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pH-sensitive and bioadhesive poly(β-amino ester)–poly(ethylene glycol)–poly(β-amino ester) triblock copolymer hydrogels with potential for drug delivery in oral mucosal surfaces

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ABSTRACT

A series of novel pH-sensitive triblock copolymers composed of poly(β-amino ester)–poly(ethylene glycol)–poly(β-amino ester) (PAE–PEG–PAE) were synthesized by conjugating poly(β-amino ester) to poly(ethylene glycol). The resulting polymers were characterized by ^{1}H and ^{13}C NMR in $CDCl_3$ and gel permeation chromatography in tetrahydrofuran. The concentrated polymer solutions (30 wt%) exhibited a gel-to-sol transition in the pH range 6.4–7.8. The gel window spanned physiological conditions (37 °C, pH 7.4). After injection into a rat, the copolymer solution (30 wt%) changed to a gel in a short time. This copolymer hydrogel showed bioadhesive properties and in vitro release of lidocaine was controllable.

1. Introduction

pH is an important environmental factor for drug delivery systems, because pH varies between many specific or pathological body sites, such as the intestine, stomach, vagina, blood vessels, and tumor sites, as well as lysosomes and endosomes. Therefore, pH-sensitive polymeric hydrogels have been extensively explored as components of drug delivery systems [1]. Both anionic and cationic forms of pH-sensitive polymers have been developed. Typical anionic pH-sensitive polymers for drug delivery consist of carboxylic acids such as poly(acrylic acid) (PAAc) [2], poly(methacrylic acid) (PMAA) [3], and poly(glutamic acid) (PLG) [4]. Typical cationic pH-responsive polymers contain amine groups and include poly-(2-[dimethylamino]ethyl methacrylate) (PDMAEMA) [5] and poly-(2-[vinylpyridine]) (P2VP) [6].

Using two of the polymers described above, a triblock copolymer, namely, poly(methyl methacrylate)–poly(2-[dimethylamino]ethyl methacrylate)–poly(methyl methacrylate) (PMMA–PDMAEMA–PMMA) [7], was synthesized by group transfer polymerization. In aqueous solution (1 wt%) the polymer formed a gel at pH 4. An aqueous solution of poly(acrylic acid)–poly(2-vinylpyridine)–poly-(acrylic acid) (PAAc–P2VP–PAAc) [8] copolymer (2.5 wt%) formed a gel at a pH of about 3.4. However, these hydrogels do not cover physiological conditions (pH 7.4, 37 °C).

In recent years, cationic pH-responsive polymers are of interest due to their ability to form an ionic complex with biomacromolecules [9]. In our previous report, we have developed cationic copolymer hydrogels based on poly(amino urethane) (PAU) and poly(amido-amine) (PAA) [9,10]. These hydrogels exhibited a sol-to-gel-to-sol (or condensed gel) transition at relatively high pH (i.e., 7.0) with increasing temperature. Their phase transition covered the physiological conditions. However, the bioadhesive properties of these above copolymers have not been reported.

Another cationic polymer is poly(β-amino ester) (PAE) [11]. PAE is easily synthesized by Michael addition polymerization and the molecular weight may be controlled without difficulty [12]; the polymer is known to be readily biodegradable and of low cytotoxicity [11,13]. PAE acts as a hydrophilic block because of ionization of tertiary amine at a relatively low pH and becomes a hydrophobic block because of deionization of tertiary amine at higher pH [13]. PAE has been widely investigated for gene delivery [11] and anionic protein release [13].

Hydrogels possess bioadhesive capabilities that are valuable in medical and dental applications [14–18], including use as tissue adhesives and as injectable carriers for drug delivery to mucosal surfaces (*e.g.*, the oral cavity and the respiratory, reproductive, and gastrointestinal tracts). Chitosan, dextran, hydroxypropylcellulose, carboxymethylcellulose, poly(acrylic acid), and polycarbophil are examples of typical bioadhesive polymers [19].

In the present study, based on the cationic PAE polymer a series of novel triblock copolymer hydrogels exhibiting pH-sensitivity and

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possessing bioadhesive properties were synthesized. PAE was added to poly(ethylene glycol) molecules (PEGs) to create pH-responsive poly(β-amino ester)–poly(ethylene glycol)–poly-(β-amino ester) (PAE–PEG–PAE) triblock copolymers. PAE–PEG–PAE copolymers were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy and gel permeation chromatography (GPC). In contrast to PAU multiblock [9] and PAA triblock copolymer [10], the PAE–PEG–PAE triblock copolymers in aqueous solutions (30 wt%) did not demonstrate a sol-to-gel-to-sol (or condensed gel) transition, but a gel-to-sol transition at pH values above 6.4 with increasing temperature.

After subcutaneous injection of a polymer solution (30 wt%, pH 6.4) into a rat, a polymeric hydrogel quickly formed in situ. The bioadhesive properties of the copolymers via interactions with mucin were also evaluated in this study and in vitro release of lidocaine demonstrated that this hydrogel could be a drug carrier in the oral mucosal surfaces.

2. Materials and methods

2.1. Materials

Poly(ethylene glycol)s (PEGs) were obtained from Sigma–Aldrich (St. Louis, MO). Lidocaine was purchased from Sigma–Aldrich, as were anhydrous benzene, anhydrous dichloromethane (DCM), acryloyl chloride (AC), triethylamine (TEA), 4,4′-trimethylene dipiperidine (TMDP), and 1,6-hexandiol diacrylate (HDA); all chemicals were used as received. Mucin from pig stomach (type III) was obtained from Sigma–Aldrich and dialyzed against de-ionized water for 1 day before use [20]. Hydrochloric acid (HCl), sodium hydroxide (NaOH), hexane, tetrahydrofuran (THF) and diethyl ether were all the products of Samchun Co. (Seoul, Korea). All other reagents were of analytical grade and were used without further purification.

2.2. Synthesis of PAE–PEG–PAE triblock copolymers

Poly(ethylene glycol) diacrylate (A–PEG–A) was synthesized by coupling AC to the hydroxyl groups at the ends of PEG in the presence of TEA as a catalyst. In a dry two-neck round-bottom flask, 10 g of PEG ($M_n = 2000$ Da) was dried for 4 h under vacuum at 120 °C and the PEG was next dissolved in 100 mL anhydrous benzene at ambient temperature under a dry nitrogen atmosphere. Next, 5.6 mL TEA and 3.6 mL AC (96%) were added at 0 °C under stirring. The reaction continued for 3 h at 80 °C. After filtering, the resulting polymer was precipitated in an excess of *n*-hexane. The precipitate was dried under vacuum at room temperature for 48 h. The final yield was approximately 90%. The PEG diacrylate was characterized by ^{1}H NMR and acrylation was 96%.

^{1}H NMR ($CDCl_3$): $\delta = 3.86$–3.49 ppm (CH_2–CH_2–O of PEG), 6.48–5.83 (*CH* of AC) (Fig. 1a).

The triblock copolymers were synthesized by Michael addition polymerization between the vinyl groups at the ends of A–PEG–A, HDA, and hydrogens of the amine groups of TMDP (Scheme 1). In a one-neck round-bottom flask 2.0 g PEG diacrylate ($M_n = 2000$ Da) was dissolved in 80 mL DCM at ambient temperature, and 4.5 g HDA and 3.2 g TMDP were added. Next, the reaction mixture was kept in an oil bath at 50 °C under reflux for 3 days under stirring. The polymer was purified as our previous study [13]: First, DCM was completely removed by evaporation at 40 °C and the dried residue dissolved in THF. The copolymer was filtered through filter paper (5C 100 circles; Toyo Roshi Kaisha, Japan). Second, THF was removed at 50 °C under reduced vacuum and the dried copolymer was dissolved in DCM and purified by precipitation into excess diethyl ether. This method was used to remove PAE homopolymer. The precipitate was dried under vacuum at room temperature for 48 h.

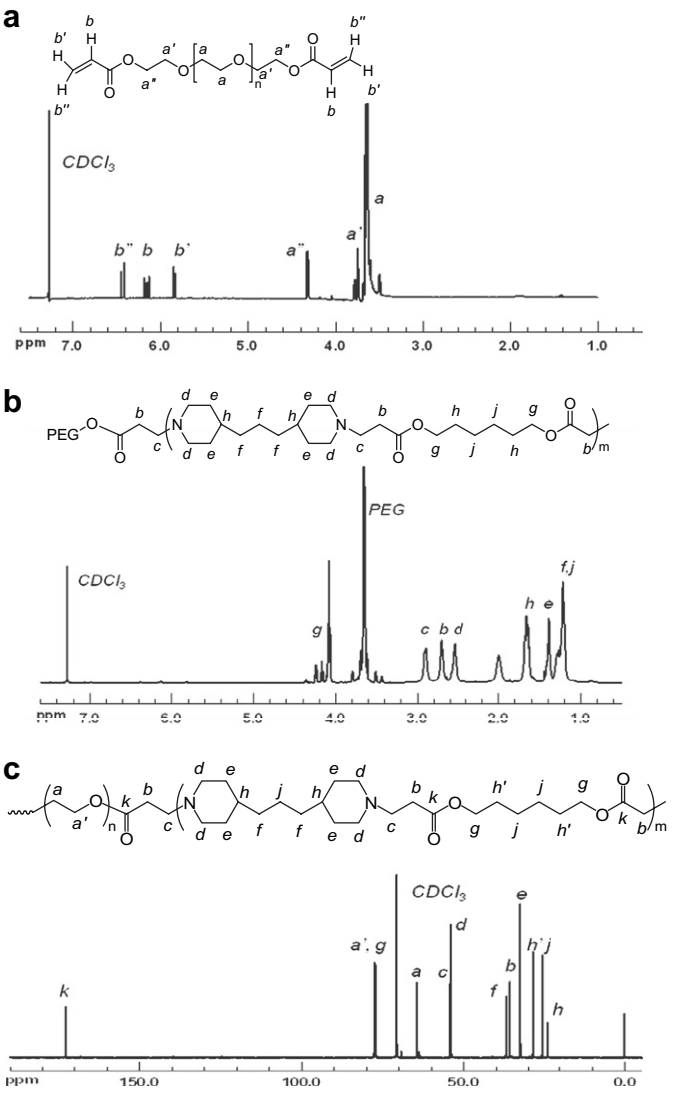
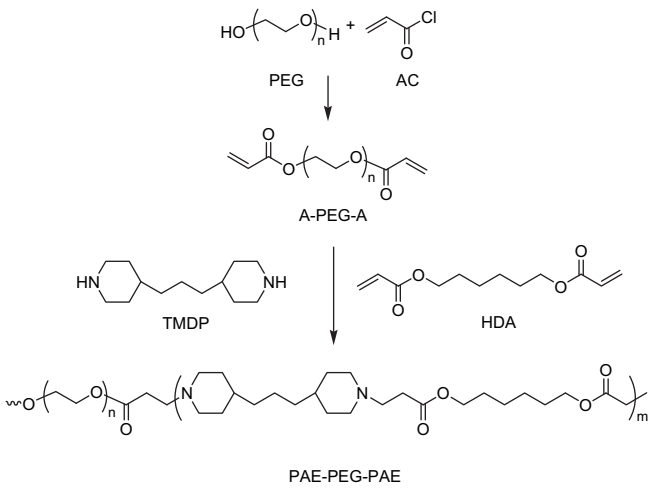


Fig. 1. ^{1}H NMR and ^{13}C NMR spectra. (a) PEG 4600 diacrylate; (b) PAE–PEG–PAE (2340–4600–2340) triblock copolymer; (c) ^{13}C NMR spectrum of PAE–PEG–PAE (2340–4600–2340).



Scheme 1. Synthesis route of the triblock copolymer PAE–PEG–PAE.

The final yield was approximately 75%. PAE–PEG–PAE copolymers of different molecular weights could be obtained by changing the feed ratios of the monomers and the PEG molecular weight. ^{1}H NMR was used to examine the chemical structures of the synthesized copolymers.

^{1}H NMR ($CDCl_3$): $\delta = 4.33–4.15$ ppm (OCO–CH_2 of HDA), 3.78–3.5 (CH_2CH_2O of PEG), 2.93 (NCH_2CH_2OCO), 2.71 (NCH_2CH_2OCO), 2.56 ($N(CH_2–)_2$ of TMDP), 1.68–1.63 ($OCOCH_2CH_2$ of HDA and $(–CH_2)_2CH–CH_2$ of TMDP), 1.44–1.4 ($((–CH_2)_2CH–CH_2$ of TMDP), 1.39–1.2 ($CH–(CH_2)_3–CH$ of TMDP and $OCO(CH_2)_2(CH_2)_2$ of HDA), (Fig. 1b).

2.3. Characterization

^{1}H and ^{13}C NMR were carried out using a 500 MHz spectrometer (Varian Unity Inova 500NB instrument) to examine the structures of polymers in $CDCl_3$.

Molecular weights of copolymers and the distribution thereof were measured by gel permeation chromatography (GPC) using a Waters Model 410 instrument with a refractive index detector (Shodex, RI-101) and two Styragel (KF-803L and KF-802.5) columns in series, at a flow rate of 1.0 mL/min (eluent: tetrahydrofuran [THF]; 40 °C). Poly(ethylene glycol) standards (Waters) were used to determine molecular weights.

2.4. Sol–gel phase diagram

The sol (flow)–gel (no flow) phase transition was recorded using the test tube inverting method [9,10]. In brief, a 4 mL test tube containing 0.5 mL of PAE–PEG–PAE triblock copolymer solution was immersed in a temperature-controlled water bath. Each sample was dissolved in phosphate buffered saline (PBS), at 30 wt%, at pH 1, over 30 min. The pH of a polymer solution was then adjusted to the required pH (*e.g.*, pH 7.4) using 5 M NaOH and 5 M HCl solutions and polymer solutions were kept at 2 °C for 1 day. The sol–gel transition was determined by inverting the vial. Samples were equilibrated for 20 min at temperature intervals of 2 °C.

2.5. Rheology

The viscosity variation of 30 wt% copolymer aqueous solutions was determined by dynamic mechanical analysis (Bohlin Rotational Rheometer). A polymer solution was placed between two 20 mm diameter plates with a gap of 0.5 mm. The controlled stress and frequency were 0.4 Pa and 1 rad s^{-1}, respectively. The heating rate was 0.2 °C min^{-1}.

The viscosity of solutions of copolymer, mucin, and copolymer–mucin mixtures was measured using plate-plate geometry, at 25 °C, at shear rates ranging from 1.99–398 s^{-1} [20,21]. All viscometric experiments were performed in triplicate. The copolymer–mucin solutions were prepared as follows. First, mucin was hydrated with distilled water by gentle stirring for 1 h at room temperature to yield a solution of 20 wt%. Second, copolymer was dissolved in distilled water to yield a solution of 10 wt% (pH 7.4). Dissolution was facilitated, and the pH of the copolymer solution adjusted, using small amounts of 5 M HCl and 5 M NaOH solutions. Next, the copolymer and mucin solutions were mixed to yield a final mucin concentration of 10 wt%, with variable polymer concentration. Each copolymer–mucin mixture was further stirred for 0.5 h at room temperature before measurement of viscosity.

2.6. In vivo gel integrity

To study the gel integrity of aqueous copolymer solutions in vivo, male Sprague-Dawley (SD) rats (Hanlim Experimental Animal Laboratory, Seoul, Korea) were used. Rats (5–6 weeks old, average body weight 200 g) were handled in accordance with the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals (NIH publication 85-23, revised 1985).

PAE–PEG–PAE (4055–4600–4055) was dissolved in water to 30 wt% and 200 μL amounts (at 20 °C and pH 6.4) were subcutaneously injected into the sides of the back. After 5 min, the rat was sacrificed and gel integrity was observed.

Table 1
Characteristics of the PAE–PEG–PAE triblock copolymers.

Polymer (PAE–PEG–PAE)	PEG[a]	M_w/M_n[b] (PEG)	M_n[b]	M_w/M_n[b]
4055–4600–4055	4600	1.07	12,710	1.36
2340–4600–2340	4600	1.07	9280	1.34
2420–2000–2420	2000	1.03	6840	1.5

[a] Provided by Aldrich.
[b] Measured by GPC.

2.7. Lidocaine loading and in vitro release

Lidocaine was added to a polymer solution (30 wt%) in PBS buffer at pH 5 to obtain a final concentration of 2 mg/mL, and stirred at 4 °C. After 12 h, the polymer solution was adjusted to pH 7.4 using a small amount of NaOH (5 M). A Franz diffusion cell with a membrane surface area of 1.766 cm^2 and a cell volume of 10 mL was used to study release of lidocaine in vitro. A cellulose

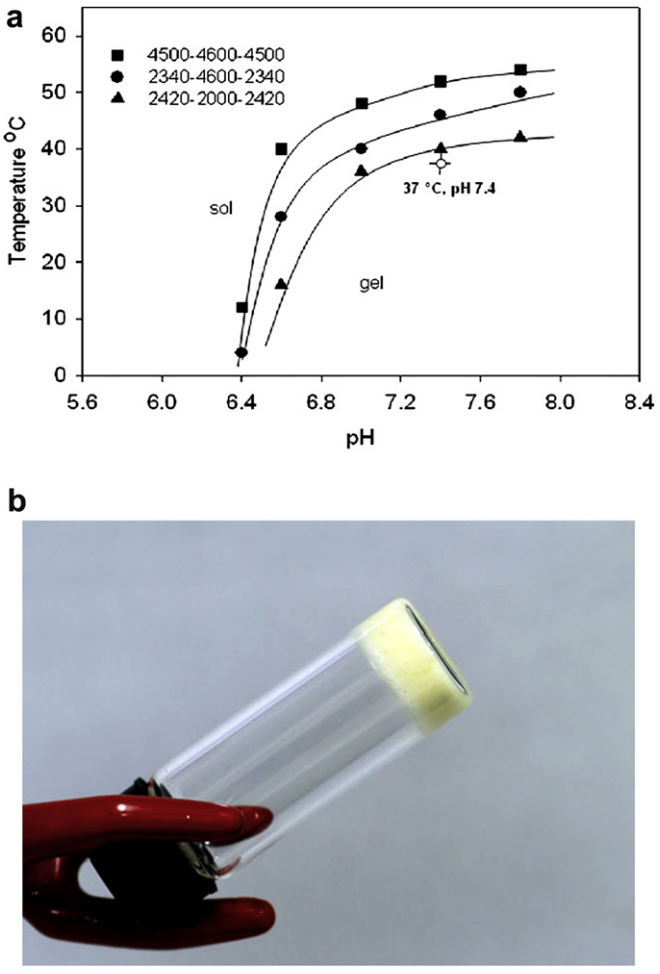


Fig. 2. (a) Gel–sol phase diagram of pH-responsive triblock copolymers in aqueous solutions (30 wt%); (b) Gel in vitro of 4055–4600–4055 copolymer solution at pH 7.4 and 37 °C.

membrane with a MW cutoff of 12,000–14,000 Da was used as an interface, and was regenerated before use. Lidocaine-loaded hydrogel (0.5 g) was placed on the donor compartment and PBS at pH 7.4 was used as the receptor medium, maintained at 37 °C with stirring at 300 rpm. At predetermined intervals, 2 mL of released medium was removed from the receptor compartment and a further 2 mL of fresh medium added. The concentration of lidocaine was determined spectrophotometrically (Biochrom Libra S22 instrument) at 263 nm [22,23].

2.8. Statistical analysis

Bioadhesive and drug release data were reported as means of three experiments. Statistical significance ($p < 0.05$) was performed using Student's *t*-test.

3. Results and discussion

3.1. Synthesis and characterization of triblock copolymers

The triblock poly(β-amino ester)s (PAE–PEG–PAE) were synthesized by Michael-type step polymerization of poly(ethylene glycol) diacrylate, TMDP, and HDA. Scheme 1 illustrates the synthesis route to the triblock copolymers. PAE block length was tuned by varying the feed ratio of PAE monomers. ^{1}H NMR and ^{13}C confirmed formation of the triblock copolymers. All protons of the PEG diacrylate and triblock copolymer were attributed as labeled in Fig. 1a and b. As shown in Fig. 1a, the protons at 3.51–3.78 ppm were assigned to the CH_2 of PEG (peak *a*, *a'*).The protons at 6.48–5.83 ppm (peaks *b*,*b'*,*b''*)were assigned to the CH of AC, thus confirming the conjugation of AC to PEG. The –CH═ proton of conjugated AC (peak *b*) and the CH_2 protons of PEG (peak *a''*) were used to calculate the acrylation yield of PEG and it was 96%. The protons at 2.93 ppm (peak *c*) produced by the reaction of TMDP with A–PEG–A and/or HDA confirmed the formation of triblock copolymers (Fig. 1b). In Fig. 1b, the peaks at 6.48–5.83 ppm was almost disappeared, indicating that most of A–PEG–A has been consumed. To further examine the structure of block copolymers, ^{13}C NMR was carried out (Fig. 1c). The signals at 35.83 ppm (peak *b*) and 54.16 ppm (peak *c*) also confirmed the formation of copolymer structure. However, the 96% acrylation yield meant that there remained a little amount of diblock copolymers. The ^{1}H NMR and ^{13}C NMR characterization clearly indicate that the successful polymerization of copolymers. The molecular weights and polydispersity indices of PAE–PEG–PAEs were measured by GPC and the data are listed in Table 1.

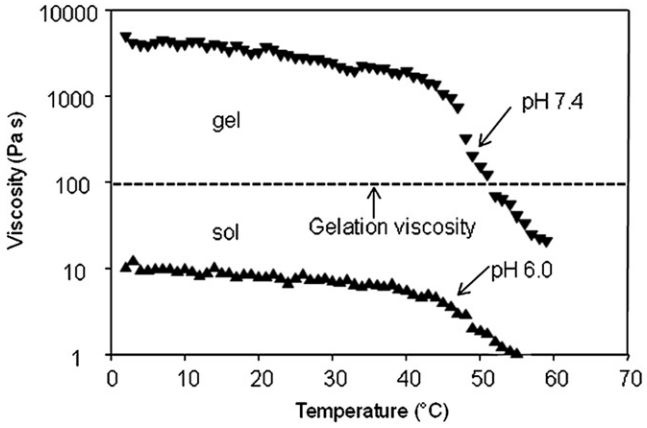


Fig. 3. Viscosity change of PAE–PEG–PAE (4055–4600–4055) block copolymer solutions (30 wt%) at different pH values.

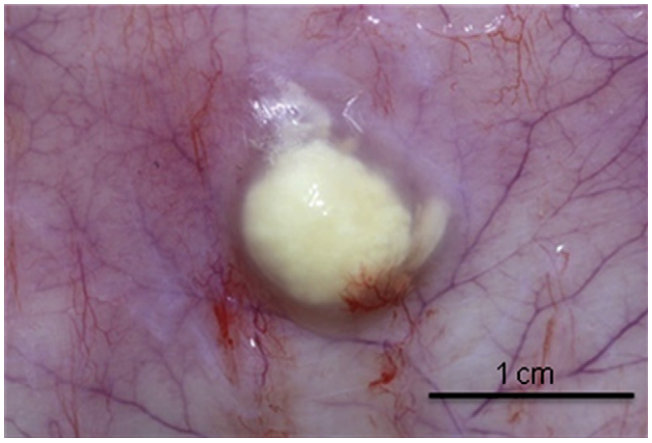


Fig. 4. Gel formation in vivo 5 min after subcutaneous injection of 30 wt% copolymer (4055–4600–4055) solution (pH 6.4) into a rat.

3.2. Sol–gel phase transition of copolymers

The sol–gel phase diagrams of PAE–PEG–PAE triblock copolymers in aqueous solution were studied by the tube inverting method. As shown in Fig. 2a, the sol–gel phase transition of copolymer solutions (4055–4600–4055) (30 wt%) showed pH-dependence at pH 6.4–7.8. At a low pH (such as pH 6.0), only some of the tertiary amines of PAE were de-ionized and PAE remained hydrophilic. The electrostatic repulsion between charged PAE blocks led to weak interactions between block copolymers [24]. Therefore, the copolymer in solution existed as a sol in the temperature range 0–60 °C. In contrast, at a higher pH (such as pH 7.4), a significant increase in the formation of clustered micelles even at low temperature resulted in a gel phase [22]. The upper transition temperature of the gel at pH 7.4 was about 52 °C. The phase transition from gel-to-sol (aggregation) at the upper transition temperature is attributed to breakage of the clustered network caused by partial dehydration of the PEG blocks [25]. The gel region at pH 7.2–7.8 was wider than that at pH 6.4–7.0, because of the greater extent of deionization of the PAE blocks.

The influence of PAE block length on copolymer phase diagrams was next studied. As shown in Fig. 2a, the gel region of 4055–4600–4055, with a PAE block length of 4055 Da, was wider than that of 2340–4600–2340 with a PAE block length of 2340 Da but with PEG of the same molecular weight (4600 Da) [26], because of an increase in hydrophobic interactions between the PAE blocks. In addition, the effect of PEG molecular weight on the sol–gel phase diagram was investigated. Fig. 2a also shows the change in the phase diagram that occurred as the PEG molecular weight was decreased from 4600 to 2000 Da. It was found that the gel-to-sol transition temperature fell from 46 °C to 40 °C at pH 7.4 with a decrease in PEG molecular weight from 4600 Da to 2000 Da, with the PAE molecular weight fixed at about 2340 Da. This is attributed to a decrease in the ratio of hydrophobic (PAE) to hydrophilic blocks with increasing PEG molecular weight [26]. Moreover, the micelle size increases with longer PEG block length [27]. Fig. 2b shows gelation in vitro at pH 7.4 and 37 °C.

3.3. Viscosity

The gel–sol transition of the copolymer PAE–PEG–PAE 4055–4600–4055 in solution was confirmed by dynamic rheological analysis at different pH values (pH 6.0 and 7.4). As shown in Fig. 3, at pH 6.0 the complex viscosity was found to decrease slightly from 10 Pa s to 1 Pa s as the temperature was increased from 2 °C to

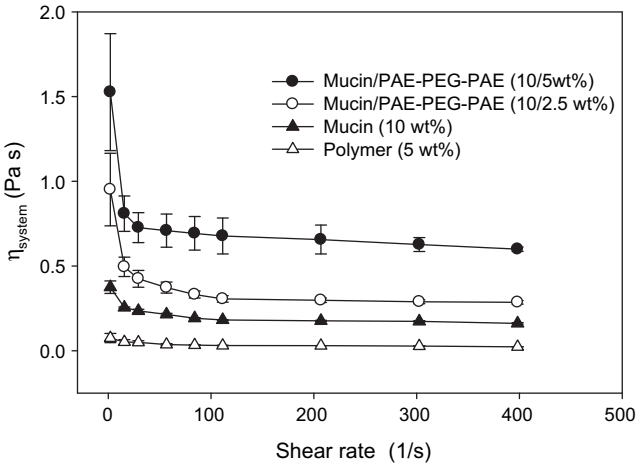


Fig. 5. Effect of PAE–PEG–PAE (4055–4600–4055) on the viscosity of mucin as a function of shear rate (s^{-1}) at 25 °C and pH 7.4. The concentration of mucin was 10 wt% in all tests.

55 °C. However, at pH 7.4, the viscosity showed a significant decrease from 4931 Pa s to 40 Pa s as the temperature of the copolymer solution was increased from 2 °C to 55 °C. This abrupt decrease in viscosity at about 50 °C is explained by dehydration of PEG at high temperatures. The square-dotted line at which the viscosity of the polymer solution was around 100 Pa s shows the gel-to-sol transition in vitro. The polymer solution was a gel when the viscosity was higher than 100 Pa s and a sol when the viscosity was lower than 100 Pa s. Also, the viscosity at pH 7.4 was higher than that at pH 6.0 because of the greater hydrophobicity of PAE blocks at pH 7.4 than at 6.0.

3.4. In vivo gel integrity

To examine injectability and gel formation, 200 μL of copolymer solution (30 wt%) at pH 6.4 and 20 °C was subcutaneously injected into a male Sprague-Dawley (SD) rat through a syringe needle. After 5 min, the rat was sacrificed and the gel morphology was observed. As shown in Fig. 4, a gel formed in situ in a short time after injection as a result of the pH and temperature change occurring after injection. This suggests that the triblock copolymer solution can be easily injected into the body and will rapidly form an in situ gel.

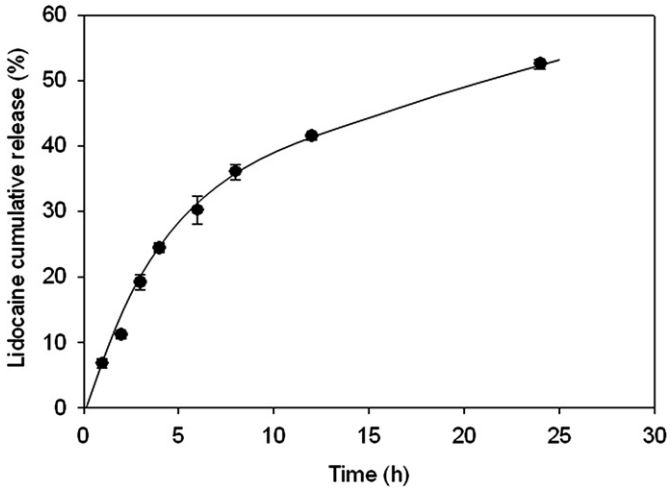


Fig. 6. In vitro release of lidocaine (2 mg/mL) from 30 wt% copolymer hydrogel (4055–4600–4055).

3.5. Bioadhesive properties

To illustrate the bioadhesive potential of the PAE–PEG–PAE copolymer, the mucoadhesive interactions of PAE–PEG–PAE and mucin from pig stomach, were investigated. Mucin from pig stomach is a high molecular weight glycoprotein ($M_w = 2 \times 10^6$) frequently used as a model mucin for evaluation of bioadhesive candidates [20,21]. The mucoadhesive properties were evaluated by the Hassan method [21]. In this approach, interaction forces in a mucin–bioadhesive polymer system are monitored by viscosity measurements. The viscosity of the mucin–bioadhesive polymer system (η_{system}) contains contributions from the viscosity of mucin (η_{mucin}), from the bioadhesive polymer ($\eta_{polymer}$), and a viscosity component resulting from bioadhesion ($\eta_{bioadhesion}$). If η_{system} is higher than the sum of η_{mucin} and $\eta_{polymer}$, the polymer is bioadhesive.

$$\eta_{system} = \eta_{mucin} + \eta_{polymer} + \eta_{bioadhesion} \quad (1)$$

Fig. 5 shows the effects of the PAE–PEG–PAE 4055–4600–4055 copolymer, at different concentrations (2.5 and 5 wt%), on the viscosity of mucin (10 wt%) at 25 °C. The viscosities of PAE–PEG–PAE copolymer–mucin mixtures at a copolymer concentration of 2.5 wt% were much higher than the sums of copolymer and mucin viscosities, indicating that the copolymer and mucin interacted. With an increase in copolymer concentration from 2.5 wt% to 5 wt% at a fixed mucin concentration of 10 wt%, the viscosity of the copolymer–mucin mixture increased because of an increase in interaction between the copolymer and mucin at the higher copolymer concentration [21]. As shown in Fig. 5, the viscosities of all samples decreased abruptly at the low shear rates (below 84 s^{-1}), but they did not show much difference at the high shear rates (above 84 s^{-1}). Thus, the viscosity at above 84 s^{-1} can be used for comparison between polymeric systems. For the mixture of mucin (10 wt%) and PAE–PEG–PAE (12.11 kDa, 2.5 wt%), the bioadhesion viscosity ($\eta_{bioadhesion}$) of 136 mPa s (at a shear rate of 93 s^{-1}) was comparable to the $\eta_{bioadhesion}$ of 137.56 mPa s obtained using a mixture of mucin (15 wt%) and chitosan (652 kDa, 1 wt%), and slightly higher than the $\eta_{bioadhesion}$ of 111.17 mPa s recorded for a mixture of mucin (15 wt%) and poly(acrylic acid) (90 kDa, 2.5 wt%), in acetate buffer at pH 5.5. The enhancement in viscosity of copolymer–mucin mixtures is attributed to ionic interactions between positive charges of the PAE–PEG–PAE copolymer and negative charges of mucin carboxylic acid (sialic acid) groups [21].

3.6. In vitro release of lidocaine from the triblock copolymer hydrogel

Lidocaine, a local anesthetic, was used as a model to examine the release behavior of the hydrogel under physiological conditions (pH 7.4, 37 °C). The drug loading concentration was 2 mg/mL. The cumulative release of lidocaine is shown in Fig. 6. As shown in Fig. 6, 53 wt% of lidocaine was released from the gel matrix after 24 h. The in vitro release profile indicates that the triblock copolymer hydrogel offers controllable release of lidocaine under physiological conditions.

4. Conclusion

A series of novel PAE–PEG–PAE copolymers were synthesized and characterized. At pH 6.4 and above, a copolymer in aqueous solution (30 wt%) exhibited a gel–sol transition with an increase in temperature. Gelation occurred as a result of self-assembly and hydrophobic interactions in the gelation pH and temperature range. The sol–gel phase diagram could be adjusted by varying the

molecular weight of PAE and PEG. The gel region spanned physiological conditions (pH 7.4, 37 °C).

The triblock copolymer (PAE–PEG–PAE) is composed of PEG and biocompatible poly(β-amino ester). This material is based on two hydrophilic blocks (PEG and PAE) that are easily dissolved in aqueous solution at a relatively low pH [28]. Such polymer solutions may thus be easily formulated with various drugs at low pH. In addition, PAE–PEG–PAE hydrogels demonstrated bioadhesive capabilities and in vitro release of lidocaine for over 1 day. Thus, PAE–PEG–PAE hydrogels are expected to form a novel class of bioadhesive hydrogels for drug delivery in the oral mucosal surfaces.

Acknowledgment

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