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Research paper

Thermosensitive poly(organophosphazene) hydrogels for a controlled drug delivery

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Abstract

Thermosensitive poly(organophosphazenes) were synthesized for a controlled release of hydrophilic polymeric model drugs such as dextran and albumin in this study. The solutions of the present polymers bearing both hydrophobic side groups of L-isoleucine ethyl ester (IleOEt) and hydrophilic groups of α-amino-ω-methoxy-PEG (M_w 550) (AMPEG550) exhibited reversible sol–gel transition behaviors with changes of temperature. Viscometric measurement indicated that the thermosensitive hydrogels with good strength could be formed from the solutions in the range of the concentrations of 7–15 wt% around body temperature. For increasing their biodegradabililites, depsipeptides of ethyl-2-(*O*-glycyl)lactate (GlyLacOEt) were also introduced to the polymer, showing enhanced degradation of hydrogels. In vitro release behaviors of hydrophilic FITC-dextran (M_w 71,600) and human serum albumin from these polymer hydrogels were sustained for about 2 weeks while those from poloxamer (Pluronic F-127) hydrogel showed a distinct initial burst. The release of FITC-dextran exhibited concentration-dependent behavior ranging from 7 to 15 wt% of the polymer solution while it was almost independent of the concentration of FITC-dextran.

Keywords: Poly(organophosphazene); Thermosensitive hydrogel; Hydrophilic polymeric drug; Injectable drug delivery system

1. Introduction

Thermosensitive polymer hydrogels have been extensively studied because of their valuable applications in drug delivery system, cell encapsulation, and tissue engineering [1–3]. Thermosensitive polymer hydrogels are formed from aqueous polymer solutions with temperature changes, which come mainly from packing of polymeric micelles or physical associations between polymer segments in aqueous solution [4]. Therefore, thermosensitive polymer hydrogels can avoid toxic organic crosslinkers usually employed to form hydrogel. In this system, various drugs can be incorporated by a simple mixing and the solution containing drugs is locally injected to specific body site. As a result, the solution is instantly converted to hydrogel at the injected site and drugs are slowly released through three-dimensional networks of the hydrogel for a long period. Loading drugs in the injectable thermosensitive polymer hydrogels by means of physical mixing is considered as simple process for drug delivery system. The injectable hydrogels can also be applied to bioactive protein delivery matrix due to its biosafety and inertness to protein drugs against heating, sonication, and organic solvents.

Recently, many studies about injectable thermosensitive polymer hydrogels showing sol–gel transition behaviors with temperature have been reported [2,4] to overcome the drawbacks of chemical crosslinked hydrogels. However, thermosensitive and biocompatible polymers, which show sol–gel transition behaviors with

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changes of temperature, were limitedly elucidated because of their inherent structural requirements. Representative thermosensitive polymers are as follows; copolymers of *N*-isopropylacrylamide (P*N*iPAAM) [5,6], PEO–PPO–PEO triblock copolymer (Poloxamer) [7,8], and PLGA–PEG–PLGA triblock copolymer (ReGel) [9,10]. However, P*N*iPAAM and poloxamer copolymers have been known as non-degradable polymers in bioenvironmental conditions. Additionally, initial burst release of hydrophilic drugs from the poloxamer hydrogel is apparently observed without additives such as methylcellulose and hydroxypropyl methylcellulose [11]. On the other hand, PLGA–PEG–PLGA triblock copolymer, a biodegradable thermosensitive polymer hydrogel, showed prolonged release period of anticancer drugs and hydrophilic protein drugs from the hydrogel [9,10] in contrast with that from poloxamer hydrogel. Ruel-Gariepy et al. [12,13] prepared thermosensitive hydrogel using chitosan/glycerophosphate complex for local delivery of antineoplastic agents. Also, PEG-grafted chitosan was suggested as an injectable thermosensitive hydrogel for sustained protein release [14]. Recently, we have reported a new class of thermosensitive and biodegradable poly(organophosphazene) hydrogels [15–17]. As reported, various hydrophobic and hydrophilic substituents can be introduced to the polymer backbone, which affords easy controlling of hydrogel characteristics such as gelation temperature, gel strength, and biodegradability. Most of the poly(organophosphazenes) synthesized, exhibited sol–gel transition properties in an aqueous solution with changes of temperature.

In this study, we synthesized thermosensitive poly(organophosphazene) gels bearing hydrophobic L-isoleucine ethyl ester (IleOEt), hydrophilic α-amino-ω-methoxy-PEG with a molecular weight of 550 Da (AMPEG550), and ethyl-2-(*O*-glycyl)lactate (GlyLacOEt) as a hydrolysis-sensitive depsipeptide. Also, their gelation properties and release behaviors of hydrophilic polymeric drugs such as FITC-dextran and human serum albumin from the polymer hydrogels were observed.

2. Materials and methods

2.1. Materials

Hexachlorocyclotriphosphazene was acquired from Aldrich and purified by sublimation at 55 °C under vacuum (about 0.1 mmHg). α-Amino-ω-methoxy-PEG (AMPEG) with a molecular weight of 550 Da was prepared by a published method [18]. The ethyl esters of amino acids were prepared according to the literature [19]. Ethyl-2-(*O*-glycyl)lactates were prepared as described by Crommen et al. [20]. Tetrahydrofuran (THF) was dried by reflux over sodium metal and distilled under nitrogen atmosphere. Poloxamer (Pluronic F-127) was purchased from Sigma–Aldrich.

2.2. Polymerization

2.2.1. Synthesis of poly(organophosphazene) containing depsipeptides

*2.2.1.1. $[NP(IleOEt)_{1.11}(GlyLacOEt)_{0.05}(AMPEG550)_{0.84}]_n$ (**1**).* Poly(dichlorophosphazene) was prepared as described previously [21]. Polymer **1** was synthesized according to the elucidated procedure [17]. Shortly explaining it, L-isoleucine ethyl ester hydrochloride (8.04 g, 41.10 mmol) suspended in anhydrous THF (100 mL) containing triethylamine (16.64 g, 164.40 mmol) was added slowly to poly(dichlorophosphazene) (4.0 g, 34.52 mmol) dissolved in dry THF (100 mL). The reaction mixture was stirred for 4 h at 4 °C and then for 20 h at room temperature. To this mixture, triethylamine (0.56 g, 5.52 mmol) and ethyl-2-(*O*-glycyl)lactate (0.37 g, 1.38 mmol) dissolved in acetonitrile (50 mL) were added, and the reaction mixture was stirred for 19 h in an ice-water bath. AMPEG550 (29.24 g, 53.16 mmol) was dissolved in THF (100 mL) containing triethylamine (29.70 g, 293.47 mmol), added to the polymer solution, and the reaction mixture was stirred for 2 days at 40–50 °C. The reaction mixture was filtered, the filtrate were concentrated, and it was poured into *n*-hexane to obtain a precipitate, which was reprecipitated twice in the same solvent system. The polymer product was further purified by dialysis in methanol for 2 days and then in distilled water for 2 days at 4 °C. The final dialyzed solution was freeze-dried to obtain pure polymer 1. Yield: 80%. ^{31}P NMR ($CDCl_3$), δ (ppm): 19.6. ^{1}H NMR ($CDCl_3$), δ (ppm): 0.8–1.0 (s, 6H), 1.1–1.3 (br, 6H), 1.3–1.6 (br, 5H), 1.6–1.9 (br, 1H), 2.8–3.1 (br, 2H), 3.4 (s, 3H), 3.5–3.9 (br, 42H), 3.9–4.1 (br, 4H), 4.1–4.3 (br, 4H), 5.0–5.1 (br, 1H).

*2.2.1.2. $[NP(IleOEt)_{1.14}(GlyLacOEt)_{0.02}(AMPEG550)_{0.84}]_n$ (**2**).* IleOEt (41.12 mmol) and GlyLacOEt (1.15 mmol), and (AMPEG 550 (55.23 mmol). Yield: 83%. ^{31}P NMR ($CDCl_3$), δ (ppm): 19.6. ^{1}H NMR ($CDCl_3$), δ (ppm): 0.8–1.0 (s, 6H), 1.1–1.3 (br, 6H), 1.3–1.6 (br, 5H), 1.6–1.9 (br, 1H), 2.8–3.1 (br, 2H), 3.4 (s, 3H), 3.5–3.9 (br, 42H), 3.9–4.1 (br, 4H), 4.1–4.3 (br, 4H), 5.0–5.1 (br, 1H).

2.2.2. Synthesis of poly(organophosphazene) without depsipeptides

Poly(organophosphazene)s were synthesized similarly by the procedure stated in the previous report [16].

*2.2.2.1. $[NP(IleOEt)_{1.18}(AMPEG550)_{0.84}]_n$ (**2**).* IleOEt (40.73 mmol) and AMPEG 550 (56.61 mmol). Yield: 70%. ^{31}P NMR ($CDCl_3$), δ (ppm): 19.6. ^{1}H NMR ($CDCl_3$), δ (ppm): 0.8–1.0 (s, 6H), 1.1–1.3 (br, 6H), 1.3–1.6 (br, 5H), 1.6–1.9 (br, 1H), 2.8–3.1 (br, 2H), 3.4 (s, 3H), 3.5–3.9 (br, 42H), 3.9–4.1 (br, 4H), 4.1–4.3 (br, 4H).

*2.2.2.2. $[NP(IleOEt)_{1.20}(AMPEG550)_{0.80}]_n$ (**3**).* IleOEt (41.42 mmol) and AMPEG 550 (55.23 mmol). Yield: 70%. ^{31}P NMR($CDCl_3$), δ (ppm): 19.6. ^{1}H NMR ($CDCl_3$),

δ (ppm): 0.8–1.0 (s, 6H), 1.1–1.3 (br, 6H), 1.3–1.6 (br, 5H), 1.6–1.9 (br, 1H), 2.8–3.1 (br, 2H), 3.4 (s, 3H), 3.5–3.9 (br, 42H), 3.9–4.1 (br, 4H), 4.1–4.3 (br, 4H).

2.3. Instruments and measurements

All reactions were carried out at an atmosphere of dry nitrogen by using standard Schlenk-line techniques. Proton-decoupled ^{31}P NMR spectra were measured with a Varian Gemini-300 spectrometer operating at 121.4 MHz using triphenyl phosphate as an external standard. ^{1}H NMR measurements were made with the same spectrometer operating 300 MHz in the Fourier transform mode. A higher resolution NMR spectrometer (Varian UI-500) was used for ^{1}H NMR studies on the phase transition behaviors in the range 5–60 °C. The viscosity measurements of aqueous polymer solutions were performed on a Brookfield RVDV-III+ viscometer between 5 and 60 °C. Gel permeation chromatography was carried out using a GPC system (Waters 1515) with a refractive index detector (Waters 2410) and two stryagel columns (Waters styragel HR 5E) connected in line at a flow rate of 0.8 mL/min at 35 °C. THF containing 0.1 wt% of tetrabutylammonium bromide was used as the solvent. Polystyrenes (M_w: 1140; 3570; 14,100; 28,700; 65,300; 181,000; 613,000; 1,010,000; and 2,660,000) were used as standards to calibrate the column.

2.4. In vitro hydrolytic degradation

The time-dependent degradation behavior of the polymers **2** and **3** was measured in terms of decrease in hydrogel mass and molecular weight. 0.2 g hydrogels of polymer **2** and **3** was soaked in 10 mL PBS buffer and then incubated at 37 °C. After 1, 3, 7, 14, 30, 45, and 60 days, the hydrogels were lyophilized and weighed. In order to measure the changes in molecular weight, 12 mL of polymer **2** and **3** solutions (2 wt%) was incubated at 37 °C. One milliliter of the solution was taken after 1, 3, 5, 7, 10, 14, 21, 30, 45, and 60 days, and molecular weight of each solution was measured by GPC.

2.5. In vitro release of FITC-dextran and human serum albumin

Twenty-five weight percentage of poloxamer solution was employed as a control hydrogel. Poloxamer is now currently available marketed product in injectable gels, so we compared our polymers with poloxamer. Poly(organophosphazenes) were dissolved in PBS buffer (0.01 M, pH 7.4) and then fluorescein isothiocyanate labeled dextran (FITC-dextran, M_w 71,600) and human serum albumin (HSA) were added to the polymer solutions at various concentrations below 4 °C. After transferring 0.5 mL of the final solution to millicell (∅: 12 mm, Millipore), the millicells containing the solution were incubated at 37 °C for 30 min, resulting in the formation of hydrogels. The hydrogel was soaked in 10 mL PBS buffer and incubated in water bath (KMC-1205SW1, Vision, Korea) at 37 °C under mild shaking motion (50 rpm). PBS buffer was periodically renewed with fresh buffer after the sampling. The released FITC-dextran concentration in the buffer was determined fluorimetrically (excitation wavelength 495 nm, wavelength emission 515 nm) by using a fluorometer (ISS K2, ISS CHAMP AIGN, IL, USA) and then the total amount released was calculated from the established standard curve. The amount of HSA released from the hydrogel was quantified by using a human albumin ELISA quantitation kit (Benthyl Laboratories, Montgomery, TX) under the conditions recommended by the manufacturer. A standard curve was made using pure HSA (Bethyl Laboratories). All experiments were carried out under light protection in triplicate.

3. Results and discussion

3.1. Characterization of poly(organophosphazenes)

Poly(organophosphazene) hydrogels have been first demonstrated by Tanigami's [22] and Allcock's [23,24] groups. The hydrogel prepared by the former group was structurally too complicated to characterize and that by the latter group, which was formed by covalent crosslinks, showed no reversible sol–gel transition behavior as well as no biodegradability. However, the hydrogel of poly(organophosphazenes) synthesized in the present work followed thermoreversible sol–gel transition behavior. Four different polymers were obtained by the types and molar ratios of substituents. The poly(organophosphazenes) synthesized are listed in Table 1 and the polymers characterized using NMR spectroscopy, GPC, and rheometer. The numerical subscriptions used in the formula are the mole ratios of AMPEG, IleOEt, and GlyLacOEt of polymers calculated from their integration ratios of ^{1}H NMR. The thermosensitive gelation behaviors of polymer **3** in PBS-buffered solution are displayed in Fig. 1. The polymers were readily soluble in water at temperatures lower than T_{ass}. As the temperature is raised, the polymer solutions became a transparent gel state (Fig. 1B). The present polymers with hydrolysis-sensitive depsipeptide (GlyLacOEt) also contain both hydrophobic moieties (IleOEt) to make a contribution to hydrophobic interactions occurring between polymer molecules and hydrophilic moieties (AMPEG550) to hydrogen bonds between polymers and water molecules as shown in Scheme 1. The facts that these two antithetic groups coexist can also explain a thermoreversible sol–gel transition behavior in agreement with the hypothesis for other polymer hydrogels such as poloxamer [7,8] and ReGel [9]. Fig. 2 shows the profiles of the time-dependent decrease in gel mass and molecular weight of the polymers **2** and **3** in the PBS buffer solution of pH 7.4 at 37 °C. The polymers were hydrolyzed in terms of both in mass loss and molecular weight decrease. However, the decrease in gel mass of polymers was observed faster

Table 1
Characteristics of thermosensitive poly(organophosphazenes)[a]

Polymer	Structure	M_w ($\times 10^4$)	T_{ass} (°C)[b]	T_{max} (°C)[c]	$V_{37\ °C}$ (Pa s)[d]	V_{max} (Pa s)[d]
1	$[NP(IleOEt)_{1.11}(GlyLacOEt)_{0.05}(AMPEG550)_{0.84}]_n$	4.4	22.9	44	65	240
2	$[NP(IleOEt)_{1.14}(GlyLacOEt)_{0.02}(AMPEG550)_{0.84}]_n$	2.8	14.9	37.9	215	245
3	$[NP(IleOEt)_{1.20}(AMPEG550)_{0.80}]_n$	4.2	18.9	37.9	182.5	207.5
4	$[NP(IleOEt)_{1.18}(AMPEG550)_{0.82}]_n$	3.9	10.9	37.9	522.5	540

[a] Viscosity was measured at 10 wt% of polymer concentration in PBS-buffered solution (0.01 M, pH 7.4).
[b] The association temperature at which the viscosity starts to increase sharply.
[c] The temperature at which viscosity reaches the maximum value.
[d] Viscosities at 37 °C and T_{max}.

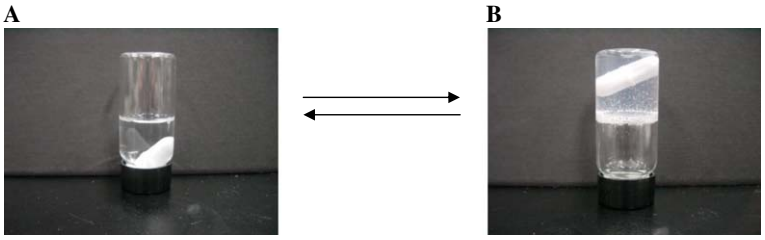
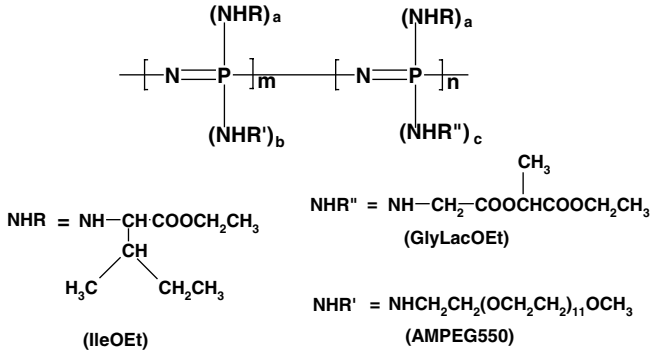


Fig. 1. Thermoreversible sol–gel transition behaviors. Poly(organophosphazene) solution at room temperature (A) was transformed to transparent hydrogel by elevating temperature to body temperature (B).



Scheme 1. Chemical structure of synthesized poly(organophosphazene).

than that in molecular weight. This result seems to be due to the dissolution of the polymer gel which is derived from the hydrolysis of the pendant ester group in the polymer resulting in the increase of T_{max} of the polymers. The rate of hydrolytic degradation of the present polymers was affected by the presence of depsipeptide (GlyLacOEt). The degradation of polymer **2** bearing IleOEt, AMPEG, and GlyLacOEt was faster than that of polymer **3** with IleOEt and AMPEG. Over 60% mass loss for polymer **2** was found after 60 days incubation, while around 20% of mass loss was observed in the case of polymer **3** during the same period. It has been reported that depsipeptide ethyl ester is more hydrolytically labile than amino acid esters. [25,26] The hydrolytic degradation of polyphosphazenes substituted with amino acid esters as side groups has been explained in terms of carboxylic acid catalyzed degradation. It has been proposed that the initiation step of hydrolytic degradation of the polyphosphazene substituted with amino acid ester is hydrolysis of pendant ester group. The carboxylic

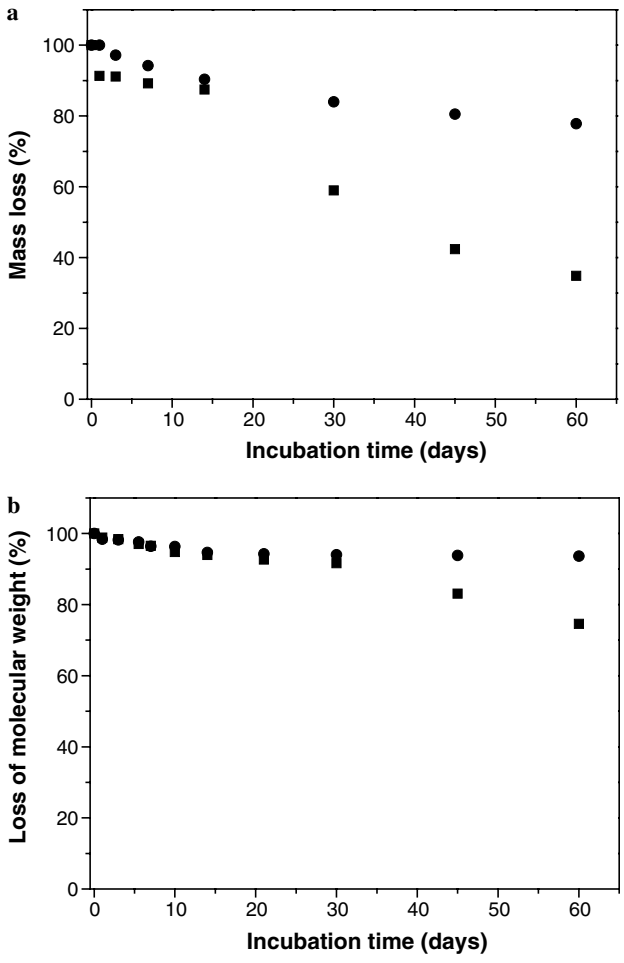


Fig. 2. Time-dependent decrease of mass (a) and molecular weight (b) of polymers **2** (■) and **3** (●) in phosphate-buffered saline solution (pH 7.4, 37 °C).

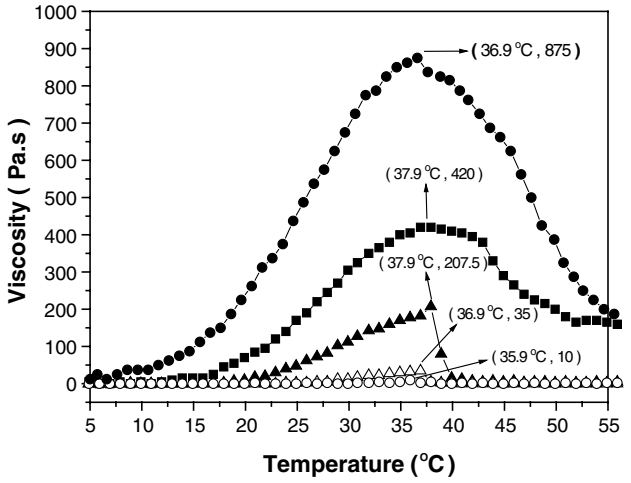


Fig. 3. Viscosity changes of polymer **3** with the various concentrations of the polymer. The concentrations were adjusted as 5 wt% (○), 7 wt% (△), 10 wt% (▲), 13 wt% (■), and 15 wt% (●), respectively.

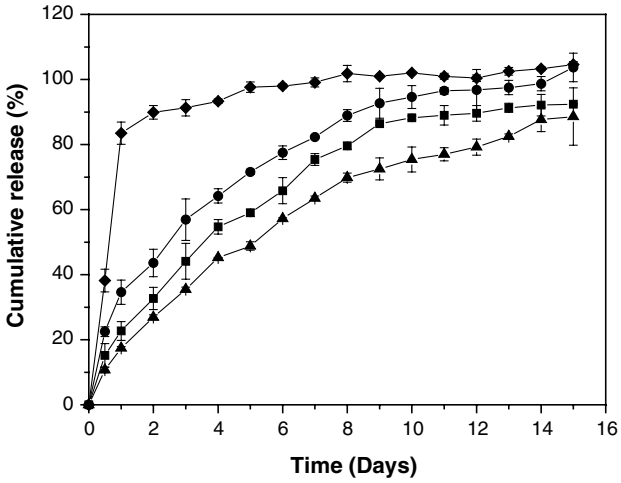


Fig. 4. Cumulative release of FITC-dextran from various polymer hydrogels at 37 °C. The concentrations of poloxamer (♦) and synthesized poly(organophosphazenes) (polymer **1**, ●; **3**, ■; **4**, ▲) were 25 and 10 wt%, respectively. FITC-dextran was dissolved in each polymer solution by 0.1% (w/v).

acid groups generated attack the polymer backbone, resulting in backbone cleavage [17,26]. Therefore, faster degradation of depsipeptide ethyl ester of polymer **2** resulted in faster loss of its mass and molecular weight.

The concentration-dependent gelation behavior of polymer **3** in phosphate-buffered saline solution (pH 7.4, 37 °C) examined by measuring the viscosity as a function of temperature is shown in Fig. 3. The synthesized polymer hydrogel showed good strength at 37 °C despite low concentration of the polymer. The viscosity of polymer **3** was largely dependent on its concentration. The V_{max} of polymer **3** of 15 wt% solution was 875 Pa s whereas its V_{max} of 7 wt% was only 35 Pa s. In the case of 10 wt% of poly(organophosphazene) solution, the viscosity was 207.5 Pa s at 37 °C. The other polymers synthesized are characterized in Table 1. These poly(organophosphazenes) showed reversible four-phase transition behaviors according to the temperature as previously reported [17]; a transparent solution under T_{ass}, a transparent hydrogel between T_{ass} and T_{max}, an opaque hydrogel over T_{max} and then a turbid solution at more elevated temperature. The decrease of viscosity beyond the T_{max} is explainable due to a collapse of the hydrogel and formation of the turbid solution.

3.2. In vitro release of FITC-dextran and HSA

Figs. 4 and 5 show cumulative amounts of FITC-dextran and human serum albumin (HSA) released from poly(organophosphazene) hydrogels at 37 °C, respectively. The release of the FITC-dextran was controlled by the polyphosphazene hydrogel and it showed a sustained release rate over two weeks, whereas the poloxamer hydrogel, which is well known as a representative injectable hydrogel, could not prevent an initial burst release of both FITC-dextran and HSA despite their high concentration as to 25 wt%. The release rate of the FITC-dextran was affected by the gelation property of the polymers. The stronger

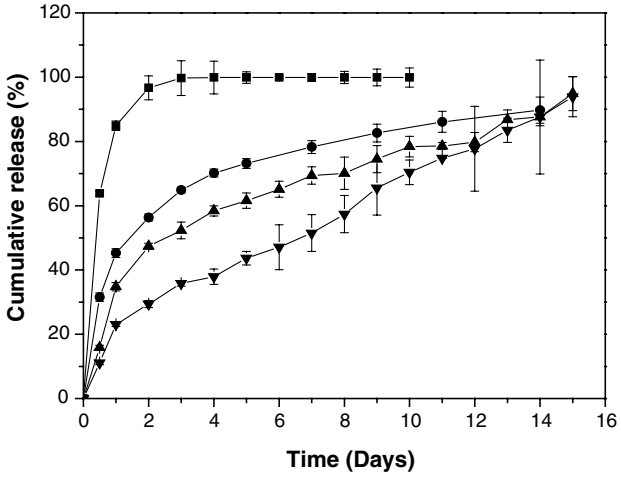


Fig. 5. Cumulative release of human serum albumin (HSA) from various polymer hydrogels at 37 °C. The concentrations of poloxamer (■) and synthesized poly(organophosphazenes) (polymers **2**, ●; **3**, ▲; **4**, ▼) were 25 and 10 wt%, respectively. HSA was dissolved in each polymer solution by 0.1% (w/v).

the gelation properties, the slower the release rate of the FITC-dextran from the gels. Generally, for an application to controlled release of hydrophilic polymeric drugs from the hydrogels, the more hardened the strength of the hydrogel, the more effective inhibition against the initial burst release. Fig. 4 corresponded precisely with this viewpoint. As a result, the release rate of the FITC-dextran decreased in the order of polymers **1**, **3**, and **4**, as shown in Fig. 4. This result was due to the fact that the stronger gelation properties at 37 °C was observed in the order of polymers **4**, **3**, and **1**, as listed in Table 1. For example, over 50% of the FITC-dextran was released in the case of polymer **1** after 3 days of incubation whereas less than 40% of FITC-dextran was released in the case of polymer **4**.

The drug release mechanism from a biodegradable hydrogel can be explained as diffusion at an initial stage and then a combination of diffusion and degradation at a later stage. The drug loaded in the hydrogel is released by diffusion through the three-dimensional network. The hydrogels with the stronger gelation properties give the smaller pore size of the network, resulting in slower release rate of the drug loaded. Such a result corresponded to the result of Fig. 5. The slower release rate of human serum albumin was observed in the polymer **4** than those in the polymers **2** and **3**. The release rate of drugs seems to be also affected by the degradation rate of the hydrogels. The release of human serum albumin from polymer **2** hydrogel was faster than that from polymer **3** hydrolgel nevertheless the viscosities of the polymers are quite close at 37 °C. However, the degradation rate of polymer **2** was faster than that of polymer **3**, as shown in Fig. 2.

Recently, Bhattarai et al. [14] demonstrated that the release periods of bovine serum albumin from the PEG-grafted chitosan hydrogel could be prolonged over one month. However, without a chemical crosslinking agent, genipin, initial burst release of protein from PEG-grafted chitosan hydrogel was apparently observed, showing short-term release periods. Among the synthesized polymers, the most effective and ineffective polymers were polymer **4** and polymer **1**, respectively, in agreement with the results listed in Table 1. Especially, polymer **1** containing depsipeptides exhibited low viscosity at 37 °C and can be easily hydrolyzed at pH 7.4 and 37 °C, which seems to provide fast release of loaded drug.

Fig. 6 shows the effect of the polymer concentration on the release of the FITC-dextran. The polymer concentration plays an important role in controlling the drug release rate. As a result, the higher polymer concentration afforded the slower drug release rate. This came from the fact that the higher polymer concentration gave the stronger gelation property as shown in Fig. 3. Such a result was consistent with the results of Figs. 4 and 5. On the other hand, drug concentration did not significantly affect the drug release rate, as shown in Fig. 7. As the polymer concentration increases, the structure of the hydrogel is more condensed. Accordingly, the release rate was controlled more strictly due to the diminishment of a drug release pathway. The poly(organophosphazenes) showing various physical properties can be synthesized by introducing diverse substituents as well as controlling a molar ratio of hydrophobic and hydrophilic groups induced to polymer backbone. On the other hand, physical properties of PEO–PPO–PEO triblock copolymers simply depend on the molar ratio of hydrophobic and hydrophilic groups, their molecular weight, or additives [7,8,11].

In conclusion, thermosensitive and biodegradable hydrogels which consist of poly(organophosphazenes) bearing both hydrophobic and hydrophilic groups with or without depsipeptides were synthesized. The polymer hydrogel followed thermoreversible sol–gel transition behaviors and comparatively had a good strength at low polymer concentrations. In vitro release behaviors of hydrophilic model drugs such as FITC-dextran and human serum albumin from these polymer hydrogels were sustained for about 2 weeks without a distinct initial burst. The release of FITC-dextran exhibited concentration-dependent behavior ranging from 7 to 15 wt% of the polymer solution, while it was almost independent of the concentration of FITC-dextran. The hydrogels in a higher polymer concentration give the smaller pore size of the network, resulting in slower release rate of the drug loaded. From the characterizations of the synthesized polymer and in vitro release behaviors of hydrophilic polymeric model drugs, it can be expected that poly(organophosphazenes) would be a predominant candidate for an injectable hydrogel applicable to bioactive protein drugs such as erythropoietin (EPO), granulocyte colony-stimulating factor (G-CSF), and human growth hormone (hGH).

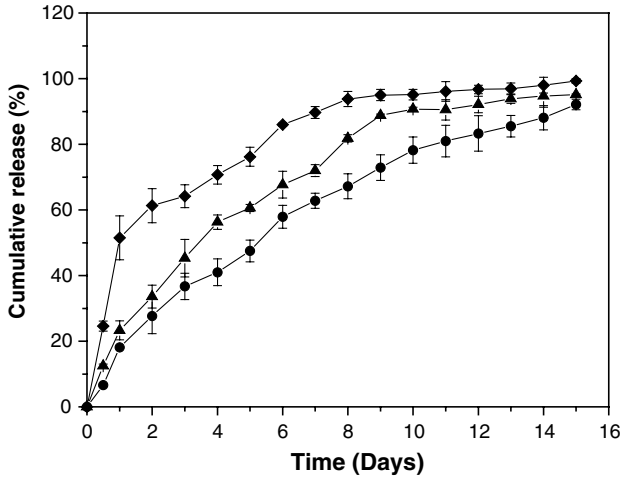


Fig. 6. Cumulative release of FITC-dextran from the hydrogel of polymer **3** with various polymer concentrations (7 wt%, ♦; 10 wt%, ▲; 15 wt%, ●) at 37 °C. Each hydrogel contained 0.1% (w/v) of FITC-dextran.

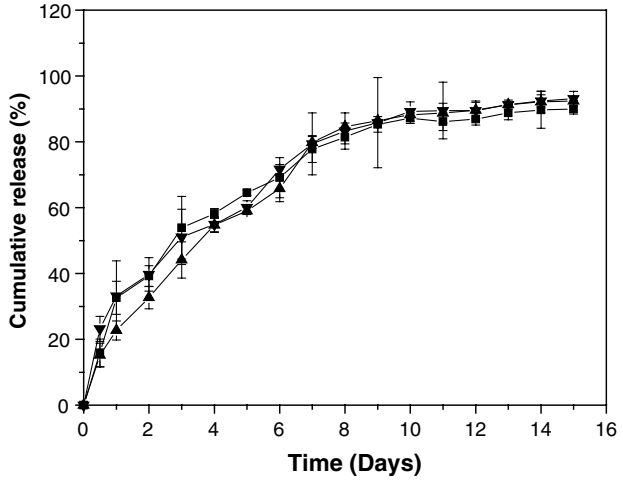


Fig. 7. Cumulative release of FITC-dextran from the hydrogel of polymer **3** at 37 °C with various drug concentrations (0.05%, ■; 0.1%, ▲; 0.5%, ▼). The concentration of synthesized poly(organophosphazene) was 10 wt%.

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