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*Research Article*

# Synthesis and Characterization of Polyphosphazenes Modified with Hydroxyethyl Methacrylate and Lactic Acid

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Poly(dichlorophosphazene) was prepared by melt ring-opening polymerization of the hexachlorocyclotriphosphazene. Poly[bis(2-hydroxyethyl-methacrylate)-phosphazene] and poly[(2-hydroxyethyl-methacrylate)-graft-poly(lactic-acid)-phosphazene] were obtained by nucleophilic condensation reactions at different concentrations of the substituents. The properties of the synthesized copolymers were assessed by FTIR, $^{1}$H-NMR and $^{31}$P-NMR, thermal analysis (DSC-TGA), and electron microscopy (SEM). The copolymers have a block structure and show two $T_g$'s below room temperature. They are stable up to a temperature of 100°C. The type of the substituents attached to the PZ backbone determines the morphology of the polymers.

## 1. Introduction

Polyesters, polyorthoesters, polyanhydrides, poly(R-amino acids), and polyphosphazenes are degradable polymers that have been investigated for a variety of biomedical applications such as sutures, drug delivery systems, and scaffolds for tissue engineering [1]. Useful properties can be obtained by blending two different polymers. However, compatible polymer blends require strong molecular interactions between polymer chains [2]. Poly(organophosphazenes) offer an appealing platform for the design and synthesis of novel biodegradable polymers as well as critical advantages for the design of biologically functional macromolecules with a broad structural diversity [3], high functional density, and tailored biodegradability [4]. These polymers are of scientific and technological concern since the first work of synthesis reported by Allcock et al. [5, 6]. Polyphosphazenes (PZs) posses special characteristics, including flame-retardant properties, high resistance to oil and solvents, and feasibility for tailored properties according to the choice of organic, inorganic, or organometallic side groups [7]. As biomaterials they have inherent advantages, due to their biocompatibility and fast degradation rate. In addition, degradation residues, phosphate, ammonia, and side groups are either nontoxic when they are present in small quantities or are easily metabolized by the human body [8, 9]. Polyphosphazenes are hybrid polymers with a flexible inorganic backbone of alternating phosphorus and nitrogen atoms and organic side groups. Their composition vary from 3 to 10,000 (–N=P–) repetitive units having two substituents (–R) attached to the phosphorus atom [7]. Polyphosphazenes are synthesized by reactions with alkoxides, aryloxides, or amines from a highly reactive macromolecular intermediate, poly(dichlorophosphazene), which is prepared by thermal ring opening polymerization

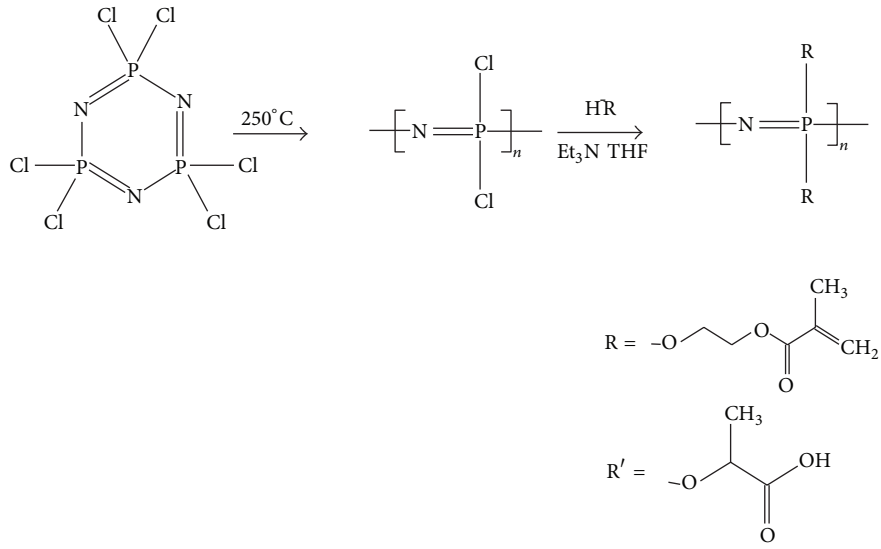



Figure 1: Synthesis by substitution of poly(organophosphazenes).

of hexachlorocyclotriphosphazene (HCCP) at 250°C. The chlorine atoms can be further replaced via nucleophilic substitution, using amino acid ester, imidazolyl, glyceryl, or glycosyl side groups that are also hydrolytically sensitive [5]. The flexible inorganic backbone of the poly(phosphazene) structure plays an important role in tissue regeneration. It can be modified with ester, anhydride, and unsaturated groups to improve chemical stability and mechanical properties. Cosubstituted poly(organophosphazenes) with unsaturated side groups are used to prepare interpenetrating polymer networks with acrylonitrile, styrene, acrylic acid, and methyl methacrylate, using sequential interpenetrating methods. Such polyphosphazenes can be readily crosslinked either by exposure to heat or to ultraviolet light [10]. In this work, poly[(2-hydroxyethyl methacrylate)-graft-poly(lactic acid)-phosphazene] and poly[bis(2-hydroxyethyl-methacrylate)-phosphazene] were synthesized by condensation polymerization reactions. The 2-hydroxyethyl methacrylate (HEMA) was selected to improve biocompatibility and bifunctionality. HEMA was firstly attached to the side chain along with glycine-ethyl ester to form a precursor with the unsaturated substituents. HEMA is used for prosthesis, teeth, and bones reconstructive materials, and it is frequently mixed with acrylic polymers, like bisphenol-A-glycidyl-dimethacrylate (Bis-GMA), in photopolymerizable dental resins. HEMA is intended to infiltrate the demineralised dentin and prevent collagen collapse [11]. HEMA melts at about –12°C. The lactic acid, LA, was selected because it is a biocompatible and biodegradable material with good mechanical properties and is neither nontoxic nor cancerogenous to the human body [5, 12]. The poly(lactic acid) (PLA) chemistry involves the processing and polymerization of lactic acid monomer. Lactic acid ($HOCH_3CHCOOH$) is a simple chiral molecule which exists as two enantiomers, L- and D-lactic acid. The polymer is relatively hard, with a glass transition temperature between 60°C and 70°C and a melting point between 170 and 180°C.

## 2. Experimental

*2.1. Materials and Methods.* Hexane (MERK), n-heptane (Aldrich), tetrahydrofuran (THF-Aldrich), and triethylamine (TEA-Aldrich) were distilled from $CaH_2$ and drying with $MgSO_4$. HEMA (Aldrich) and acid lactic (Purac H588) were distilled just before use. HCCP (Aldrich) was purified by two times sublimation (30°C/0.1 mmHg). The melting point of the purified HCCP was 113-114°C.

ATR infrared spectra were obtained in a Thermo Nicolet Avatar 360 FTIR Spectrometer (Thermo Scientific, USA). The $^1H$ (400 MHz) and $^{31}P$ (161.9 MHz) Nuclear Magnetic Resonance (NMR) spectra were recorded in the Fourier transform mode with $CDCl_3$ as solvent (Bruker Avance NMR 400, USA). Chemical shifts were relative to tetramethylsilane at $\delta = 0$ ppm for protons and carbons. The phosphorus chemical shifts were relative to external 85% $H_3PO_4$ at $\delta = 0$ ppm. The glass transition temperatures ($T_g$) were measured by differential scanning calorimetry (DSC) at a heating rate of 10°C/min from –100 to 150°C under dry nitrogen atmosphere (MDSC 2910 TA Instruments, USA). The thermogravimetric analysis (TGA) were measured in the range of 25–600°C at a heating rate of 10°C $min^{-1}$ using dry nitrogen as purge gas (SDT Q600 TA Instruments, USA). Finally, the morphology of the copolymers were characterized by Scanning Electron Microscopy at an acceleration voltage of 20 kV (JSM5900-LV SEM, JEOL, USA).

*2.2. Syntheses of Polymers.* The scheme of the poly(organophosphazenes) synthesis by nucleophilic substitution is shown in Figure 1. The single substituted and cosubstituted PZs were obtained from poly(dichlorophosphazene) as described below. The poly(dichlorophosphazene) (PZ) was obtained by melt ring-opening polymerization of hexachlorocyclotriphosphazene (HCCP) under vacuum at 250°C for 3 h. After this time, the polymer was dissolved at room

temperature in anhydrous THF, and it was separated by precipitation into n-heptane. Its characteristics were 98% yield; characteristic IR bands were 1215 and 748 $cm^{-1}$ (linear phosphazene); $^{31}$P-NMR peak at −16.1 ($\delta$ = ppm relative to 85% of $H_3PO_4$ at 0 ppm).

The substitution of poly(dichlorophosphazene) (PZ) with HEMA was made at two molar relations: 1 : 3 and 1 : 6 mmol PZ-HEMA. Triethylamine (TEA) was added at 1 : 1 mmol relation HEMA : TEA as effective acceptor to trap hydrogen chloride. The PZ was dissolved in THF (10 mL) under stirring, after 10 min HEMA and TEA were added and the glass vial reactor was kept for two days at room temperature. The product was purified following the procedure described for PZ; the yield was 51%. The phosphazene backbone characteristic IR bands ($cm^{-1}$) were 2947 ($CH_2$), 1720 (C=O), 1635 (C=C), 1473 (CO–O), 1033 (P–O–C), 1168 (phosphazene backbone C–O), and the $^{31}$P-NMR peaks: 1.5 ($\delta$ = ppm); $^1$H-$NMR_{HEMA}$ [13] at 6.0 (1H), 5.4 (1H), 4.3 (2H), 2.0 (3H), and 1.7 (2H) ($\delta$ = ppm).

The substitution reactions of PZ with HEMA and LA were carried out in a similar way. The PZ : HEMA : LA molar relation was 1 : 3 : 3 mmol, and for HEMA-TEA the relation was 1 : 1 mmol. The product was purified following the procedure described for PZ; obtaining a 50% yield [14]. The typical IR bands ($cm^{-1}$) were 3452 (polymeric –OH), 2947 ($CH_2$), 1745 and 1724 (C=O), 1635 (C=C), 1477 and 1150 (CO–O), 1037 (P–O–C), and 1172 (phosphazene backbone) and the $^{31}$P-NMR peaks 1.5 and 0.6 ($\delta$ = ppm); $^1$H-$NMR_{HEMA}$, 6.0 (1H), 5.4 (1H), 4.3 (3H), 2.0 (2H), and 1.7 (2H) ($\delta$ = ppm), as well as $^1$H-$NMR_{LA}$ peaks: 1.3 (3H), 3.5 (1H), and 11.5 (1H) ($\delta$ = ppm).

## 3. Results and Discussion

In the Figure 2(a) we show the IR spectra of PZ-HEMA-1: 3; PZ-HEMA-1: 6, PZ-HEMA-PLA and the Figure 2(b) present de comparative groups (zoom) between the blank and substituent copolymers. The band at 1170 $cm^{-1}$ corresponds to the phosphazene backbone. The substitution of the chlorine on PZ chain (Figure 2(b)) by the two components is observed by the elimination or reduction of peak in 748 $cm^{-1}$, also by the presence of a band at 1035 $cm^{-1}$corresponding to the interaction P–O–C.

With the formation of a new band at 1720 $cm^{-1}$ for PZ-HEMA and the evidence of two shifts of similar intensities at 1724 and 1745 $cm^{-1}$ for PZ-HEMA-LA, the carbonyl groups of the monomers could be confirmed within the copolymer due the substitution of the chlorines.

Additionally, the new bond P–O–C could be confirmed too with the absence of the band of the OH at 3516 $cm^{-1}$ and the presence of the double bonds bands in 1635 $cm^{-1}$ for the HEMA (Figure 2(a)). In the case of lactic acid, the OH band decreases for primary alcohol, but remain present for the polymeric OH in 3452 $cm^{-1}$, an indication that we conservated the OH of lactic acid in the copolymer.

The stepwise substitution reactions of PZ were monitored by $^{31}$P-NMR spectroscopy (Figure 3). The PZ spectrum shows a peak at −16.1 ppm corresponding to low molecular

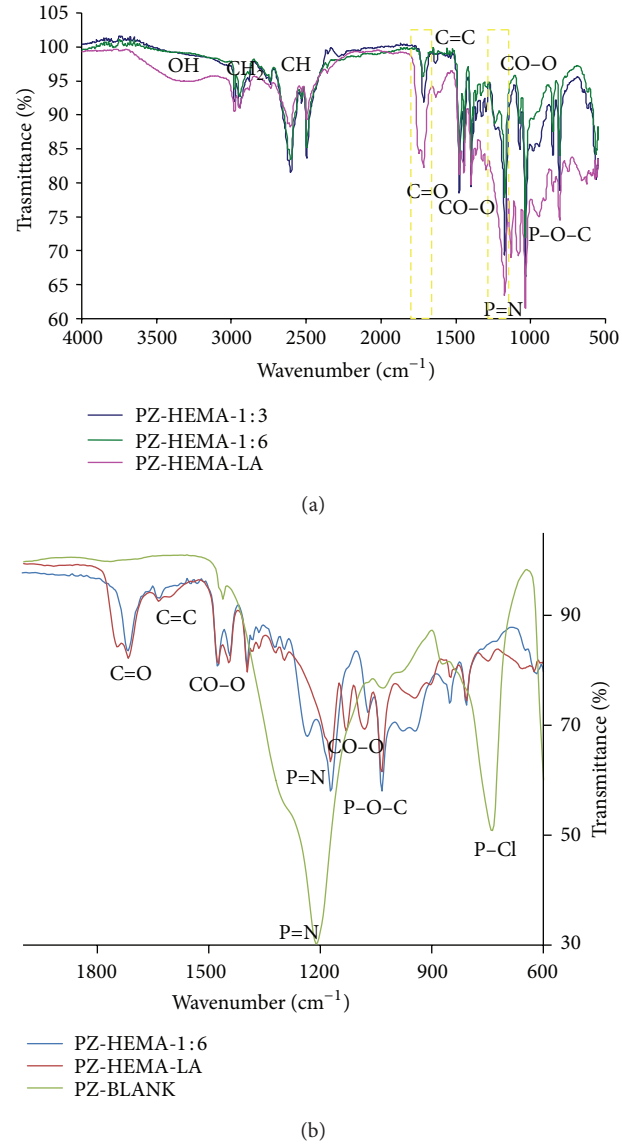



Figure 2: FTIR spectra of (a) PZ-HEMA-1:3, PZ-HEMA-1:6, and PZ-HEMA-LA and (b) PZ-BLANK, PZ-HEMA-1:6, and PZ-HEMA-LA.

weight $[P(Cl_2)=N]_n$ [15], while the polymers PZ-HEMA-1:3, PZ-HEMA-1:6, and PZ-HEMA-PLA show a peak in positive values; it may be presumed that chlorine atoms were completely replaced by subsequent reaction. The peak at 1.5 ppm is assigned to modified phosphazene $[P(OR)_2=N]_n$. In addition, the PZ-HEMA-1:3 shows a peak at 20 ppm which is assigned to [R–P=O]. When the HEMA ratio was increased to 6 mmol a complete chlorine substitution was obtained, the spectrum only presents one peak; in another hand, for PZ-HEMA-LA, another peak appears at 0.6 ppm assigned to the substitution of chlorine by LA.

The $^1$H NMR spectrum of PZ-HEMA-1:6 and PZ-HEMA-LA is shown in Figure 4. We observed the peaks corresponding to different hydrogens of the organic substituents. The presence of the signals at 6 and 5.58 ppm indicates that

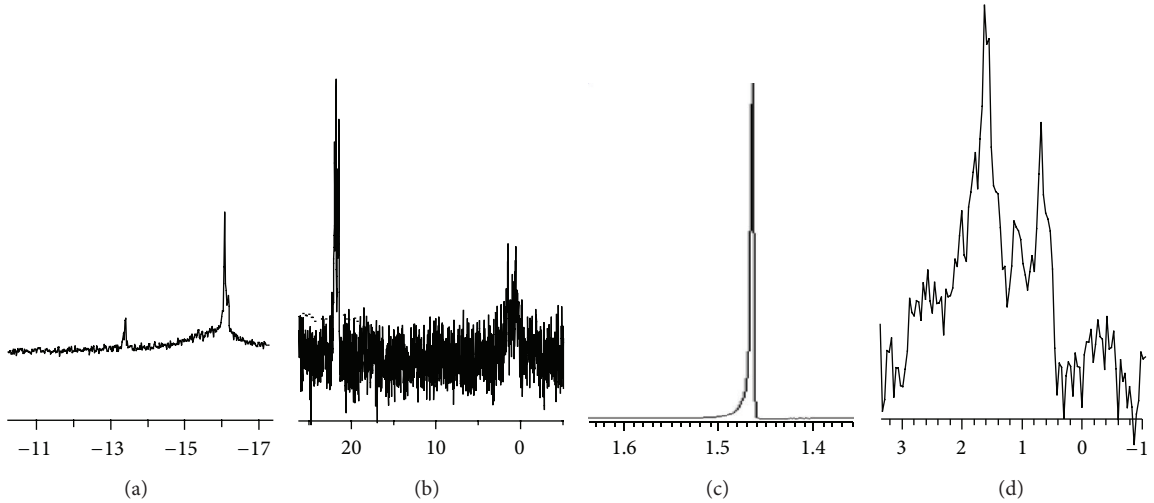
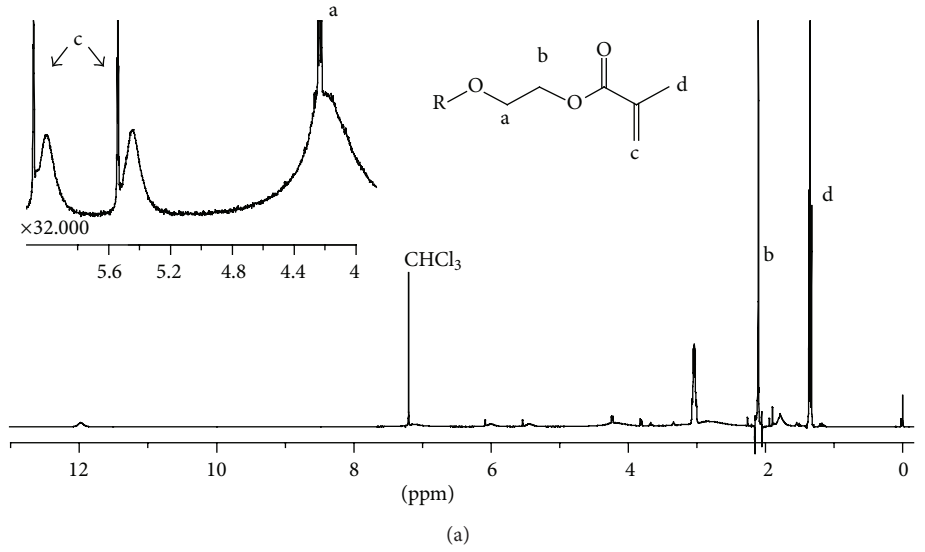



Figure 3: $^{31}$P NMR spectra of (a) PZ, (b) PZ-HEMA-1 : 3, (c) PZ-HEMA-1 : 6, and (d) PZ-HEMA-LA.



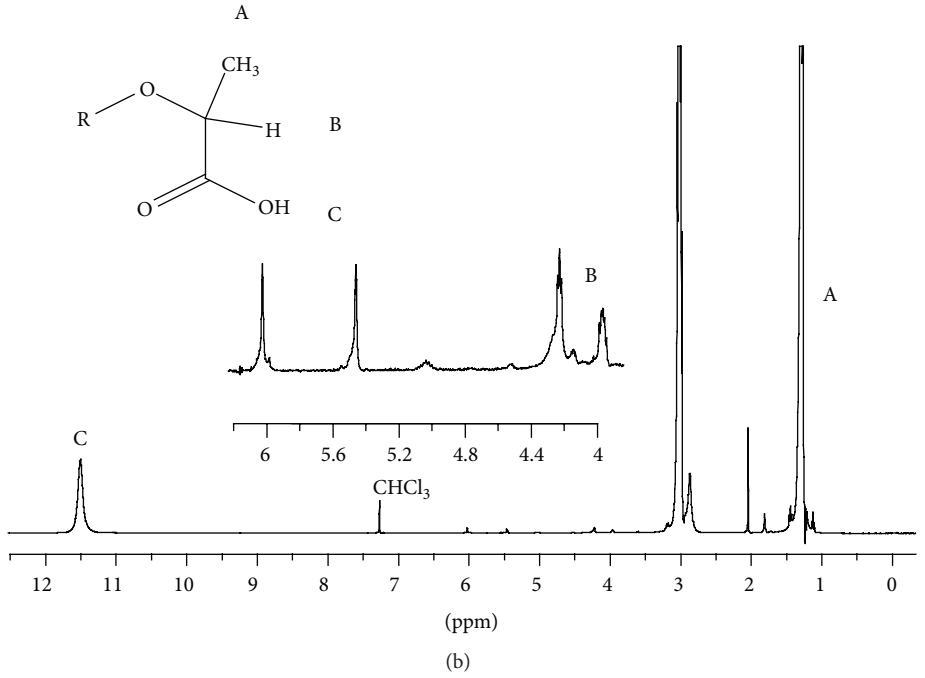




Figure 4: $^{1}$H NMR spectra of (a) PZ-HEMA-1 : 6 and (b) PZ-HEMA-LA.

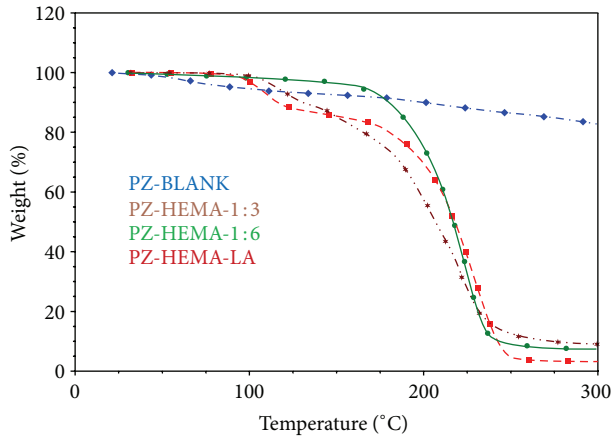



Figure 5: TGA thermograms of PZ BLANK, PZ-HEMA-1:3, PZ-HEMA-1:6, and PZ-HEMA-LA.

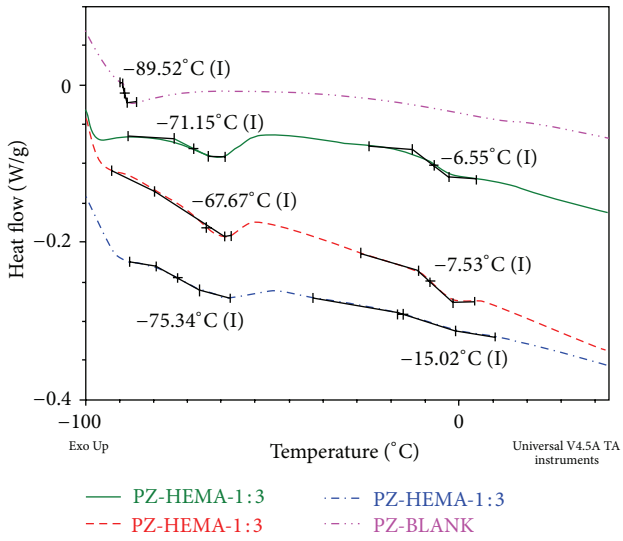



Figure 6: DSC Thermograms of PZ, PZ-HEMA-1:3, PZ-HEMA-1:6, and PZ-HEMA-LA.

the majority of the end double bonds are on the material. In addition, the peaks to OH in 4.9 ppm (HEMA) and 3.4 ppm (AL) are not present in the spectrum.

The thermal stability of the polymers was analyzed by TGA (Figure 5). PZ lost about 5% of weight between 50°C and 100°C due to residual monomer evaporation. Between 200°C and 300°C there is another 5% loss of weight, which is attributed to the elimination of chlorine. Nevertheless, the PZ is fairly stable up to 300°C.

In contrast, when the inorganic back bone is substituted for organic molecules the temperature of decomposition decreased at ~225°C; according to the literature, the pure poly(HEMA) began its decomposition at ~300°C. This means that HEMA was grafted in the inorganic chain and changed the thermal stability of PZ.

PZ-HEMA and PZ-HEMA-LA are quite stable up to 100°C, the stability of PZ-HEMA increases with the content of HEMA attached on PZ because of the good thermal stability of HEMA, the initial thermal decomposition of poly(HEMA) exhibited at 195°C [16]. In PZ-HEMA-LA the decomposition temperature of LA starts at 109°C, this value is much less than of the initial decomposition of the PLA at ~300°C [17]. Excluding monomer evaporation in PZ, its thermal stability is greater than that observed in the copolymers.

The thermal transitions of the polymers were determined by DSC (Figure 6). The obtained data indicate that all polymers are flexible above 0°C. PZ showed a single $T_g$ at −90°C while both PZ-HEMA and PZ-HEMA-LA have two $T_g$'s: (a) for PZ-HEMA-1:3 −71°C and −6.6°C; (b) for PZ-HEMA-1:6 −67°C and −7.5°C; and (c) for PZ-HEMA-LA −75°C and −15°C. The lowest $T_g$ value shown by each copolymer corresponds to the PZ backbone. The $T_g$ of PZ-HEMA-LA at −15°C corresponds to the LA grafted on the PZ backbone. The $T_g$ of PZ-HEMA at about −7°C is attributed to the HEMA chemically attached to the PZ backbone. The observed $T_g$ temperatures are similar to those reported elsewhere [14, 18].

The properties of the poly(organophosphazenes) depend on the type of side groups linked to the polymer chain. If the side groups are small or are highly flexible organic units, like 2-butenoxy or trifluoroethoxy, the polymers will show low glass transition temperatures (−100 to −30°C) [16].

The surface of the polymers was examined by SEM (Figure 7). The PZ was an amorphous white solid and shows a semiuniform surface while the copolymers show distinctive characteristics. PZ-HEMA-1:3 and PZ-HEMA-1:6 show a rod like microstructure that is enhanced as the concentration of HEMA; it is possible that polyphosphazene had a crosslinking reaction between itself and conducive to a geometry structure. PZ-HEMA-PLA shows a rod structure with more plastic appearance. Thus, morphology depends on the type of the substituent attached to the PZ backbone [19].

After obtaining the copolymers, it is intended to add them to an acrylic resin to increase the mechanical properties and subsequently will be made of composite fibers by electrospinning technique to improve their lifetime.

## 4. Conclusions

Poly(dichlorophosphazene) was prepared directly by melt ring-opening polymerization of hexachlorocyclotriphosphazene. This polymer was useful for the design and synthesis of Poly [(2-hydroxyethyl-methacrylate)-graft-poly(lactic-acid)-phosphazene] and poly[bis(2-hydroxyethyl-methacrylate)-phosphazene] by ring-opening polymerization reactions, at different concentrations of the substituents. The incorporation of organic substituents HEMA and AL was proved by FTIR, NMR, and DSC. All polymers are flexible above 0°C and are thermally stable up to 100°C. The morphology of the polymers was considerably modified by the incorporation of substituents and will be of great importance when testing copolymers in dental resins. The PZ-HEMA-1:6 copolymer yields the best results and suggest that it could potentially be used in biomedical applications such as dental resins.

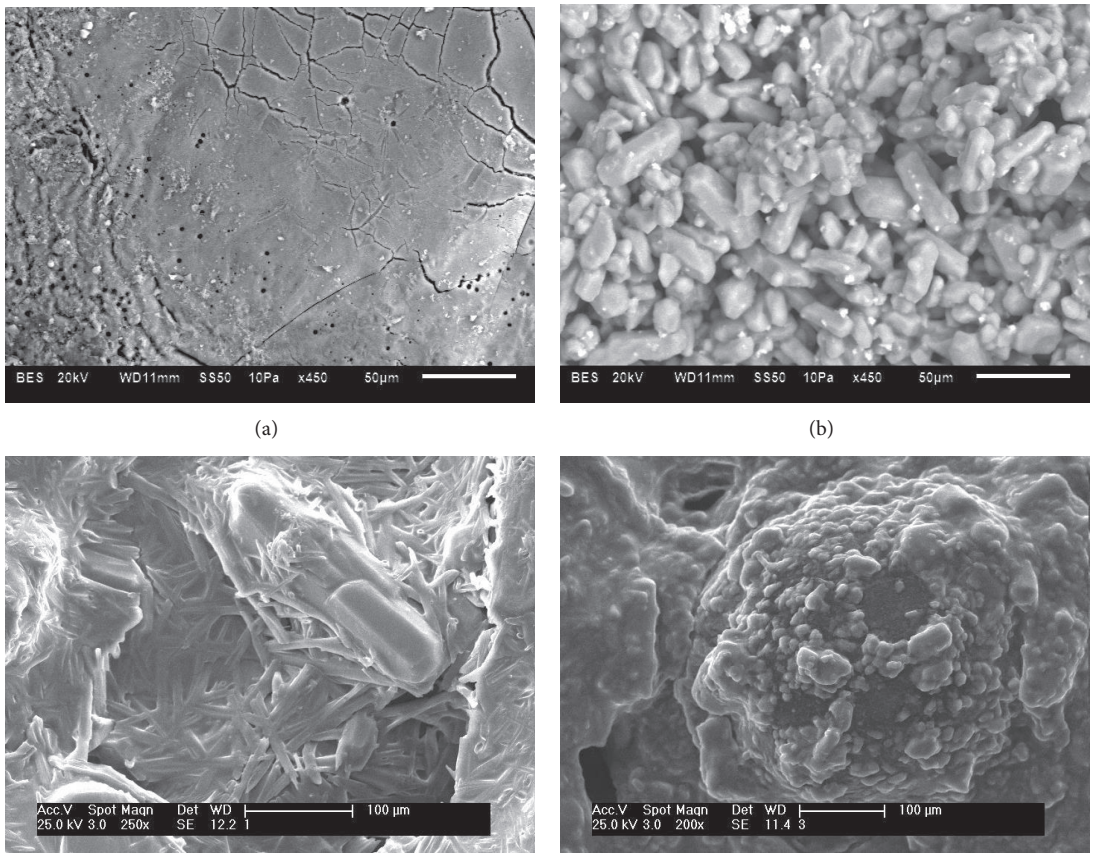



Figure 7: SEM images of (a) PZ, (b) PZ-HEMA-1 : 3, (c) PZ-HEMA-1 : 6, and (d) PZ-HEMA-LA.

## Conflict of Interests

The authors do not have a direct financial relation or conflict of interests with the commercial identities mentioned in this submitted paper, and the commercial trademarks such as Bruker Avance, Thermo Scientific, TA Instruments, and JEOL, only were reported to guarantee the reproducibility, in the same conditions, of the different tests.

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