Effect of Side Group Chemistry on the Properties of Biodegradable L-Alanine Cosubstituted Polyphosphazenes

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Biodegradable polyphosphazenes have been investigated for a variety of applications, such as controlled drug delivery matrixes, tissue-engineering scaffolds, membranes, and bone-type composites. In this study we have evaluated the effect of side group chemistry on the properties of biodegradable phosphazene polymers that contain ethyl alanato side groups together with ethyl glycinato, *p*-methylphenoxy, or *p*-phenylphenoxy side groups. The polymers were synthesized by a macromolecular substitution route. The molecular weights of aryloxy/amino acid ester cosubstituted polymers were much higher than the amino acid ester substituted polyphosphazenes described earlier. Polymer properties, such as glass transition temperature, hydrolytic degradation, surface wettability, tensile strength, and modulus of elasticity varied over a wide range following changes to the type of co-substituents on the polymer backbone. The glass transition temperatures varied from −10 to 35 °C and increased with the bulkiness of the side groups. Polymer films in phosphate buffer saline solution showed molecular weight declines ranging from 58% to >80% and mass loss ranging from 4% to 90% over a period of 7 weeks. Water contact angles for polymer films varied from 63° to 107°, with the highest angles for the alanine ethyl ester and *p*-phenylphenoxy cosubstituted polyphosphazene. The tensile strengths were in the range of 2.4−7.6 MPa and the modulus of elasticity was in the range of 31.4−455.9 MPa. Thus, in this study we have demonstrated the tunability of biodegradable polyphosphazenes to suit a range of biomedical applications.

Introduction

Degradable polymers have been investigated for a variety of biomedical applications such as sutures, drug delivery vehicles, and tissue engineering scaffolds.[1−4] The type of application determines the required material properties. Well-known examples of degradable polymers include polyesters, polyorthoesters, polyanhydrides, poly(α-amino acids), and polyphosphazenes.[1,5−7] Polyphosphazenes, although a relatively new addition to this list, offer an appealing platform for the design and synthesis of novel biodegradable polymers and for efficient control over the degradation rates and other material properties.[8]

Polyphosphazenes are hybrid polymers with a backbone of alternating phosphorus and nitrogen atoms and with two organic side groups attached to each phosphorus atom. These polymers are synthesized by the reactions of alkoxides, aryloxides, or amines with a highly reactive macromolecular intermediate, poly(dichlorophosphazene).[8] Because a large number of different side groups can be introduced in these reactions, a wide range of properties may be generated with this polymer system. Specific side groups such as amino acid esters, glucosyl, glyceryl, glycolate, lactate, and imidazole sensitize the polymer backbone to hydrolysis.[8−13] On the other hand, hydrophobic side groups such as aryloxy, fluoroalkoxy, and C_4 and higher alkoxy units protect the polymer backbone against hydrolysis. Therefore, a cosubstituted polymer, with both hydrolysis-sensitizing and hydrolysis-retarding groups offers considerable opportunities for controlling the rate of degradation through changes in the ratio of the two side groups.

Among the various classes of degradable polyphosphazenes, poly[(amino acid ester) phosphazenes] have met with the most success in terms of potential biomedical applications. These polymers are synthesized by the attachment of an ester derivative of naturally occurring amino acids to the phosphazene backbone via the amino terminus. Hydrolysis of these polymers gives biologically benign products which include the amino acid group, an alcohol from the ester, and a pH buffered system of phosphate and ammonia.[10,14] The degradation rate depends on the type of α-substituent and ester unit present in the amino acid side group.[15] These polymers have been investigated for various potential applications including drug delivery vehicles and tissue-engineering scaffolds.[8]

The aim of the present study was to evaluate the effect of side group chemistry on the properties of poly[(amino acid ester)phosphazenes]. The base polymer selected for structural and property comparisons was poly[bis(ethyl alanato)phosphazene] (**1**) because this polymer can be readily synthesized as a single substituent or a cosubstituent polymer. Veronese and co-workers reported the use of polymer **1** as a membrane for tissue regeneration in the treatment of periodontal disease.[16] Polymer **1** has also been studied as a successful nerve guide conduit for the regeneration of severed nerves.[17] Laurencin and

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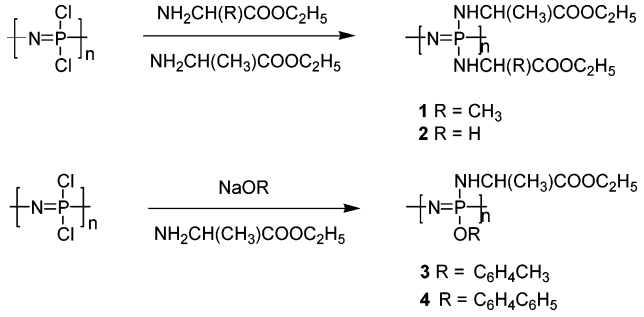
Scheme 1. General Synthetic Scheme for Polymers **1**−**4**



co-workers demonstrated the osteocompatibility of the same polymer as a tissue-engineering scaffold.[18,19]

In this paper we describe the synthesis, characterization, and properties of poly[bis(ethyl alanato)phosphazene] and its co-substituted analogues: poly[(ethyl alanato)$_1$ (ethyl glycinato)$_1$ phosphazene] (**2**), poly[(ethyl alanato)$_1$ (*p*-methyl phenoxy)$_1$ phosphazene] (**3**), and poly[(ethyl alanato)$_1$ (*p*-phenylphenoxy)$_1$ phosphazene] (**4**). These polymers were synthesized by the macromolecular substitution route. Hydrolytic degradation of the polymers was studied by following molecular weight decline and mass loss in phosphate buffer saline solution, over a period of 7 weeks. Mechanical properties of the polymers were measured by micro-tensile testing.

Experimental Section:

Reagents and Equipment. Synthesis reactions were carried out under an atmosphere of dry argon using standard Schlenk line techniques. Hexachlorocyclotriphosphazene (Ethyl Corp. and PCS) was obtained from a trimer−tetramer mixture by recrystallization from heptane followed by sublimation (30 °C/0.2 mmHg). Poly(dichlorophosphazene) was prepared by the ring-opening polymerization of hexachlorotriphosphazene in a sealed evacuated Pyrex tube at 250 °C. The same batch of poly(dichlorophosphazene) was used in the synthesis of polymers **1**−**4**. Ultrapure, anhydrous tetrahydrofuran (THF), toluene, and triethylamine were obtained from a solvent dispensing system designed by J C Meyer. L-Alanine ethyl ester hydrochloride (Chem Impex International Inc), L -glycine ethyl ester hydrochloride, 4-methylphenol, 4-phenylphenol (Aldrich), and sodium hydride (60% dispersion in mineral oil, Aldrich) were used as received. Spectra/Por regenerated cellulose dialysis membranes with a molecular weight cutoff of 12000−14000 were used for purification of the polymers. ^{31}P NMR (145 MHz) and ^{1}H NMR (360 MHz) data were obtained with use of a Bruker 360 MHz spectrometer. ^{31}P NMR chemical shifts are reported in ppm relative to 85% H_3PO_4 at 0 ppm. Gel permeation chromatography (GPC) was carried out with use of a Hewlett-Packard HP-1090 liquid chromatograph fitted with an HP-1047A refractive index detector and two phenogel 10 μm linear columns (Phenomenex), calibrated with polystyrene standards (Polysciences). The samples were eluted at 40 °C with a 0.1 wt % solution of tetra-*n*-butylammonium nitrate (Aldrich) in THF (EM Science). Glass transition temperatures were determined from a TA Instruments Q10 differential scanning calorimetry (DSC) apparatus with a heating rate of 10 °C/min. Water contact angle measurements were obtained using a Rame'-Hart contact angle goniometer. A conventional dual-stage scanning electron microscope (SEM) (FEI-Philips XL 20) was used to study the surface morphology of the degrading films. The samples were gold-coated and viewed under a SEM at a working distance of 8 mm, with an accelerating voltage of 20 kV. Tensile tests were carried out using an Instron 5866 instrument equipped with a 100 N load cell and operated at a crosshead speed of 5.08 mm/min at room temperature (20−25 °C). The reported results are mean values of three measurements for each sample.

Table 1. Characterization Data for Polymers **1**−**4**

polymer	^{1}H NMR[a] (ppm)	^{31}P NMR[a] (ppm)	M_N (g/mol)	M_W (g/mol)	T_g (°C)
1	4.1−4.08 (br, 3.6H, −C*H*−, −C*H*$_2$−, −N*H**−), 1.4−1.27 (br, 3H, −C*H*$_3$−), 1.2−1.19 (t, 3H, −C*H*$_3$−)	−3.5	8.9×10^4	1.96×10^5	−10
2	4.2−3.6 (br, 7.5H, 3x −C*H*$_2$−, −C*H*−, −N*H**−), 1.4 (br, 3H, −CH$_3$−), 1.3 (br, 6H, 2 −CH$_3$−)	−2.43	1.5×104	3.7×104	−9
3	7.7−6.4 (br, 4H, −C$_6$*H*$_4$−), 4.2−3.9 (br, 3.8H, −C*H*$_2$−, −C*H*−, −N*H**−), 2.2−1.9 (br, 3H, −C$_6$H$_4$−C*H*$_3$), 1.1−0.7 (br, 6H, 2x −CH$_3$−)	−5.8, −7.7, −18.1	3.3×10^5	9.7×10^5	−6
4	7.8−7.2 (br, 9H, −C$_6$*H*$_4$C$_6$*H*$_5$), 4.8−3.9 (br, 3.8 H, −C*H*−, −C*H*$_2$−, −N*H**−), 1.3−0.6 (br, 6H, 2x −C*H*$_3$−)	−5.2, −7.3, −17.97	1.02×10^6	1.9×10^6	35

[a] NMR recorded in d_8-THF solution. *NH protons were difficult to quantify by ^{1}H NMR.

Synthesis of Polymer 1. L-Alanine ethyl ester was prepared by treatment of alanine ethyl ester hydrochloride (106.04 g, 0.690 mol) in refluxing THF (500 mL) with triethylamine (288 mL, 2.071 mol). After the solution had been stirred for 24 h, the reaction mixture was filtered and the filtrate was added to a stirred solution of poly(dichlorophosphazene) (20.00 g, 0.173 mmol) in THF (2000 mL). The reaction mixture was then stirred at room temperature for 48 h. The insoluble salts were removed by filtration and a white fibrous polymer was obtained by precipitation of the viscous polymer solution into hexanes. Purification of the polymer was accomplished by repeated precipitations from THF into hexanes (3×), followed by dialysis against a THF/methanol (50/50) mixture for 3 days.

Synthesis of Polymer 2. The mixed-substituent polymers were synthesized by sequential addition of the two side groups. The bulky substituent was added first in stoichiometric amounts, followed by an excess of the second reagent. For polymer **2**, a stoichiometric amount of L-alanine ethyl ester (14.58 g, 0.095 mol) was added to a solution of poly(dichlorophosphazene) (10 g, 0.086 mol) in THF (1000 mL). The reaction mixture was stirred for 24 h and partial replacement of the chlorine was confirmed by ^{31}P NMR. Excess amounts of L-glycine ethyl ester (48.18 g, 0.345 mol), in the presence of excess triethylamine were then added to the reaction mixture to complete the substitution. The mixture was stirred for 48 h. The insoluble salts were removed by filtration and a yellow, adhesive polymer was obtained by precipitation of the viscous polymer solution into hexanes. Purification of the polymer was accomplished by repeated precipitations from THF into hexanes (3×), followed by dialysis against methanol for 5 days.

Synthesis of Polymer 3. Poly(dichlorophosphazene) (20.0 g, 0.173 mol) was dissolved in THF (2000 mL). In a separate reaction vessel, *p*-cresol (20.53 g, 0.190 mol) was added to a suspension of sodium hydride (4.36 g, 0.173 mol) in THF (250 mL) and the reaction was allowed to proceed for 24 h. Sodium *p*-methylphenoxide solution was then added dropwise to the polymer solution. The reaction was allowed to proceed at room temperature for 24 h. L-Alanine ethyl ester (79.54 g, 0.518 mol) in THF (700 mL) was then added to the reaction mixture that contained the partially substituted polymer. The reaction solution was then heated at reflux for 48 h. The polymer was purified by repeated precipitations from THF into hexanes (3×) and methanol (2×).

Synthesis of Polymer 4. The synthesis of polymer **4** was accomplished in a manner similar to polymer **3**. A stoichiometric amount of the more bulky side group, sodium salt of *p*-phenylphenol (32.31 g, 0.173 mol), was added to poly(dichlorophosphazene) solution (20 g, 0.173 mol) followed by the addition of excess amounts of L-alanine ethyl ester (116.64 g, 0.759 mol). The polymer was purified by repeated precipitations from THF in to hexanes (3×) and methanol (2×).

Hydrolysis of Polymers 1−4. Rectangular-shaped polymer films (0.5 × 0.5 × 0.1 cm) cast from concentrated THF solutions were used for these experiments. Three samples of each polymer, immersed in phosphate buffer solution (pH 7.4), were placed in a constant shaker bath, maintained at 37 °C. After 1, 3, 5, and 7 weeks, the samples were removed from the buffer solution and dried under vacuum. The dried samples were weighed and then dissolved in THF for molecular weight analysis. A small piece of each sample was set aside for analysis of surface morphology by SEM.

Detection of Hydrolysis Products of Polymers 1−4. Aliquots from the solutions (distilled water and phosphate buffer solution) that contained the polymer samples were analyzed for hydrolysis products. The presence of amino acids and ammonia were detected qualitatively with the use of ninhydrin. A 1.0 M solution of ninhydrin in ethanol was added to the experiment media. Formation of an intense violet coloration within minutes was evidence for the presence of ammonia or amino acid. For the detection of phosphates, aliquots were taken from aqueous media containing the polymer films. Addition of silver nitrate yielded a yellow precipitate of silver phosphate. ^{1}H NMR spectroscopy was used for the detection of alcohols.

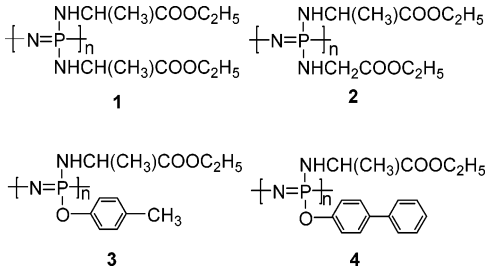


Figure 1. Polymer structures of L-alanine cosubstituted polyphosphazenes. **1**: poly[bis(ethyl alanato)phosphazene]; **2**: poly[(ethyl alanato)$_1$ (ethyl glycinato)$_1$ phosphazene]; **3**: poly[(ethyl alanato)$_1$ (*p*-methyl phenoxy)$_1$ phosphazene]; **4**: poly[(ethyl alanato)$_1$ (*p*-phenylphenoxy)$_1$ phosphazene].

Results and Discussion

Synthesis and Characterization. Synthesis of the polymers was accomplished via a macromolecular substitution route which involved two steps: thermal ring-opening polymerization of hexachlorotriphosphazene at 250 °C to form poly(dichlorophosphazene), followed by sequential substitution of the labile chlorine atoms of poly(dichlorophosphazene) by the sodium salt of the corresponding alcohol or by an ester-protected amino acid. This synthetic route is summarized in Scheme 1. For the synthesis of polymer **1**, an excess of the amino acid ester was used to complete the chlorine substitution. For the mixed substituent polymers, the bulky side group was added first in stoichiometric amounts, and then an excess of the second side group was added. The extent of the substitution was determined by ^{31}P NMR. For polymers **3** and **4** the reaction mixture was refluxed for 2 days to ensure complete chlorine replacement.

The synthesized polymers were characterized by NMR, GPC, and DSC (Table 1). NMR spectroscopy was used to confirm the ratio of the two side groups and the substitution pattern for the mixed substituent polymers. ^{1}H NMR revealed a 1:1 ratio of the cosubstituents for polymers **2**, **3**, and **4**. The ^{31}P NMR spectrum for polymer **2** showed a single peak at −2.4 ppm. Because the two side groups in this polymer are attached to backbone phosphorus through a nitrogen atom, it is difficult to differentiate between geminal (same side group) and nongeminal (different side groups) substitution peaks. Thus, the structure shown in Figure 1 and Scheme 1 is an oversimplification since the repeating units can bear the same side group or two different side groups. Polymers **3** and **4** showed three different peaks in the ^{31}P NMR spectra. The most prominent peak, corresponding to nongeminal substitution, was observed around −7 ppm. For polymer **3**, this peak accounted for 82% of the total substitution and for polymer **4** 76% of the total substitution. Thus, the sequential mode of substitution and the steric hindrance by the aryloxy groups resulted in predominantly nongeminal substitution.

The aryloxy/amino acid ester substituted polymers (**3**, **4**) had a higher molecular weight than the amino acid ester substituted polymers (**1**, **2**). A possible explanation for this could be the occurrence of side reactions. Reactions of amino acid ester units with the chlorine atoms on the phosphazene backbone results in the formation of hydrogen chloride, which normally reacts with excess triethylamine in solution to form a salt. However, the liberated HCl could also attack the phosphazene backbone and result in a decrease in molecular weight. In the case of the amino acid ester phosphazenes, the backbone is completely exposed for this type of side reaction to occur. In the case of aryloxy cosubstituted polymers, the bulky aromatic groups can provide an effective shielding of the phosphazene backbone and thus prevent molecular weight decline.

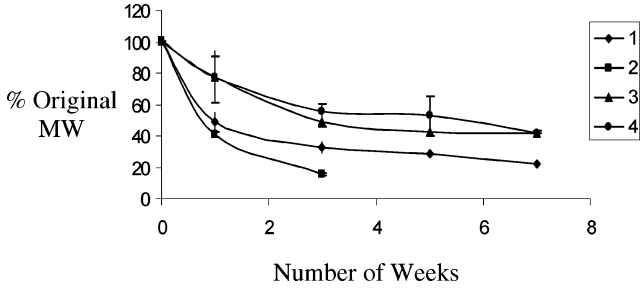


Figure 2. Molecular weight decline for polymers **1**, **2**, **3**, and **4** in PBS solution at 37 °C. Molecular weight for polymer **2** could not be recorded beyond 3 weeks due to rapid hydrolysis.

Polymers **3** and **4** showed an increase in glass transition temperature in comparison to polymer **1**. The cosubstituents in the case of polymer **3** and **4** were *p*-methylphenol and *p*-phenylphenol groups, respectively. Polymer **1** has a T_g of −10 °C which increased to −6 °C for polymer **3** and 35 °C for polymer **4**. The glass transition temperature increased with an increase in the bulkiness of the side group. Bulky side groups restrict the conformational mobility of the phosphazene backbone and thus yield a more rigid polymer. We observed that the biphenyl units were more effective in raising the glass transition temperature of the polymer as compared to single phenyl units. This is attributed to a higher steric bulk and the possibility of $\pi-\pi$ stacking of the biphenyl units.[20]

Hydrolytic Degradation. Hydrolytic degradation of these polymers was studied in phosphate buffer saline at 37 °C by monitoring the molecular weight decline as well as the mass loss over a period of 7 weeks. As shown in Figure 2, all the polymers showed a significant decline in molecular weight. The molecular weight loss decreased in the following order, **2** > **1** > **3**, **4**. This trend can be explained on the basis of the differences in the bulkiness and hydrophobicity of the side groups and also the differences in the initial molecular weight of the polymers. From the literature, it is known that poly[(amino acid ester) phosphazenes] degrade by a random chain scission of the backbone. Several possible mechanisms have been proposed by which this random chain scission can be initiated.[8] In one, water hydrolyzes the ester units of the side groups to form the corresponding polymer-bound amino acid with a deprotected carboxylic acid unit. The phosphorus atoms in the backbone are then susceptible to attack by the carboxylic acid units. In a second mechanism, it has been suggested that water displaces the amino acid esters from the phosphorus atoms to form a hydroxyphosphazene species, which then undergoes chain cleavage to phosphates and ammonia. In both the proposed mechanisms, it is the formation of hydroxyphosphazene species that is responsible for the hydrolytic instability of the polymer. If access to this intermediate is blocked, for example, by hydrophobic or very bulky side groups, then hydrolysis is retarded. For polymer **2**, cosubstitution of alanine ethyl ester units with glycine ethyl ester units reduces the steric shield that can protect the polymer backbone against hydrolytic cleavage and leads to a faster loss in molecular weight. Another factor that might contribute to this fast degradation is the molecular weight of the polymer. Because the initial molecular weight was relatively low, this allowed a greater degree of swelling and thus more water uptake. For polymers **3** and **4**, the bulky aromatic groups increase the overall shielding of the polymer backbone and thus result in a slower molecular weight decline. Also the aromatic groups increase the overall surface hydrophobicity of the polymer (Table 2), which reduces the ingress of water to the phosphazene backbone.

Table 2. Static Water Contact Angle on Polymer Films **1**−**4**

polymer	1	2	3	4
water contact angle	72.92 ± 0.36	62.85 ± 4.89	101.05 ± 0.99	106.50 ± 1.42

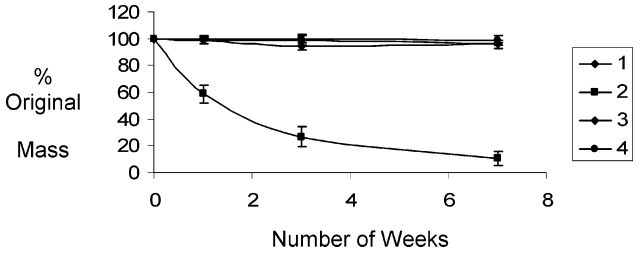


Figure 3. Mass loss recorded for polymers **1**−**4** in PBS solution at 37 °C.

Degradation in PBS solution was also monitored by recording mass loss over a period of 7 weeks. With the exception of polymer **2**, none of the polymers showed a substantial decrease in weight (Figure 3). In the first week itself, polymer **2** lost 40% of its original mass. By week 7, 90% of the original mass was lost. The products of hydrolysis were identified as phosphates, ammonia, amino acid, and the alcohol derived from the ester group on the amino acid unit (Experimental Section). The fast hydrolysis rate of polymer **2** is comparable to depsipeptide, imidazole, or lactic acid ester substituted polyphosphazenes. In contrast, other polymers in the series did not show any significant decrease in mass, with mass loss for these polymers being only 4−5%. This difference in mass loss can be attributed to the differences in the molecular weight and hydrophobicity of the degrading units. For polymers **1**, **3**, and **4**, both the hydrophobicity and molecular weight of the degrading units would be higher than for polymer **2** and thus these films did not record a significant mass loss.

The surface wetting properties of polymers **1**, **2**, **3**, and **4** were examined by static water contact angle measurements (Table 2). Cosubstitution of alanine ethyl ester groups with glycine ethyl ester units increased the surface hydrophilicity and gave a contact angle for polymer **2** of 62.85°. Cosubstitution with aryloxy units increased the surface hydrophobicity, with the highest contact angle recorded for polymer **4** at 106.50°.

The change in surface morphology following hydrolytic degradation was examined by SEM. Figure 4 shows the surfaces of polymers **1** and **2**. Prior to the polymer films being immersed in PBS solution, the surface of the films appeared smooth. After 7 weeks in the medium, the film for polymer **1** showed a rough surface with formation of small pores, indicating surface erosion. Similar results were observed for polymers **3** and **4**. SEM images for polymer **2** showed both small and large pores at 3 weeks, indicating a simultaneous surface and bulk erosion. The degradation of this polymer was rather fast as most of the film material had dissolved by 3 weeks and the surface morphology could not be recorded beyond this time.

Mechanical Properties. Results from tensile testing for polymers **1**, **2**, **3**, and **4** are shown in Figure 5. The modulus of elasticity and tensile strength were similar for polymers **1** and **2**. However, these values increased with the introduction of aryloxy side groups. Polymer **4** showed a 5-fold increase in modulus of elasticity and a 2-fold increase in tensile strength, when compared to polymer **1**. Because the mechanical properties of a polymer depends on factors such as glass transition temperature and molecular weight, the aryloxy cosubstituted polymers showed higher strength. Thus, these results illustrate the positive effect of cosubstitution with bulky aromatic groups

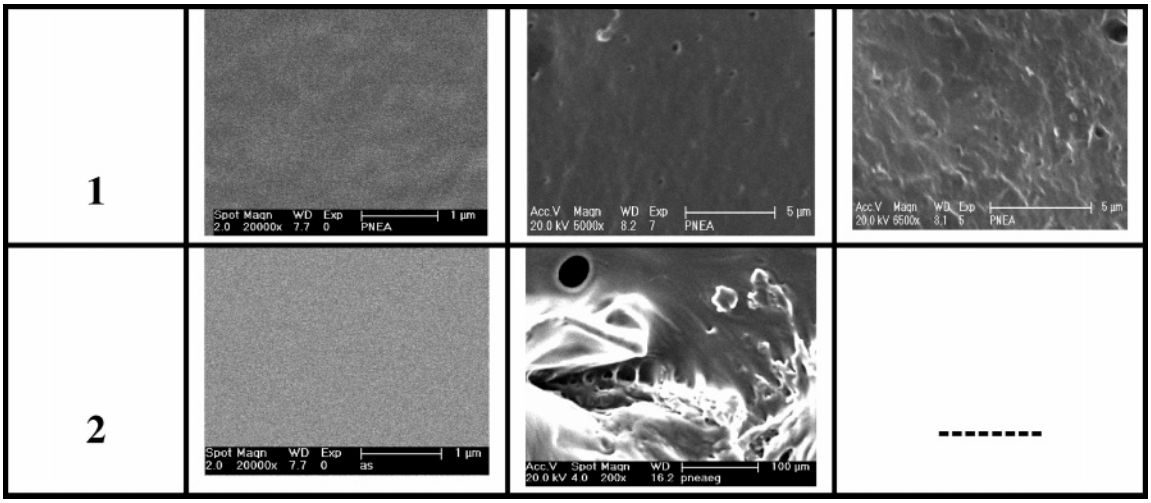


Figure 4. Scanning electron micrographs of polymer films in PBS, at 37 °C.

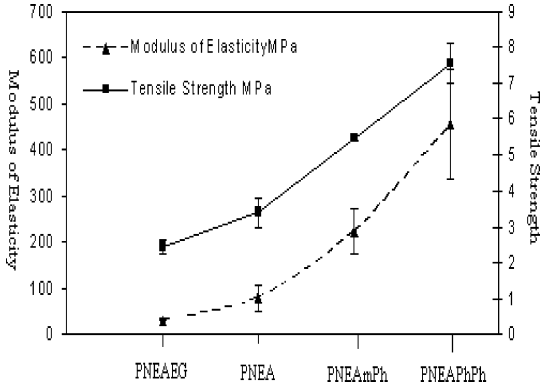


Figure 5. Tensile strength and modulus of elasticity at maximum load for polymers **1** (PNEA), **2** (PNEAEG), **3** (PNEAmPh), and **4** (PNEAPhPh).

on the mechanical properties of poly[(amino acid ester)-phosphazenes].

Conclusions

Polyphosphazenes that contain ethyl alanato side groups together with other amino acid ester or aryloxy side groups can be readily synthesized by the macromolecular substitution route. The types of cosubstituents on the polymers affect properties such as molecular weight, glass transition temperature, and hydrophobicity, which in turn affect properties such as degradation rate and tensile strength. Combination of alanine ethyl ester units with glycine ethyl ester side units leads to a drastic increase in the hydrolysis rate and also increases the surface hydrophilicity. Combinations of alanine ethyl ester side group with bulky aromatic groups lead to polymers with higher molecular weights. These polymers show a substantial increase in glass transition temperature, hydrophobicity, and tensile properties. The properties can be tuned further by changes in the ratios of the two side groups.

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