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Synthesis and Characterization of Covalently Interconnected Phosphazene−Silicate Hybrid Network Membranes

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A method for the cross-linking of water-soluble polyphosphazenes via a sol−gel condensation is described. Precursor polymers were produced by covalently binding an organosilicon alkoxide to the terminus of pendent oligoethylenoxy chains on poly[bis(methoxyethoxyethoxy)phosphazene]. Subsequent hydrolysis and condensation of these precursors yielded hybrid silicate networks with covalently integrated polyphosphazenes. The hybrid networks showed high water uptake values (up to 1570 wt %). The release of Rose Bengal, Biebrich Scarlet, and FITC−albumin from the phosphazene−silicate matrix was studied over time as a function of network density. These hydrogels are of interest as potential materials for use in membranes or biomaterials.

Introduction

Sol−gel derived hybrid networks have emerged in recent years as a class of materials well-suited for surface functionalization and diffusion-related applications.[1−3] The sol−gel process is characterized by repeated hydrolysis and condensation reactions of organometallic alkoxides under mild conditions to provide a variety of inorganic oxide networks.[4−6] The incorporation of organic or polymeric materials into a sol−gel system provides access to organic−inorganic hybrid polymeric networks, particularly when the organic components can withstand the mild sol−gel conditions.

Polyphosphazenes have a highly flexible phosphorus−nitrogen backbone, and their properties can be tailored by the incorporation of various substituents.[7,8] In particular, water-soluble poly[bis(methoxyethoxyethoxy)phosphazene] (MEEP) has attracted much attention due to its potential applications in biomaterials and in drug delivery devices.[9,10] MEEP solutions and radiation cross-linked gels have a lower critical solution temperature (LCST) at 80 °C and have been suggested for potential applications in thermosensitive drug release devices.[11] Other related polyphosphazenes with different alkyl ether side groups show different LCST values, some close to human body temperature.[9] Hydrogels formed after γ-ray irradiation of MEEP can be utilized in responsive membranes, and these have been used for the immobilization of enzymes.[12] Because un-cross-linked MEEP has a low glass transition temperature, it is a viscoelastic gum that can flow when subjected to an external force. Thus, radiation or chemical cross-linking is often needed in order to optimize the properties of MEEP for applications.[13] The cross-linking density of γ-ray cross-linked hydrogels depends on the radiation dose in a manner that can be utilized to change the properties. Other techniques available to cross-link MEEP to mechanically stable materials include chemical,[14] UV−photochemical,[15] or blending with other polymers.[16] The combination of a sol−gel derived silicate network with MEEP provides a facile synthetic route to unique hybrid materials. The rigidity of a silicate network and the low dimensional stability of MEEP can be mutually compensated by the sol−gel method.[5,17−21]

In this work, we have synthesized a polymeric sol−gel precursor. The precursor polymer was prepared by covalent

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linkage of MEEP to an organosilicon alkoxide, followed by hydrolysis and condensation of the resultant inorganic component. The structural characterization was performed by FT-IR, NMR, and solid-state ^{29}Si NMR. The water-swelling behavior of cross-linked hybrid membranes was also investigated. In addition, slow release experiments with dye molecules and a protein were conducted to evaluate these materials as potential selective membranes.

Experimental Section

Materials. 3,4-Dihydro-2*H*-pyran, pyridinium *p*-toluenesulfonate (PPTS), 3-isocyanatopropyltriethoxysilane, di-*n*-butyltin dilaurate (DBTDL), Rose Bengal, and Biebrich Scarlet were obtained from Aldrich and were used as received. Sodium hydride (60% suspension in mineral oil) was obtained from Fluka and was used as received. Fluorescein isothiocyanate conjugate bovine albumin (FITC−albumin) was obtained from Sigma and was used as received. Diethylene glycol and di(ethylene glycol) monomethyl ether were vacuum distilled over CaH_2 before use. 2-[2-(Tetrahydropyranyloxy)ethoxy]ethanol was synthesized following the procedure reported by Allcock and Kim.[22] All the solvents were distilled and purified by procedures reported in the literature.[23] Hexachlorocyclotriphosphazene (Ethyl Corp./Nippon Fine Chemical Co.) was recrystallized from heptane and sublimed at 40 °C (0.05 mmHg). Poly(dichlorophosphazene) was obtained by the thermal ring-opening polymerization of hexachlorocyclotriphosphazene.[24] All reactions were carried out under an inert atmosphere of dry argon. Dialysis experiments were carried out to remove salts and oligomeric products. Spectra/Por dialysis membranes with molecular weight cutoff of 12000−14000 Da were employed.

Equipment. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded with use of a Bruker AMX-360 NMR spectrometer operated at 360, 146, and 90.27 MHz, respectively. ^{1}H and ^{13}C NMR spectra were referenced to solvent signals, while ^{31}P NMR chemical shifts are relative to an external 85% phosphoric acid reference, with positive shift values downfield from the reference. Solid-state NMR was obtained using a Chemagnetics CMX-300 NMR spectrometer operating in the quadrative mode at 59.07 MHz for ^{29}Si. Molecular weights were estimated using a Hewlett-Packard HP1090 gel permeation chromatograph equipped with a HP-1047A refractive index detector. The samples were eluted with a 0.1 wt % solution of tetrabutylammonium nitrate in THF. The GPC system was calibrated with polystyrene standards (Polysciences). UV/Vis spectra were obtained using a Hewlett-Packard 8452A spectrophotometer. Fluorescence spectra were obtained with use of a Yobin Yvon Fluoromax 2 spectrometer. For measurements of the emission spectra, emission and excitation slit widths were set at 3 and 1.5 nm, respectively, and an excitation wavelength of 490 nm was used. DSC measurements were carried out using a Perkin-Elmer-7 thermal analysis system. Glass transition temperatures were obtained by heating the polymer samples from −150 to 100 °C at a rate of 20 and 40 °C/min, under an atmosphere of dry nitrogen.

Synthesis of 2-[2-(Tetrahydropyranyloxy)ethoxy]ethanol. A methylene chloride solution (200 mL) of 3,4-dihydro-2*H*-pyran (25.20 g, 300 mmol) with pyridinium *p*-toluenesulfonate (PPTS) (7.60 g, 30 mmol) was added to the solution of diethylene glycol (42.5 g, 400 mmol) in methylene chloride (500 mL). The solution was stirred for 2 h at 0 °C and allowed to warm to room temperature. Then, the solution was washed with three times with water, and the solvent was removed by reduced pressure rotary evaporation. The oily product was isolated by column chromatography. ^{1}H NMR (CDCl_3): δ 1.41−1.87 (br, 6 H, $\text{-OCH}_2\text{C}H_2\text{C}H_2\text{C}H_2\text{CHO-}$), 3.40−3.87 (m, 10 H, $\text{HOC}H_2\text{C}H_2\text{OC}H_2\text{C}H_2\text{O-}$, $\text{-OC}H_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CHO-}$), 4.61 (t, 1 H, $\text{-OC}H\text{O-}$).

Synthesis of Polymer 1 (5:95). Di(ethylene glycol) monomethyl ether (13.7 g, 114 mmol) was added to sodium hydride (4.56 g, 114 mmol) in dry tetrahydrofuran (THF) (300 mL). Once the sodium salt was formed, a solution of poly(dichlorophosphazene) (7.0 g, 60 mmol) in THF (500 mL) was added under an atmosphere of argon. The reaction mixture was stirred at room temperature for 5 h. The second sodium salt, 2-[2-(tetrahydropyranyloxy)ethoxy]ethanol (18 mmol), was added, and the mixture was stirred at room temperature for 5 h and heated to 50 °C for 10 h. After completion of the reaction, the crude polymer was purified to remove remaining salts by dialysis against water (3 times) and then methanol (3 times). The solvent was removed by reduced pressure rotary evaporation, and the remaining polymer was redissolved in THF and precipitated into hexane. The recovered material was dried under vacuum at approximately 50 °C for 2 days. The final product was obtained as a soft, highly viscous material. Yield: 14.1 g (81%); ^{1}H NMR (CDCl_3): δ 1.42−1.84 (br, $\text{-OCH}_2\text{C}H_2\text{C}H_2\text{C}H_2\text{CHO-}$), 3.31 (S, $\text{-OC}H_3$), 3.40−3.80 (br, $\text{P-OCH}_2\text{C}H_2\text{OC}H_2\text{C}H_2\text{O-}$, $\text{-OC}H_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CHO-}$), 4.17 (br, $\text{P-OC}H_2\text{CH}_2\text{-}$), 4.56 (s, $\text{-OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}H\text{O-}$); ^{13}C NMR ($\text{CDCl}_3$): δ 19.49, 25.41, 26.45, 30.55, 58.79, 62.09, 64.97, 66.59, 70.22, 70.36, 70.56, 71.92, 77.20, 98.87; ^{31}P NMR (CDCl_3): δ −8.01; $M_n = 149000$, $M_w/M_n = 2.2$.

Synthesis of Polymer 2 (5:95). An absolute ethanol solution (250 mL) of polymer **1** (5 g, 17.2 mmol) and PPTS (0.50 g, 2 mmol) was stirred at 60 °C for 5 h. After cooling to room temperature, the polymer was purified by dialysis against water (3 times) and then methanol (3 times). The solvent was removed by reduced pressure rotary evaporation, and the remaining polymer was redissolved in THF and precipitated into hexane to yield viscous liquid. Yield: 3.60 g, (74%); ^{1}H NMR (CDCl_3): δ 3.32 (s, $\text{-OC}H_3$), 3.37−3.68 (br, $\text{P-OCH}_2\text{C}H_2\text{OC}H_2\text{C}H_2\text{O-}$), 4.03 (br, $\text{P-OC}H_2\text{CH}_2\text{-}$); ^{13}C NMR ($\text{CDCl}_3$): δ 59.25, 61.96, 65.50, 65.73, 70.67, 70.79, 71.01, 72.35, 73.05; ^{31}P NMR (CDCl_3): δ −7.87; $M_n = 108000$, $M_w/M_n = 2.1$.

Preparation of the Polyphosphazene-Silicate Hybrid Network. The precursor polymer **3** (5:95) was prepared by allowing polymer **2** (5:95) (2.0 g, 7.1 mmol) to react with 3-isocyanatopropyltriethoxysilane (0.18 g, 0.71 mmol) in THF (50 mL) with a catalytic amount of di-*n*-butyltin dilaurate (DBTDL) at room temperature for 3 h and at 60 °C for 2 h. This solution was used for the in situ sol−gel process. The sample for NMR analysis was obtained by precipitating the solution into hexane and drying under vacuum at 25 °C for 12 h. For polymer **3** (5:95); ^{1}H NMR (THF-d_8): δ 0.52 (tri, J = 8.2 Hz, $\text{-CH}_2\text{C}H_2\text{Si-}$), 1.19 (tri, J = 7.06 Hz, $\text{-Si(OCH}_2\text{C}H_3)_3$), 1.68 (quin, J = 8.4 Hz, $\text{NHCH}_2\text{C}H_2\text{CH}_2\text{Si-}$), 2.94 (tri, J = 5.92 Hz, $\text{-NHC}H_2\text{CH}_2\text{-}$), 3.21 (s, $\text{-OC}H_3$), 3.37−3.75 (br, $\text{P-OCH}_2\text{C}H_2\text{OC}H_2\text{C}H_2\text{O-}$), 3.69 (tet, J = 7.06 Hz, $\text{-Si(OC}H_2\text{CH}_3)_3$), 4.01 (br, $\text{P-OC}H_2\text{CH}_2\text{-}$); ^{13}C NMR (THF-$d_8$): δ 9.86, 15.88, 16.60, 25.89, 29.07, 45.87, 60.44, 63.72, 67.46, 69.65, 72.61, 72.83, 74.38,

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Scheme 1. Strategy for Synthesis of the Polymers

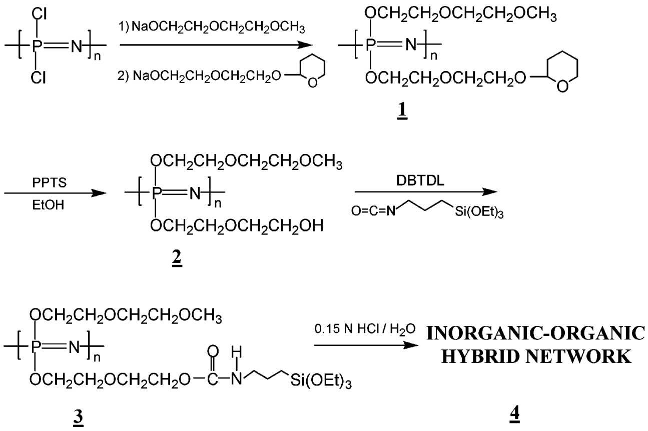

Table 1. Properties of Polymers

side group ratio	functional group ratio[a] (mol %)	M_n[a] (M_w/M_n)[b] before deprotection	M_n[a] (M_w/M_n)[b] after deprotection	T_g[c] (°C) before deprotection	T_g[c] (°C) after deprotection
(5:95)	4.5	149000 (2.2)	108000 (2.1)	−78.4	−76.8
(10:90)	9	105000 (2.5)	97000 (3.2)	−73.3	−71.2
(15:85)	13	215000 (3.3)	165000 (2.0)	−73.0	−72.2
(20:80)	18	119000 (2.5)	105000 (3.3)	−71.4	−70.6
(30:70)	27	230000 (2.6)	170000 (2.4)	−70.8	−68.9

[a] Calculated by ^{1}H NMR spectra. [b] Measured by GPC. [c] Measured by DSC (20 °C/min).

158.18. Hydrochloric acid (0.15 N, 3 mL) was added to the precursor polymer solution, and the mixture was stirred at 50 °C for 2 h. The sol was poured onto a flat Teflon mold to obtain a gel film. The gelation was carried out at room temperature for 2 days. The gel was further dried at 60 °C for 4 days and at 40 °C under vacuum for 3 days.

Results and Discussion

Preparation of Silicate Hybrid Networks. As shown in Scheme 1, the precursor polymer **3** was prepared from poly(dichlorophosphazene) using a nucleophilic substitution reaction with the sodium salt of di(ethylene glycol) monomethyl ether and monoprotected di(ethylene glycol). The substitution ratio of the monoprotected di(ethylene glycol) unit and the hydrophilic monomethyl diethyleneoxy unit was varied from 5:95 to 30:70 [polymer **1** (5:95) to **1** (30:70)] (Table 1). Polymer **1** was purified using dialysis against water and methanol to remove the remaining salts and excess alcohols. Finally, polymer **1** was precipitated into hexane. The substitution ratios were calculated from ^{1}H NMR spectra. Thus, the proton peaks of ethyleneoxy groups at 3.31 (CH_3O-) and 4.17 ppm (-P-O-CH_2-) were compared with the protons from tetrahydropyranyloxy at 4.56 and 1.42−1.84 ppm. The functional group ratios estimated from ^{1}H NMR spectra were well-matched with the feed ratios (Table 1). Deprotection of the tetrahydropyranyloxy group from polymer **1** produced hydroxyl functionalized polymer **2,** which was confirmed by ^{1}H NMR spectra (Figure 1). After deprotection, the proton peaks from the tetrahydropyranyloxy units (4.56 and 1.42−1.84 ppm) disappeared. For the synthesis of precursor polymer **3**, fully dried polymer **2** was allowed to react with 3-isocyanatopropyltriethoxysilane in the presence of DBTDL. Hydrolytic gelation was initiated with an acid catalyst. The reaction between the hydroxyl groups and the isocyanate gave a urethane (-OC(═O)NH-) linkage which could be utilized by the allophanate or biuret reaction.[25] The methylene proton peak (-NH-CH_2-) adjacent to the urethane linkage appeared at 2.97 ppm and confirmed the formation of the urethane linkage (Figure 1). The substitution ratio of the cross-linkable unit and the hydrophilic monomethyl diethyleneoxy unit was calculated using polymer **3** and showed similar values to polymer **1**.

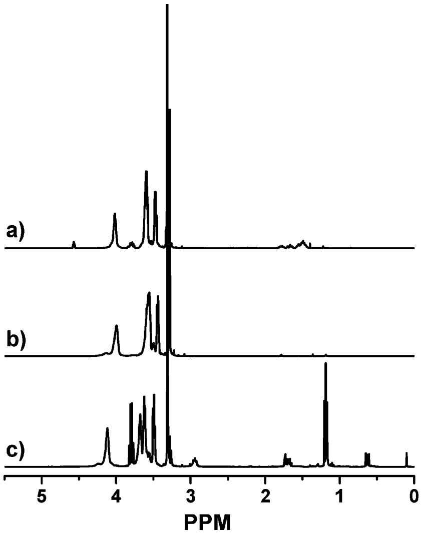

Figure 1. ^{1}H NMR spectra of (a) **1** (20:80), (b) **2** (20:80), and (c) **3** (20:80).

Characterization of Membranes. The polyphosphazenes and gel films were characterized by Fourier transform infrared (FT-IR) spectroscopy. After the deprotection of polymer **1**, a strong -OH stretching band near 3100−3600 cm^{-1} was detected, and this group was utilized for reaction with 3-isocyanatopropyltriethoxysilane. In addition, the polyphosphazene−silicate network showed a characteristic urethane absorption band at 3350−3400 cm^{-1} (NH), which was overlapped by the hydrolyzed silicon alkoxide (Si-OH) and carbonyl absorptions of the urethane group at 1720 cm^{-1} (C═O). Thus, the hydroxyl group of polymer **2** was consumed and formed the urethane linkage. Further characterization was performed by solid-state ^{13}C CP/MAS and ^{29}Si NMR spectroscopy. Complete hydrolysis was generally obtained with an acid catalyst in THF. Solid-state ^{29}Si NMR was used for evaluation of the degree of condensation in the insoluble network by examining the contribution of various silicon species present in the condensed materials. Shea et al.[26] reported that a modified form of Q^n notation can be used to describe siloxanes and silsesquioxanes. In this representation, silsesquioxanes with one siloxane bond are denoted as T^1, those with two siloxane bonds, T^2, and those three siloxane bonds, T^3 (Figure 2). The contribution of the various silicon species (T^1, T^2, and T^3) can be quantified and the degree of condensation can be calculated according to the equation:[26]

$$\text{degree of Condensation} = \frac{(0.5)[\text{area}T^1] + (1.0)[\text{area}T^2] + (1.5)[\text{area}T^3]}{1.5}$$

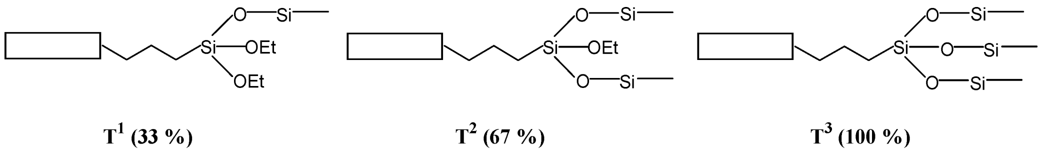

Figure 2. Modified Q^n notation for silsesquioxane silicons (each structure shown with degree of condensation).

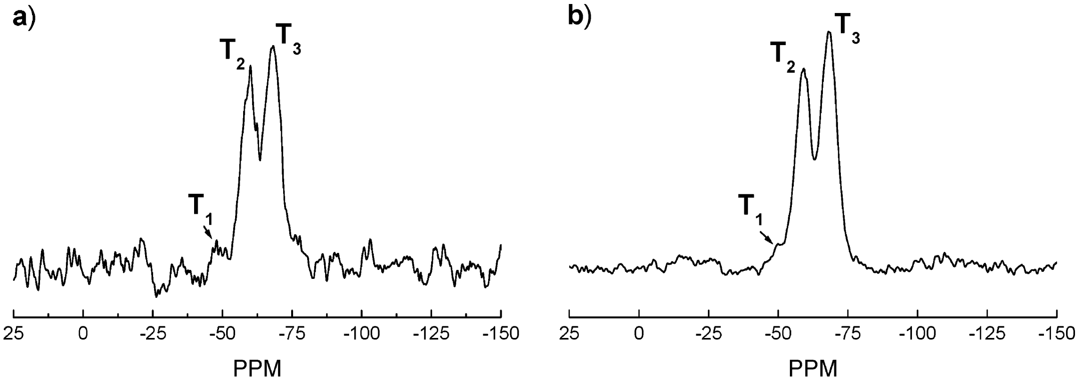

Figure 3. (a) Solid-state ^{29}Si 1 pulse proton decoupling NMR spectrum and (b) ^{29}Si CP/MAS NMR spectrum of cross-linked film **4** (20:80).

Table 2. Properties of Phosphazene−Silicate Hybrid Network

film	mol % of cross-linking units[a]	degree of condensation		water uptake[d] (%)	amount of loading (%)		
		1 pds[b]	CP/MAS[c]		Rose Bengal	Biebrich Scarlet	FITC−albumin
4 (10:90)	9	83.0	90.0	1570[e]			
4 (15:85)	13	90.8	88.5	1196	13.3	9.3	1.2
4 (20:80)	18	83.7	82.5	435	8.6	6.5	0.24
4 (30:70)	27	85.4	85.2	141	0.75	0.29	0.15

[a] Mole % of silicon ethoxide units in polyphosphazene. [b] Calculated from ^{29}Si 1 pulse H decoupling NMR spectrum. [c] Calculated from ^{29}Si CP/MAS NMR spectrum. [d] Water uptake values after 1 week. [e] Water uptake value after 24 h.

The integrals of T^1, T^2, and T^3 were measured by ^{29}Si 1 pulse proton decoupling NMR spectroscopy (Figure 3). The integrals quantitively reflect the amount of each type of ^{29}Si. We also used ^{29}Si cross-polarization magic-angle spinning (CP/MAS) NMR techniques, but the signal intensity was not quantitative because different ^{29}Si peaks may be excited more efficiently by the cross polarization than others. However, in our case, the integral ratios between ^{29}Si 1 pulse proton decoupling and ^{29}Si CP/MAS NMR showed similar values.[27]

The calculated degrees of condensation for the gel films from ^{29}Si 1 pulse proton decoupling and ^{29}Si CP/MAS NMR are listed in Table 2. The degree of condensation of cross-linked films **4** (10:90)−**4** (30:70) varied from 83.0 to 90.8%, values that are similar to those from the base-catalyzed sol−gel reaction.[26] Kim and co-workers reported a fully hydroxyl functionalized polyphosphazene−silicate hybrid network that had approximately 82% condensation.[5] The increased degree of condensation for this present system is attributed to the solubility of the MEEP component in THF, as well as in water and ethanol, which are byproducts of the gelation.

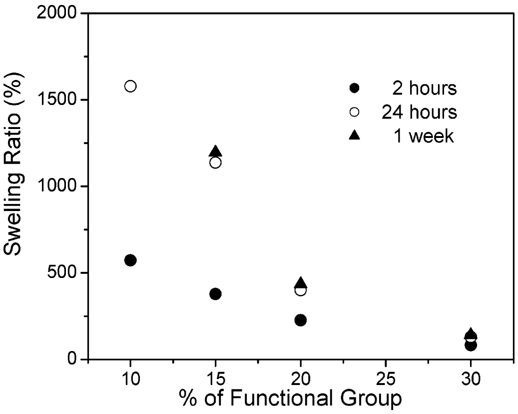

Figure 4. Water uptake of polyphosphazene-silicate hybrid networks after (●) 2 h, (○) 24 h, and (▲) 1 week.

Water-Swelling Behavior. The water-swelling behavior of cross-linked films **4** (5:95, 10:90, 15:85, 20:80, and 30:70) was studied and compared with that of MEEP cross-linked by γ-radiation. Cross-linked film **4** (5:95) became soluble in water within 2 h due to a low cross-link density. However, films **4** (10:90−30:70) were not soluble in water and had sufficient mechanical strength to form stable hydrogels. Each dry film was weighed, then immersed in 100 mL of deionized water. Periodically, the swollen film was removed from the water and weighed after removal of the surface liquid. The water uptake was calculated using the following equation:

$$\text{water uptake} = \frac{[(W_s - W_d)]}{W_d} \times 100$$

where W_d is weight of dried gel and W_s is weight of swollen gel.

The water uptake values of the hybrid network are listed in Table 2. Cross-linked film **4** (10:90) showed a high water uptake value of 1570%, which is higher than that of 6 Mrad γ-ray cross-linked MEEP (925%). An increase in the mol % of cross-linking units resulted in lower water uptake values. In addition, the gel films attained equilibrium during the first 24 h with no clear change during the following 7 days (Figure 4). The hybrid networks retained the reversible

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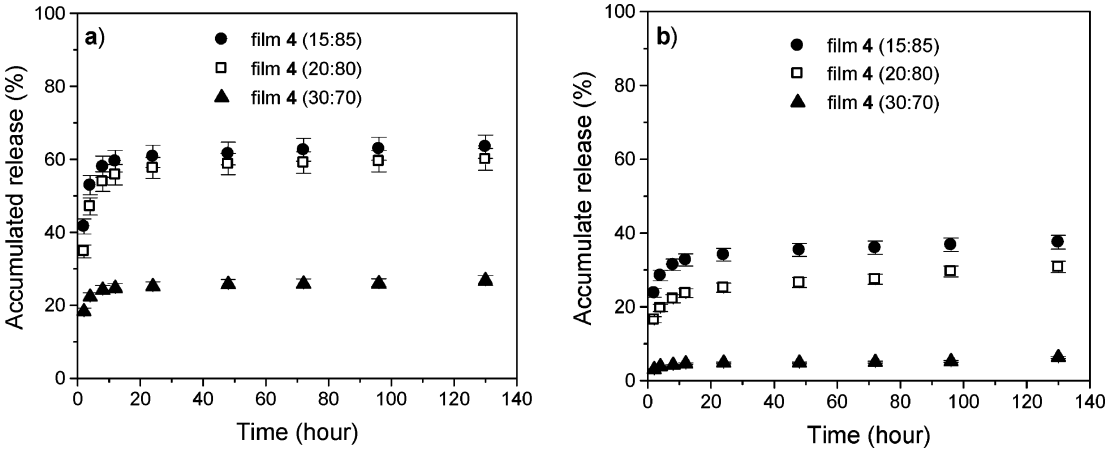

Figure 5. Cumulative release of (a) Rose Bengal and (b) Biebrich Scarlet from hydrogels.

responsive behavior of radiation cross-linked MEEP. In other words, above 80 °C the gels contracted and became opaque, and below this temperature they expanded and became transparent. The degree of expansion and contraction was less in the more highly cross-linked materials.

Guest Molecules Release Study. A measure of the water-filled free volume of a hydrogel is the rate of release of small molecules or macromolecules trapped in the lattice. These data are also of interest for the relationship to biomaterials studies.[28,29]

Rose Bengal and Biebrich Scarlet (molecular diameters ≈ 12 and 13 Å, respectively) were chosen for entrapment and slow release experiments. The small-molecule release study was conducted with cross-linked film **4** (15:85, 20:80, and 30:70). Each film was immersed in a solution of Rose Bengal or Biebrich Scarlet (1.0 g/100 mL solution) for 24 h at room temperature. The hydrogel films were then transferred to identical solutions to allow equilibration of solute within and outside the hydrogel. The loaded hydrogel was washed with water before being transferred to the test vial, which contained 100 mL of water. The aqueous medium was removed and analyzed using a UV/Vis spectrophotometer at each time interval and was replaced by 100 mL of water. Linearity between the concentration of each dye molecule and its absorbance at 548 nm (for Rose Bengal) and 506 nm (for Biebrich Scarlet) was obtained. The rate of release of dye molecules from the hydrogel was then calculated from these standard concentration−absorbance plots. The release profiles of Rose Bengal and Biebrich Scarlet in hybrid network 4 (15:85, 20:80, and 30:70) are shown in Figure 5a,b.

The model protein, FITC−albumin (approximate size ≈ 80 Å), was chosen for encapsulation and slow release experiments.[30] The model protein release study was conducted using the same method as for the small molecule release study. The collected aqueous medium was analyzed using a spectrofluorometer at each time interval. Linearity between the concentration of FITC−albumin and its emission intensity at 516 nm was obtained. The rate of release of FITC−albumin from the hydrogel was then calculated from these standard concentration−emission intensity plots. The release profile of FITC−albumin in the hybrid network is shown in Figure 6. A clear initial burst was evident due to the release into solution of molecules at the surface of the hydrogel, and this was subsequently followed by a second slower phase, in which molecules were released from within the matrix (Figure 7). From the dyes and FITC−albumin release data, the rate of dye release was dependent on the cross-link density. Variations in the amount of cross-linking provides the network with different swelling ratios and the different spacing between hybrid networks for dyes and FITC−albumin release. Increasing the ratio of cross-linking units (from 15 to 30 mol %) yields a more rigid hybrid network, which hampers the release of dye and FITC-albumin. Conversely decreasing the ratio of cross-linking

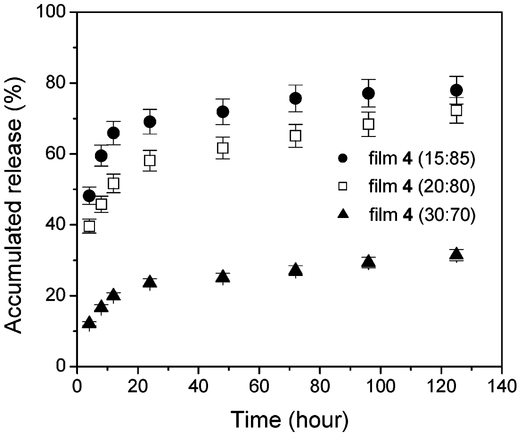

Figure 6. Cumulative release of FITC-albumin from hydrogels.

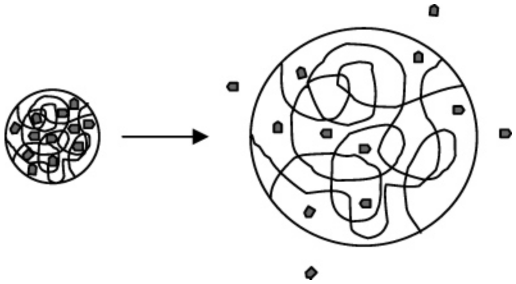

Figure 7. Schematic representation of dye release from the hydrogel.

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units should provide highly swellable networks that may facilitate dye or FITC-albumin passage.

The loading efficiency (weight of loaded dye in film/weight of film) was calculated and is listed in Table 2. In the case of Rose Bengal, the dye was entrapped in the polymeric network in the range of 0.75−13.3% of the original dry film. More swellable networks absorbed more dye in the interior and on the surface. In addition, Biebrich Scarlet was entrapped in the range of 0.29−9.3%. When normalized for similar dye concentrations the rates of release are 0.52% for **4** (30:70), 11.7% for **4** (20:80), and 16.7% for **4** (15:85). These values are similar to that of Rose Bengal. The loading efficiency of FITC-albumin, both calculated and entrapped, are in the range of 0.15−1.2%, which is a much lower value than for the small dye molecules. This low loading efficiency of FITC−albumin is due to its larger size and higher molecular weight (66 kDa) than either dye. The hydrogel loaded with FITC−albumin showed a sustained release behavior much like small dye molecules after the initial burst and liberation.

Conclusions

An organo-modified sol−gel precursor of a polyphosphazene and its silicate hybrid network was synthesized. The precursor polymers were prepared by combining MEEP with an organosilicon alkoxide (triethoxysilane group), which was incorporated in the side group system by covalent bonding. After hydrolysis and condensation reactions, the precursor became a covalent interconnected hybrid material with controlled morphologies and physical properties. Variation in the cross-link density allowed control over the rate of release or transport of small molecule dyes or a protein.

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