carbonyl, amide, or amine functionalities, as shown in Figure 1. The carbonyl hydrogen bonding was confirmed by ATRIR, with the formation of a new band at 1735 cm^{-1}.[26] This shift was detected in polymers **2**−**6**, with polymer **6** showing evidence of two shifts of equal intensities at 1735 and 1750 cm^{-1}.

Extensive hydrogen bonding creates a network that counteracts the inherent flexibility of the phosphazene backbone. Hydrogen bonding may also occur with the amino proton next to the polymer skeleton, or with the backbone nitrogen atoms as well, which would generate a stronger network that further limits the motion of the backbone.

Formation of Polymer Blends with PLGA. The blended films were characterized using DSC and SEM techniques to determine polymer miscibility. Miscible blends were obtained with PLGA 50:50, where a single transition in the thermogram was detected, with the exception of polymers **4** and **5**. Three compositions of polymer **2**/PLGA (50:50) (25:75, 50:50, and

Table 4. ATRIR Data for Polymer **2** and the Blends of PLGA with Polymer **2**

composition	N−H stretch	C=O stretch	amide I	amide II
polymer **2**	3300	1736	1644	1558, 1547, 1259
PLGA (50:50)/25% **2**	3300	1749, (1735)[a]	1636	1559, 1542, 1268
PLGA (50:50)/50% **2**	3300	1734, (1750)[a]	1636	1558, 1540, 1259
PLGA (50:50)/75% **2**	3300	1734	1636	1559, 1542, 1261
PLGA (85:15)/25% **2**	3300	1734, (1750)[a]	1635	1560, 1540, 1266
PLGA (85:15)/50% **2**	3300	1734, (1750)[a]	1636	1559, 1540, 1266
PLGA (85:15)/75% **2**	3300	1734, (1750)[a]	1636	1560, 1540

[a] Shoulder to the majority peak.

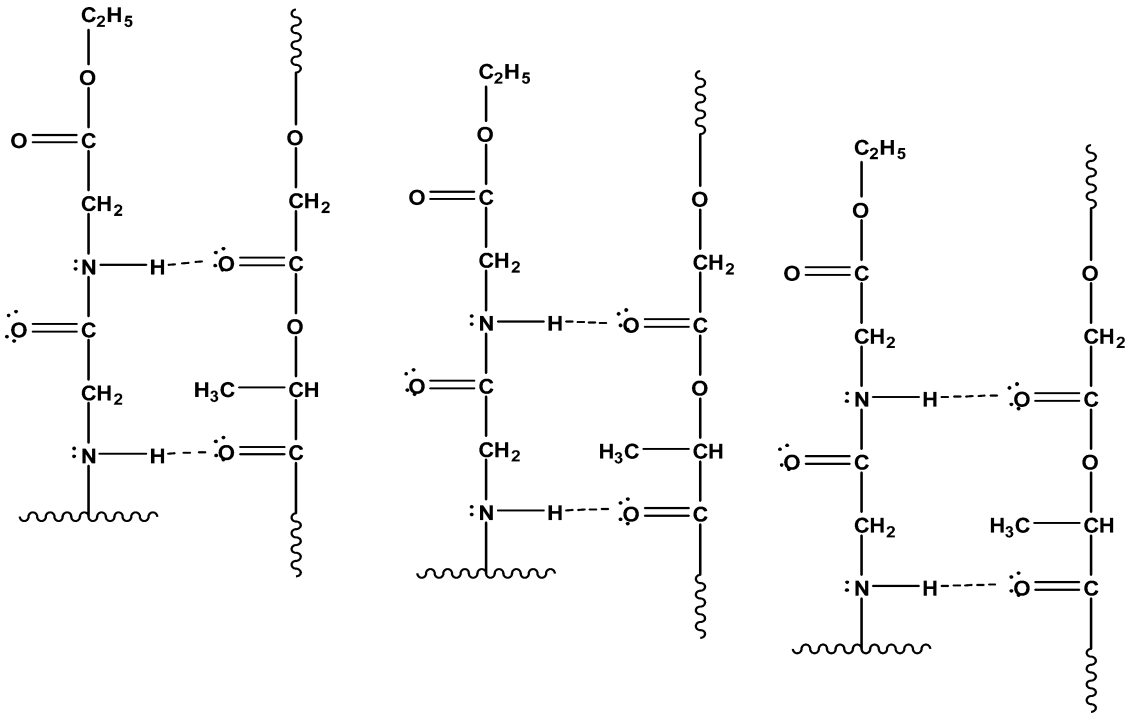


Figure 2. Disruption of hydrogen bonding when PLGA is added to polymers **2**−**5**. Hydrogen bonding occurs between the carbonyl oxygen of PLGA and the amino acid.

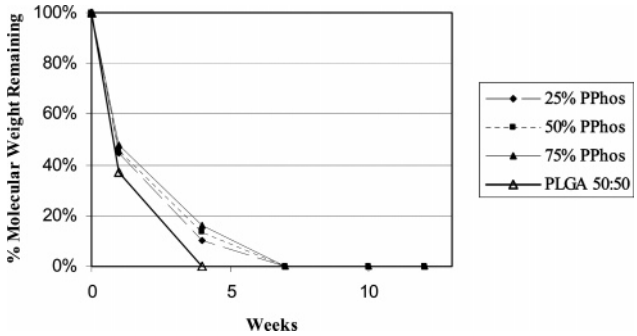


Figure 3. Hydrolytic degradation profile of polymer **2** blended with PLGA (50:50). The standard deviation for each time point is as follows: week 1, 25% polymer **2**: 0.67%; 50% polymer **2**: 0.76%; and 75% polymer **2**: 2.83%. Week 4, 25% polymer **2**: 2.24%; 50% polymer **2**: 0.27%; and 75% polymer **2**: 0.27%.

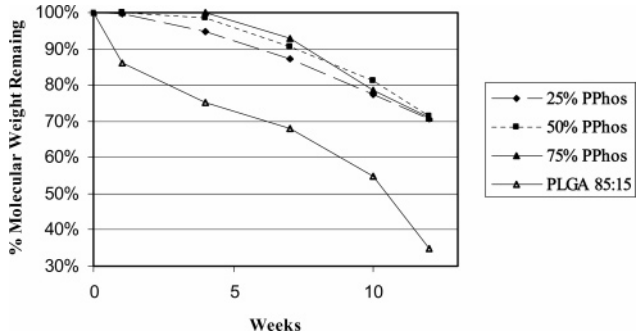


Figure 4. Hydrolytic degradation profile of polymer **2** blended with PLGA (85:15). The standard deviation for each time point is as follows: week 1, 25% polymer **2**: 0.19%; 50% polymer **2**: 0.31%; and 75% polymer **2**: 0.56%. Week 4, 25% polymer **2**: 3.64%; 50% polymer **2**: 1.01%; and 75% polymer **2**: 0.80%. Week 7, 25% polymer **2**: 6.40%; 50% polymer **2**: 0.45%; and 75% polymer **2**: 1.83%. Week 10, 25% polymer **2**: 2.15%; 50% polymer **2**: 1.63%; and 75% polymer **2**: 3.13%. Week 12, 25% polymer **2**: 4.73%; 50% polymer **2**: 0.76%; and 75% polymer **2**: 0.63%.

75:25) showed glass transitions at 19.4, 21.2, and 23.9 °C, respectively. Completely miscible blends of polymer **3**/PLGA (50:50) (25:75, 50:50, and 75:25 blend compositions) showed single thermal transitions at 14.3, 26.9, and 27.4 °C, respectively. Polymer **6**/PLGA (50:50) blends (25:75, 50:50, and 75:25 blend compositions) showed thermal transitions at 13.9, 13.4, and 14.9 °C, respectively. Films that contained 25% polymers **4** or **5** gave completely miscible blends with PLGA (50:50), with single thermal transitions occurring at 17.7 or 17.2 °C, respectively. SEM studies further supported this evidence, with no phase separation being detected for any of the blended films that were identified as miscible by DSC. These data give evidence that the miscibility is favored by an increasing amount of dipeptide, but some glycine ethyl ester component is needed. The glycine ethyl ester side group increases the solubility and lowers the glass transition temperature, presumably making the

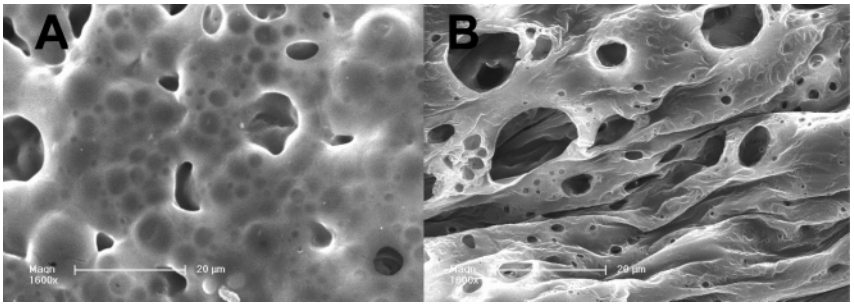


Figure 5. PLGA (50:50)/polymer **2** blends (25% PLGA/75% polymer **2**) of week 1 (A) and week 4 (B) with scale bars of 20 μm.

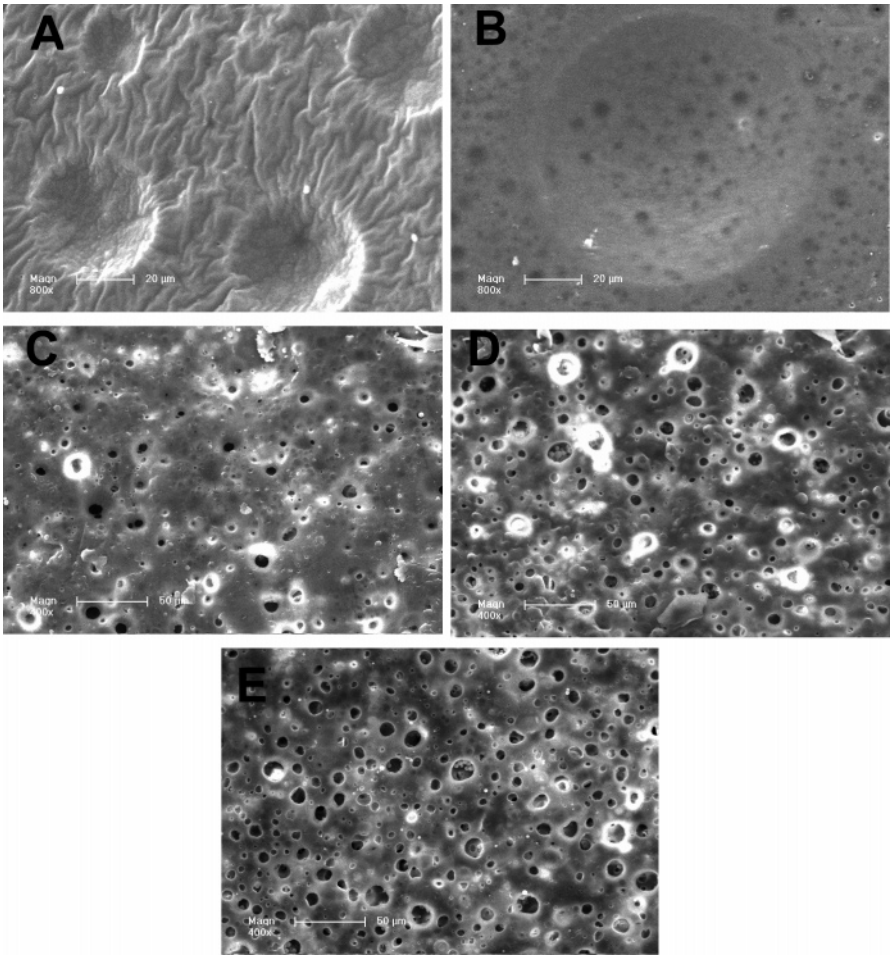


Figure 6. PLGA (85:15)/polymer **2** blends (25% PLGA/75% polymer **2**) of weeks 1 (A), 4 (B), 7 (C), 10 (D), and 12 (E). Panels A and B have scale bars of 20 μm and panels C−E have scale bars of 40 μm.

hydrogen-bonding protons more available to PLGA (50:50). Thus, it is proposed that miscibility occurs when extensive hydrogen bonding involves the interaction of the amide or amine protons on the phosphazene and the carbonyl units in the backbone of PLGA, as shown in Figure 2.

Only polymer **2** formed completely miscible blends with PLGA (85:15) at all compositions, with single thermal transitions at 26.2 °C for the 25:75 **2**/PLGA (85:15) blend, 39.6 °C for the 25:75 **2**/PLGA (85:15) blend, and 46.3 °C for the 25:75 **2**/PLGA (85:15) blend, respectively. Films that contained 25% polymers **4** and **6** with PLGA (85:15) also formed completely miscible blends with PLGA (85:15), with single thermal transitions at 25.0 and 17.5 °C, respectively. All other blends containing polymers **3**−**6** and PLGA (85:15) showed a transition that was evidence for partial miscibility, but multiple thermal transitions were detected indicative of phase separated polymers. This could be due to the restriction of hydrogen bonding between polymers **3**−**6** and PLGA (85:15) or the inability of PLGA (85:15) to break up the tightly hydrogen-bonded network present within the polyphosphazene domains. Polymer **5** did not form miscible blends, probably due to strong hydrogen

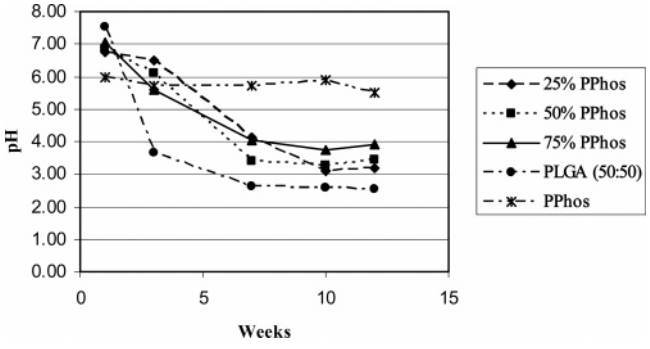


Figure 7. pH of PLGA (50:50)/PPhos blends in aqueous media.

bonding between polymer **5** molecules. For polymers **3**, **4**, and **6**, it is speculated that insufficient hydrogen-bonding protons are present to interact with the carbonyl units of PLGA (85:15), perhaps due to steric effects generated by the methyl group on the lactide repeat unit. This interpretation was also supported by ATRIR experiments, where the detected carbonyl stretch located at 1750 cm^{-1} is indicative of nonhydrogen-bonded free carbonyl groups.

A feature of polymers **2**, **3**, and **5** blended with PLGA was the plasticizing effect by each polymer on the other. The glass transition temperatures of polymers **2**, **3**, and **5** and of PLGA were higher than the glass transition temperatures of the blended materials. Thus, the hydrogen-bonding network associated with polymers **2**, **3**, and **5** appears to be disrupted by the addition of PLGA. This was detected by ATRIR when comparing the pure polyphosphazene to the blend. The pure polyphosphazene had a significant carbonyl band at 1735 cm^{-1} that is indicative of a hydrogen-bonded carbonyl function. Two peaks were detected for the blend, at 1750 and 1735 cm^{-1}, with the former showing evidence of carbonyl units that were hydrogen bonded. Polymers **2**, **3**, and **5** probably disrupt the crystalline order of PLGA. This was suggested by DSC scans, which indicated a loss of the hysteresis transition that is observed with PLGA alone. These interactions between the polymers appear to involve a mutual plasticization that allows more chain mobility.

Polymer **2**, PLGA (50:50), PLGA (85:15), and the corresponding blends of these polymers were also studied for their hydrophobicity. PLGA (50:50) showed consistent water contact angles at the surface of 73°, with PLGA (85:15) and polymer **2** having static water contact angles of 84°. The blends of polymer **2** and PLGA (50:50) gave consistent water contact angles of 83°, and blends of polymer **2** and PLGA (85:15) gave consistent water contact angles of 84°. From these water contact angles, it was concluded that none of the blended polymer films was hydrophilic at the surface, thus inhibiting the uptake of water into the solid film.

Hydrolysis of Poly[(ethyl glycinato)$_{0.5}$(glycyl-ethyl glycinato$_{1.5}$-phosphazene]/PLGA Blends. Polymer **2** was blended with PLGA (50:50) and PLGA (85:15) in molar compositions of 25:75, 50:50, and 75:25 polymer **2**/PLGA and then cast into films. The solid films were allowed to hydrolyze in an aqueous medium for 12 weeks. Hydrolysis of the blends was compared to the hydrolysis behavior of the pure polymers. The pH, molecular weight loss, and surface degradation were monitored over that period of time. Polymer **2** was used because it was completely miscible with PLGA (50:50) and (85:15).

Unblended polymer **2** was completely hydrolyzed in less than 1 week, and no solid film remained. Pure PLGA (50:50) was completely hydrolyzed after a period of 4 weeks, whereas when blended with polymer **2**, it had retained a significant molecular weight (M_w = 7500 g/mol) of PLGA (50:50) at 4 weeks. Figure 3 shows that blended films of 25% polymer **2** and 75% PLGA (50:50) underwent a 90% decrease in molecular weight after hydrolysis for 4 weeks. After 7 weeks, the solid films of all blend compositions were completely hydrolyzed. At no time was evidence obtained by GPC that polymer **2** resisted hydrolysis. ^{31}P NMR spectroscopy supported this evidence because a peak at 0 ppm from phosphates replaced the peak from the polyphosphazene. Figure 5 shows the SEM images of the solid films at weeks one and four. The rough surface is indicative of surface hydrolytic degradation.

The hydrolysis of PLGA (85:15) was also retarded when it was blended with all the variants of polymer **2**, as shown in Figure 4. Pristine PLGA (85:15) showed a decrease in molecular weight after 4 weeks (M_w = 68 500 g/mol). However, after 12 weeks, only a 28% (M_w = 57 600 g/mol) decrease occurred in the molecular weight of PLGA (85:15) when it was blended with polymer **2**. The molecular weight decline of pure PLGA is accelerated by the acidity of the surrounding solution. The SEM images shown in Figure 6 illustrate the increased roughness of the blend caused by surface hydrolysis. This roughness is probably aided by the faster hydrolysis of the phosphazene component of the film.

Thus the rate of molecular weight decline of PLGA was retarded by the hydrolysis products from polymer **2**. This suggests that the acidity generated by the hydrolysis of PLGA is slightly buffered by the phosphates and ammonia produced from the hydrolyzed phosphazene backbone. This slows the acid-catalyzed hydrolysis of PLGA.[27] As shown in Figure 7, the hydrolysis of polymer **2** gave aqueous media with a pH of 5.5−6. However, when the blend containing 75% polymer **2** and 25% PLGA (50:50), pH 4, was detected after 12 weeks, whereas non-blended PLGA (50:50) generates a hydrolysis medium with a pH of 2.5. Thus, as the amount of polymer **2** in the blend is increased, the pH of the solution is raised slightly, but significantly.

Conclusion

Novel polyphosphazenes that contain varying ratios of glycyl-glycine ethyl ester dipeptides have the ability to form miscible blends with PLGA (50:50) as well as with PLGA (85:15). This is due to the strong hydrogen bonding between the constituents. The most useful ratio of glycyl-glycine ethyl ester to glycine ethyl ester in the polyphosphazene was 75% glycyl-glycine ethyl ester and 25% glycine ethyl ester (polymer **2**). A plasticizing effect was detected in each blend that is probably due to the disruption of the hydrogen-bonding network formed within the pristine polyphosphazene. Complete hydrolysis of this polymer **2** occurs in less than a week, but polymer **2** retards the hydrolysis of PLGA, due to the buffering capability of the polyphosphazene hydrolysis products. These results suggest a method for fine-tuning the hydrolytic erosion behavior of PLGA in a way that may be beneficial for tissue engineering matrices, drug delivery, and device design.

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