Hydrogen Bonding in Blends of Polyesters with Dipeptide-Containing Polyphosphazenes

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ABSTRACT: New biomedically erodible polymer composites were investigated. Polyphosphazenes containing the dipeptide side groups alanyl–glycine ethyl ester, valinyl–glycine ethyl ester, and phenylalanyl–glycine ethyl ester were blended with poly(lactide-*co*-glycolide) (PLGA) with lactic to glycolic acid ratios of 50 : 50 [PLGA (50 : 50)] and 85 : 15 [PLGA (85 : 15)] with solution-phase techniques. Each dipeptide ethyl ester side group contains two N—H protons that are capable of hydrogen bonding with the carbonyl functions of PLGA. Polyphosphazenes that contain only the dipeptide ethyl ester groups are insoluble in organic solvents and are thus unsuitable for solution-phase composite formation. To ensure solubility during and after synthesis, cosubstituted polymers with both dipeptide ethyl ester and glycine or alanine ethyl ester side groups were used. Solution casting or electrospinning was used to fabricate polymer blend matrices with different ratios of polyphosphazene to polyester, and their miscibilities were estimated with differential scanning calorimetry and scanning electron microscopy techniques. Polyphosphazenes with alanyl–glycine ethyl ester side groups plus the second cosubstituent were completely miscible with PLGA (50 : 50) and PLGA (85 : 15) when processed via solution-casting techniques. This suggests that the hydrogen-bonding protons in alanyl–glycine ethyl ester have access to the oxygen atoms of the carbonyl units in PLGA. However, when the same pair of polymers was electrospun from solution, the polymers proved to be immiscible. Solution-cast miscible polymer blends were obtained from PLGA (50 : 50) plus the polyphosphazene that was cosubstituted with valinyl–glycine ethyl ester and glycine ethyl ester side groups. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 115: 431–437, 2010

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INTRODUCTION

An important technical challenge is to design and synthesize new biomedical materials that have specific combinations of chemical and biological properties.[1–3] Synthetic polymers have been employed for biomedical applications that range from bioerodible sutures[4] to tissue engineering scaffolds.[5] The target application determines the properties needed. A primary concern is that, for many applications, no single polymer system provides all the required properties. To address this problem, many researchers have employed advanced techniques to synthesize complex polymer architectures (i.e., multiple block copolymers, star polymers, and comb polymers) that possess an array of properties.[6–8] However, the sophisticated synthetic procedures that are required often limit the general availability of such materials.

Useful combinations of properties can sometimes be obtained by the physical blending of two or more different polymers to produce a homogeneous alloy.[9–11] However, the miscibility of a polymer blend is complicated because of the unfavorable thermodynamics that exist when two high-molecular-weight polymers are combined. Therefore, strong molecular interactions between the polymer chains are needed to allow the fabrication of miscible polymer blends.[12–14] The most common type of interaction involves hydrogen bonding.[15,16]

Polyphosphazenes are hybrid inorganic–organic polymer systems with a high degree of tailorability through the use of macromolecular substitution reactions to link various side groups to the polymer backbone. This has allowed the synthesis of several hundred different polyphosphazenes with widely different properties.[17] Polyphosphazenes that bear amino acid ester units covalently linked to the backbone through the amino terminus can be

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hydrolytically sensitive and appropriate for bioerosion to nontoxic products. The hydrolysis rate generally depends on the hydrophobicity and steric characteristics of the units located at the α carbon of the amino acid residues.[18,19] Amino acid ester units also possess a hydrogen-bonding proton at the N terminus. This is available for interactions with other polymers in polymer blends. The hydrogen-bonding capabilities have been used in a previous study of blends of polyphosphazenes with poly(lactide-*co*-glycolide) (PLGA).[20] In that work, it was found that miscible blends can be formed between polyphosphazenes that contain glycine ethyl ester side groups plus PLGA with a lactic to glycolic acid ratio of 50 : 50 [PLGA (50 : 50)]. Alanine ethyl ester phosphazene polymers also form miscible blends with PLGA (50 : 50). However, the steric hindrance of the methyl group at the alanine α carbon places some restrictions on the formation of hydrogen bonding with PLGA.[21] Moreover, when valine or phenylalanine ethyl esters were linked to the polyphosphazene backbone, no miscibility with PLGA was detected, probably because of the steric hindrance by the substituent at the α carbon that shields the N—H function and prevents that proton from engaging in hydrogen bonding. Polyphosphazenes with glycyl–glycine ethyl ester side groups have shown good miscibility with PLGA (50 : 50) and with PLGA with a lactic to glycolic acid ratio of 85 : 15 [PLGA (85 : 15)]. However, the hydrolysis of this system is too rapid for use in hard tissue engineering applications.[21] Moreover, the high percentage of lactide in PLGA (85 : 15) limits its miscibility with other polyphosphazenes, especially when insufficient opportunities exist for hydrogen bonding.

In an earlier article,[22] we described the synthesis of polyphosphazenes that have side groups derived from the dipeptides alanyl–glycine ethyl ester, valinyl–glycine ethyl ester, and phenylalanyl–glycine ethyl ester. The use of these dipeptide ethyl esters was driven by the need to slow the hydrolysis rate by the inclusion of amino acid substituents with more hydrophobicity and shielding at the α carbon than in glycine. This design also offers a second site per side chain for hydrogen bonding between the polyphosphazene and polymers that contain carbonyl groups. Polyphosphazenes that bear only dipeptide ethyl ester side groups are difficult to synthesize because of their insolubility, but polymers with both dipeptide ethyl ester and glycine or alanine ethyl ester cosubstituents are accessible. The presence of two types of side groups in the polymer and the ability to vary the ratios allow control of the hydrolysis rate, and this should also affect hydrogen bonding with other bioerodible polymer systems such as PLGA. In this work, these mixed-substituent polyphosphazenes were blended with PLGA (50 : 50) and PLGA (85 : 15) via solution-casting techniques and electrospinning. The blends were studied with differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). The materials were also analyzed with attenuated total reflectance infrared (ATRIR) techniques to detect hydrogen bonding between the component polymers.

EXPERIMENTAL

Reagents and equipment

All polyphosphazene synthesis reactions were carried out with the reactants under a dry argon atmosphere with standard Schlenk line techniques. Tetrahydrofuran (THF) and triethylamine (both from EMD, Gibbstown, NJ) were dried with solvent purification columns.[23] Chloroform (EMD), isobutyl chloroformate (Aldrich), PLGA (50 : 50) (Ethicon Division of Johnson and Johnson, Somerville, NJ; weight-average molecular weight = 2,000,000), PLGA (85 : 15) (Ethicon Division of Johnson and Johnson; weight-average molecular weight = 4,800,000), Boc-phenylalanine, Boc-valine, and Boc-alanine (all from Aroz Technologies, Cincinnati, OH), alanine ethyl ester hydrochloride (Chem Impex, Wood Dale, IL), and glycine ethyl ester hydrochloride (Alfa Aesar, Ward Hill, MA) were used as received. The dipeptide ethyl esters were synthesized with previously reported techniques.[24,25] Poly(dichlorophosphazene) was prepared by the thermal ring-opening polymerization of recrystallized and sublimed hexachlorocyclotriphosphazene (Fushimi Chemical Co., Marugame, Japan) in evacuated Pyrex tubes at 250°C.[26] ^{31}P- and ^{1}H-NMR spectra were obtained with a Bruker (Billerica, MA) 360 WM instrument operated at 145 and 360 MHz, respectively. Glass-transition temperatures (T_g's) were measured under a nitrogen atmosphere with a TA Instruments (Nwe Castle, DE) Q10 DSC apparatus with a heating rate of 10°C/min and a sample size of about 10 mg. Gel permeation chromatograms were obtained with a Hewlett–Packard (Santa Clara, CA) HP 1100 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 m*M* solution of tetra-*n*-butylammonium nitrate in THF. The elution times were calibrated with polystyrene standards. SEM was obtained with a Philips (Hillsbora, OR) FEI Quanta 200 environmental scanning electron microscope with an Oxford Inca energy-dispersive X-ray spectroscopy (EDS) apparatus. SEM samples were prepared by the placement of a polymer sample onto carbon tape followed by its insertion into the SEM equipment, and a low-vacuum mode was used for

TABLE I
Electrostatic Fiber Spinning Concentrations (%) and Voltages (kV) for Combinations of Polymers 1–7 with PLGA

Polymer	PLGA (50 : 50)	PLGA (85 : 15)
1	15%, 18.5 kV	8%, 11 kV
2	15%, 15 kV	8%, 18 kV
3	15%, 18.5 kV	8%, 17 kV
4	15%, 17 kV	8%, 17 kV
5	15%, 17 kV	8%, 18 kV
6	15%, 17 kV	10%, 16.5 kV
7	15%, 17 kV	10%, 18 kV

imaging. Images were obtained under the following conditions: a source voltage of 20 keV, a pressure of approximately 0.88 Torr, and a working distance of approximately 10 mm. ATRIR scans of the films were analyzed with a Digilab (Randolph, MA) FTS 7000 spectrometer with a zinc selenide ATR crystal with 32 scans per sample.

Synthesis of polymers 1–7

Polymers **1–7** were synthesized according to a protocol described elsewhere.[22] The synthesis of polymer **2** is described here as a general illustration. Poly(dichlorophosphazene) (2.00 g, 17.3 mmol) was dissolved in 200 mL of THF. Alanyl–glycine ethyl ester hydrochloride (3.90 g, 17.3 mmol) was suspended in 150 mL of THF, and triethylamine (7.23 mL, 51.9 mmol) was added. This suspension was refluxed at 70°C for 24 h and then filtered and added to the polymer solution. Glycine ethyl ester hydrochloride (7.25 g, 51.9 mmol) was suspended in 150 mL of THF, and triethylamine (24.1 mL, 173 mmol) was added. This suspension was refluxed at 70°C for 24 h, then filtered to remove triethylamine hydrochloride, and finally added dropwise to the polymer solution. This solution was stirred at room temperature for 24 h and refluxed for 48 h. The solvent was removed under reduced pressure to yield a yellow solid. The polymer was purified by dialysis (molecular weight cutoff = 12,000–14,000) versus methanol for 3 days. The yields of the polymers were typically in the range of 70–80% with respect to the amounts of poly(dichlorophosphazene) used.

Fabrication of polymer blends via solution casting

Three blend compositions were fabricated for each polyphosphazene/polyester system. The compositions contained 25, 50, or 75 wt % polyphosphazene with respect to the organic polymer. The organic polymers consisted of PLGA (50 : 50) or PLGA (85 : 15). Each pair of component polymers (0.1 g) was individually dissolved in 1 mL of chloroform. The polyphosphazene solution (0.1 g/1 mL) was added to the organic polymer solution (0.1 g/1 mL), and the mixture was stirred for 1 h. The combined solution of the two polymers was allowed to stand undisturbed for 1 h to confirm that solution-phase miscibility existed. The solutions were then poured into film-casting trays, air-dried for 24 h, and vacuum-dried for 1 week. Each polymer blend was cast as a single replicate film that was analyzed with DSC (4–10 cycles until a stable profile was obtained) and SEM techniques.

Fabrication of polymer fiber blends via electrospinning

Blends of three weight compositions were fabricated for each polyphosphazene/polyester system. The compositions contained 25, 50, or 75 wt % polyphosphazene with respect to the organic polymers. The two polymers were dissolved simultaneously at the appropriate concentrations (Table I). One milliliter of a sample was spun in each experiment. A standard spinning distance of 20 cm and a flow rate of 1 mL/h were used for each sample. After the electrospinning process was complete, the single replicate fibers were removed from the aluminum foil collector screen and were analyzed with DSC and SEM techniques.

RESULTS AND DISCUSSION

Synthesis of polymers 1–7

The synthesis of these polymers has been described elsewhere.[22] These syntheses involve a macromolecular substitution route with the generation of a cosubstituent distribution indicated for polymers **2–7**. The only dipeptide that could be used as the sole substituent in the polyphosphazene was alanyl–glycine ethyl ester, which was used to produce polymer **1**. Polymers **2–7** contained cosubstituent side groups (glycine ethyl ester or alanine ethyl ester). The structures of polymers **1–7** are shown in Figure 1. The characterization and physical properties of polymers **1–7** are described elsewhere.[22] It should be noted that the chain mobility (as defined by T_g) becomes more restricted as the dimensions of the side groups increase. The amino acid esters impart hydrolytic

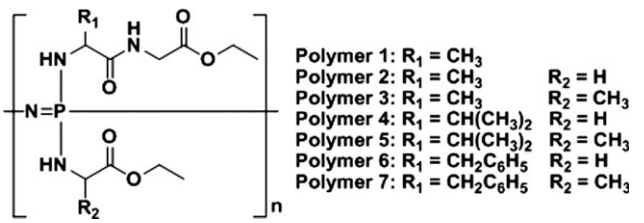

Figure 1 Molecular structures of polymers **1–7**.

TABLE II
DSC Analysis of the Polymer Blends

Blend	Polymer						
	1	**2**	**3**	**4**	**5**	**6**	**7**
A	Yes (28°C)	Yes (25°C)	Yes (17°C)	Yes (20°C)	Partial	No	No
B	Partial	Yes (34°C)	Yes (27°C)	Yes (25°C)	Partial	No	No
C	Partial	Yes (40°C)	Yes (30°C)	Partial	Partial	No	No
D	Yes (28°C)	Yes (27°C)	No	No	No	No	No
E	Partial	Yes (35°C)	No	No	No	No	No
F	Partial	Yes (39°C)	No	No	No	No	No

Blends A–C were blends of polymers **1–7** with PLGA (50 : 50). Blends D–F were blends of polymers **1–7** with PLGA (85 : 15). Blends A and D contained 25% polyphosphazene, blends B and E contained 50% polyphosphazene, and blends C and F contained 75% polyphosphazene.

sensitivity to the polyphosphazenes, whereas the dipeptide ethyl esters provide an additional hydrogen-bonding proton from the amide function.

The choice of dipeptide side groups was based on the need to reduce the hydrolytic sensitivity of the polymer through protection of the polyphosphazene backbone by means of the hydrophobic and steric character of R_1. When R_1 is hydrogen, the polyphosphazene hydrolyzes rapidly. An increase in the steric bulk of R_1 from hydrogen to methyl, isopropyl, or benzyl reduces the hydrolysis rate. However, the increased steric bulk associated with R_1 also limits the ability of a hydrogen atom at the free N terminus to undergo hydrogen bonding with the carbonyl groups of PLGA. The glycine ethyl ester component of the dipeptide was chosen for its ability to undergo hydrogen bonding with these polyesters and in principle allow the two different types of polymers to be miscible. The presence of alanine ethyl ester as a proximal side group could affect the blend miscibilities because the amino proton is more sterically shielded with respect to interactions with the organic polymer.

Solution-cast blends of polymers 1–7 with PLGA

Polymers **1–7** were codissolved with PLGA (50 : 50) or PLGA (85 : 15) in chloroform, and films were cast by solvent evaporation. Each film was then dried for 1 week *in vacuo* to ensure the removal of all the solvent. The microscale blend miscibility of the films was examined with DSC and SEM techniques. The DSC results indicated that polymers **1–4** were miscible with PLGA (50 : 50). However, only polymers **1** and **2** were miscible with PLGA (85 : 15). Miscible blends were recognized by a single T_g detected for the blended matrix. The miscibility results for all the fabricated blends are shown in Table II. SEM images of polymers **1–7** blended with PLGA showed no ordered domains within the films.

Polymer **1** was miscible with both PLGA (50 : 50) and PLGA (85 : 15) in compositions of 25% polyphosphazene **1** and 75% PLGA, with transitions detected at 28°C for both PLGA compositions. All the other combinations of polymer **1** with PLGA produced partially miscible materials, with three glass transitions detected for each combination: two of the transitions represented the parent polymers, and one transition that occurred between the parent transitions represented the partially miscible blend. Polymer **2** was miscible with PLGA (50 : 50) and PLGA (85 : 15), regardless of the blend composition. Representative DSC traces of polymer **2**/PLGA are shown in Figure 2. Single thermal transitions (indicating compatible blends) were detected for blends with 25, 50, or 75% polymer **2** at 25, 34, and 40°C, respectively, and PLGA (50 : 50). Single thermal transitions were also found for the same compositions of polymer **2** and PLGA (85 : 15) at 27, 35, and 39°C, respectively.

Polymer **3** was also miscible with PLGA (50 : 50) in all blend compositions, with single thermal transitions detected for each combination at 17, 27, and 30°C. However, when polymer **3** was blended with PLGA (85 : 15), immiscibility was detected by DSC

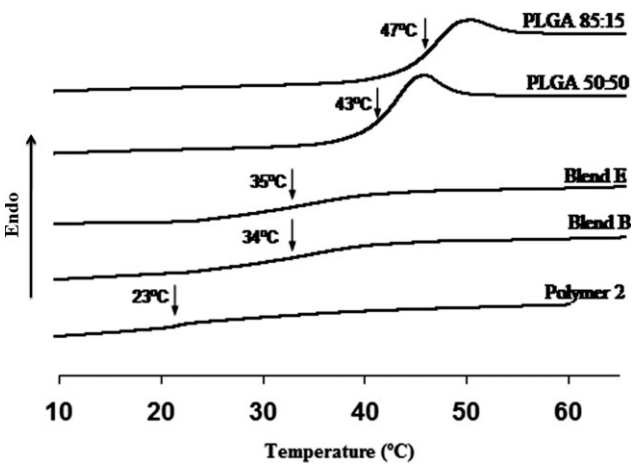

Figure 2 DSC traces for polymer **2**, PLGA (50 : 50), PLGA (85 : 15), blend B [50% polymer **2** and 50% PLGA (50 : 50)], and blend E [50% polymer **2** and 50% PLGA (85 : 15)]. The arrows represent the locations of the measured T_g values.

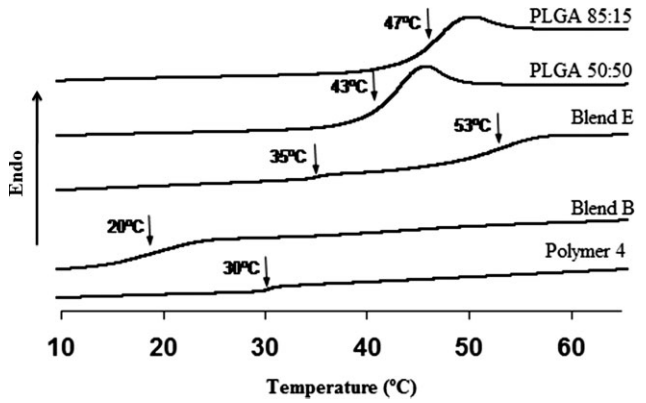

Figure 3 DSC traces for polymer **4**, PLGA, blend B [50% polymer **4** and 50% PLGA (50 : 50)], and blend E [50% polymer **4** and 50% PLGA (85 : 15)]. The arrows represent the measured T_g values.

techniques because transitions from the two parent polymers were found at 25°C for polymer **3** and at 50°C for PLGA (85 : 15). The crystalline melting temperature for PLGA (85 : 15) was also detected at 55°C. This was presumably a result of a complete loss of miscibility between the polymers. The crystalline regions normally present in the PLGA domains were not detected in the miscible or partially miscible blends.

Polymer **4** showed similar behavior. It was miscible with PLGA (50 : 50) but immiscible with PLGA (85 : 15), as illustrated in Figure 3. When blended with PLGA (50 : 50), single thermal transitions were found at 20°C for the 25% composition of polymer **4** with PLGA (50 : 50) and at 20°C for the 50% composition. A 75% ratio of polymer **4** to PLGA (50 : 50) yielded only partial miscibility on the basis of thermal analysis, but two transitions were detected at 27 and 37°C. However, there was no evidence of a crystalline melting transition. When polymer **4** was blended with PLGA (85 : 15), the crystalline melting transition was detected as well as the transitions for the parent polymers.

Blends of polymer **5** with PLGA (50 : 50) were only partially miscible because three thermal transitions were present. Blends of polymer **5** and PLGA (85 : 15) were immiscible because the transitions for the parent polymers were found together with the crystalline melting transition of PLGA. Blend immiscibility was also detected for polymers **6** and **7** when they were combined with either PLGA (50 : 50) or PLGA (85 : 15).

PLGA (50 : 50) has fewer lactide units in the polymer chain than PLGA (85 : 15), and this may allow better interactions between the polyphosphazene side groups and the PLGA chains. Reduced steric hindrance within the side groups allows hydrogen bonding to be more accessible, thus creating better blend miscibility, as was the case for PLGA (50 : 50) with polymers **1**–**4**. The dipeptide side group on the polyphosphazene chain has a similar influence on the formation of miscible blends. Polyphosphazenes with alanyl–glycine ethyl ester side groups (polymers **2** and **3**) were miscible with PLGA (50 : 50), regardless of the composition of the blended film. However, only polymers **1** and **2** were miscible with PLGA (85 : 15). This suggests that steric hindrance inhibited the interaction between polymer **3** and PLGA (85 : 15), preventing hydrogen bonding between the polyphosphazene side chains and the PLGA backbone. This is supported by ATRIR data for the blends indicating a strong carbonyl hydrogen-bonding interaction from the absorption at 1735 cm^{-1}.[27] All the immiscible materials lacked this vibrational band. Nonsterically hindered polyphosphazene amino side groups are needed to maximize the hydrogen-bonding interactions as the steric hindrance within the PLGA backbone increases (as the monomer ratio changes). For example, the use of alanine ethyl ester in polymer **3** limits the ability of the amino proton at the alanine side group to interact with the carbonyl groups in PLGA (85 : 15). Therefore, only partially miscible blends can be fabricated by solution-casting techniques.

A similar trend is found for polymers **4** and **5**. Polymer **4** interacts with PLGA (50 : 50) to form a miscible blend, whereas polymer **5** does not. The more sterically hindered the dipeptide becomes, the less steric hindrance can be tolerated on the amino acid if blend miscibility is to be retained with PLGA. This suggests that the glycine ethyl ester side groups in polymer **4** favor the interactions that lead to miscibility, whereas the alanine ethyl ester side group hinders such interactions and therefore allows only partial miscibility. The steric hindrance of the dipeptide unit also limits the hydrogen bonding between the polyphosphazene and the PLGA backbone. The isopropyl side chain at the α-carbon position of valine also minimizes the ability of the amine proton to interact with the PLGA (50 : 50) backbone. The steric hindrance is too great to allow polymer blends between PLGA (85 : 15) and polymer **4** or **5**. Polymers **6** and **7** suffer from so much hindrance from

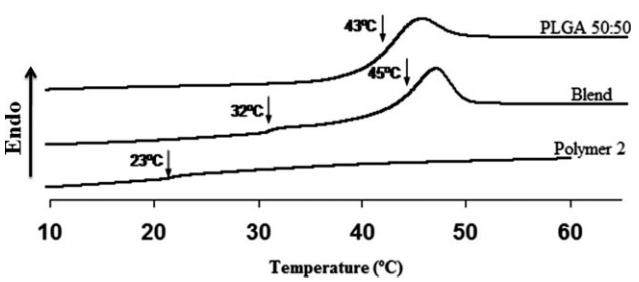

Figure 4 DSC traces of polymer **2**, PLGA (50 : 50), and a 1 : 1 blend of these two polymers after electrostatic spinning. The arrows represent the measured T_g values.

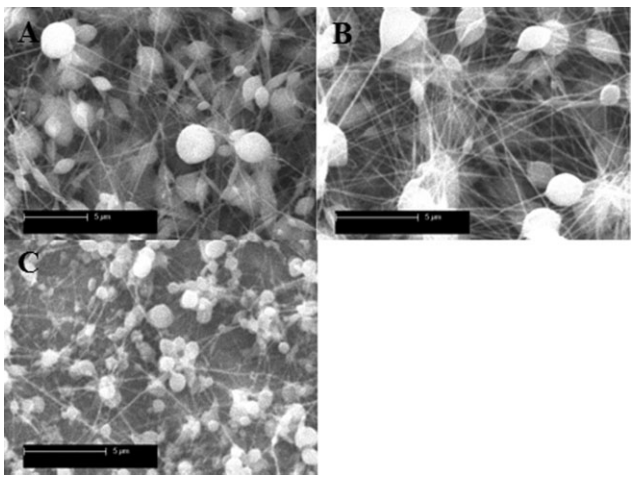

Figure 5 SEM images of electrostatically spun blends of polymer **2** and PLGA (50 : 50) with polymer **2** concentrations of (A) 25, (B) 50, and (C) 75%.

the dipeptide side group that only minimal interaction occurs between the polyphosphazene and PLGA, and this causes the blends to be completely immiscible.

Electrostatic spinning of blends of polymers 1–7 and PLGA (50 : 50) or PLGA (85 : 15)

The parent polymers were individually dissolved in 1 mL of chloroform and then combined in a 1 : 1 mixture. No solution phase separation was detected at this stage. The blend compositions had 25, 50, or 75% concentrations of polymers **1–7** with respect to the weight of PLGA. These solutions were then electrostatically spun onto an aluminum collector. The fibers were studied with SEM and EDS techniques, and the blend miscibilities were determined by thermal analysis (DSC). No miscible blends could be produced via this processing technique.

Thus, although solution-cast films of polymer **2** showed complete miscibility with PLGA, similar solutions converted into nanofibers via electrostatic spinning underwent phase separation. DSC analysis of a 1 : 1 fiber mixture of polymer **2** with PLGA (50 : 50), as shown in Figure 4, revealed two thermal transitions; the first at 32°C (representative of polymer **2**) and the second at 45°C [typical of PLGA (50 : 50)]. The crystalline melting transition of PLGA (50 : 50) at 50°C was also present. Figure 5 shows an SEM analysis that indicates a bead/fiber morphology, with the fibers probably containing the PLGA component and the beads containing polymer **2** on the basis of EDS analysis. Immiscibility existed for all nanofiber mixtures of polymers **1–7** with PLGA, and SEM micrographs displayed the same bead/fiber morphology. Thus, immiscibility in the nanofiber system occurred independently of the composition of PLGA.

There are two explanations for the phase separation. First, although the solution-cast blends might allow microscale miscibility, the diameters of the nanofibers formed by electrospinning may be too small to allow miscibility at the lower micro- or nanoscale. The nanofibers had diameters of less than 700 nm and the beads had diameters of 1–3 μm. The second explanation could be connected to the electrospinning process. The electrostatic potential of the polymers might be different, and this could favor separation of the polymers in solution just before spinning. This would cause the fibers and beads to extrude as separate polymer domains.

CONCLUSIONS

Polyphosphazenes with dipeptide ethyl ester side groups (polymers **1–4**) formed compatible blends with PLGA (50 : 50). Microscale miscibility was also achieved between polymer **1** or **2** and PLGA (85 : 15). However, electrostatic spinning of the binary systems with PLGA yielded immiscible blends, probably because of the submicrometer-scale features of the electrospun fibers. We conclude that the behavior of the polyphosphazene with PLGA is dominated by steric hindrance at the R_1 position on both the dipeptide and amino acid side groups along the polyphosphazene backbone. Thus, the more sterically hindered the dipeptide becomes, the less steric hindrance can be tolerated on the amino acid if blend miscibility with PLGA is to be retained.

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