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In situ gelling aqueous solutions of pH- and temperature-sensitive poly(ester amino urethane)s

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ABSTRACT

A series of novel pH- and temperature-sensitive multiblock poly(ester amino urethane)s were synthesized. The copolymers were characterized by ^{1}H NMR, FT-IR and GPC. In the multiblock copolymers, the tertiary amino groups of the poly(amino urethane) segments act as pH-responsive moieties, while the PCL–PEG–PCL blocks act as biodegradable and temperature-sensitive segments. At a relatively high pH (7.0 or above), the multiblock copolymer aqueous solution showed a sol-to-gel-to-aggregation transition with increasing temperature. In contrast, at a lower pH (below 7.0), the polymer solution always existed as a sol state within the experimental temperature range. The gel window covers the physiological conditions. After subcutaneous injection of the 20 wt% multiblock copolymer solutions into mice, polymeric hydrogels were formed *in situ* in a short time. The *in vitro* release of an anticancer drug, paclitaxel, persisted over 1 month under physiological conditions.

1. Introduction

Stimuli-sensitive hydrogels are highly attractive materials for their extensive applications in pharmaceutical, biochemistry, biomedical and related fields [1–8]. Recently, the thermosensitive linear and star-shaped block copolymers comprising poly(ethylene glycol) (PEG) and various hydrophobic blocks have been extensively studied [9–19]. The use of block copolymer hydrogels consisting of hydrophilic PEG and hydrophobic biodegradable aliphatic polyesters, such as poly(caprolactone) (PCL), poly(D,L-lactic acid) (PDLLA) and poly(D,L-lactic acid-*co*-glycolic acid) (PLGA), is due to their biocompatibility and biodegradability [20–22]. These hydrogels have been shown to exhibit sol-to-gel (lower) and/or gel-to-sol (upper) transitions with increasing temperature. The lower phase transition is important for drug delivery applications, because the solution flows freely at room temperature and forms a gel at body temperature [23–25]. Polyurethanes have also been extensively investigated as biomaterials due to their excellent biocompatibility and mechanical properties [26,27]. However, the reports on *in situ* forming hydrogels based on polyurethanes are relatively limited.

Intelligent polymers and hydrogels responding to multiple stimuli, especially to both temperature and pH, have attracted increasing interest [28–36]. In recent years, hydrogels bearing cationic groups have received considerable attention for drug delivery systems because of their diversity in terms of chemical structures, molecular weights and ability to bind biomacromolecules through electrostatic interactions [37]. Natural cationic polysaccharides such as chitosan [38] and synthetic cationic polymers such as poly(amido amines) [39,40], poly(ethylene imine) [41] and polylysine [42], have been used for the delivery of protein, gene and drug molecules. Synthetic polymers bearing piperazine groups, such as poly(*N*-acryloyl-,*N*′-alkyl piperazine-*co*-methyl methacrylate) and poly(β-amino ester), respond to a narrow pH change in the region of pH 6–7.4 and therefore have potential in biomedical applications [43,44].

In this work, a series of novel pH- and temperature-sensitive poly(ester amino urethane)s bearing piperazine groups were synthesized by the condensation polymerization of OH–PCL–PEG–PCL–OH, bis-1,4-(hydroxyethyl)piperazine (HEP) and 1,6-diisocynato hexamethylene (HDI) using dibutyltin dilaurate as a catalyst. The resulting polymers were characterized by ^{1}H NMR, FT-IR and gel permeation chromatography (GPC). The pH/temperature-dependent sol–gel phase transition behaviors of the polymer solutions were studied by tube inverting method, and the *in vivo* gel formation of the multiblock polymer solution was investigated. Additionally, the *in vitro* release of an anticancer model drug, i.e. paclitaxel, from the copolymer hydrogel was studied under physiological conditions.

2. Experimental

2.1. Materials and methods

Poly(ethylene glycol) (PEG) ($M_n = 2000$), ε-caprolactone (CL), dichloroethane (anhydrous), toluene (anhydrous), dibutyltin(II)

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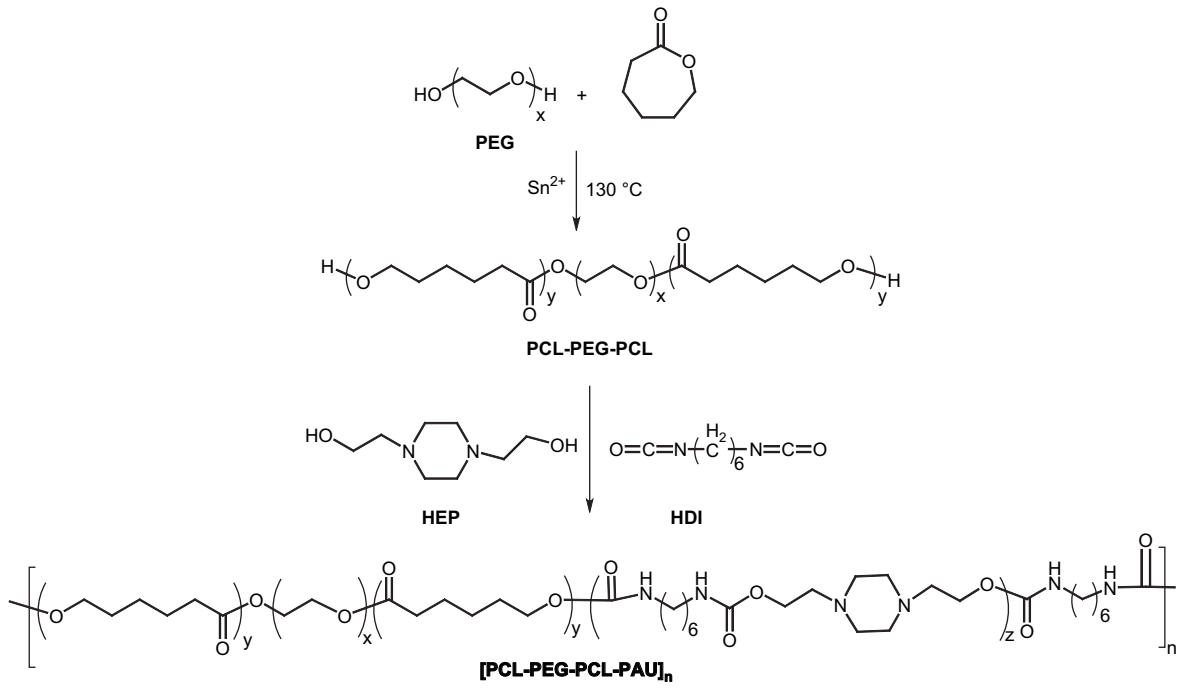

Scheme 1. Synthesis route of the multiblock copolymer ([PCL–PEG–PCL–PAU]$_n$).

dilaurate, bis-1,4-(hydroxyethyl)piperazine, 1,6-diisocyanato hexamethylene, and phosphate buffer saline (PBS) tablets were purchased from Sigma–Aldrich. PEG ($M_n = 1750$) was purchased from ID Biochem, Inc (Korea). All other chemicals were of reagent grade and used as-received. Diethyl ether, chloroform, and tetrahydrofuran were obtained from Samchun Chemical Co. (Korea) and were used as-received. Paclitaxel (Genexol; Samyang Genex) was used as-received and its purity was over 99%.

2.2. Synthesis of PCL–PEG–PCL triblock copolymer

The PCL–PEG–PCL triblock copolymer was synthesized by ring-opening polymerization of ε-CL using PEG as the initiator and $Sn(Oct)_2$ as the catalyst, respectively. The ratio of PEG/PCL was adjusted by varying the feed ratio of PEG and ε-CL. The detailed procedure is as follows: PEG and $Sn(Oct)_2$ were added to a two-neck round-bottom flask. The flask was placed in an oil bath at 110 °C and dried under vacuum for 4 h. After cooling the flask to room temperature, ε-CL was added under dry nitrogen, and the resulting reaction mixture was further dried under vacuum at 60 °C. After 1 h, the temperature was raised slowly to 130 °C, and the reaction was performed over a period of 24 h under dry nitrogen atmosphere. The reactants were then cooled to room temperature and dissolved in dichloromethane, and the resulting product was precipitated in excess diethyl ether. The precipitated block copolymer was dried in a vacuum at 40 °C for over 48 h, affording a yield of over 80%.

2.3. Synthesis of [PCL–PEG–PCL–PAU]$_n$ multiblock copolymer

The multiblock copolymers (denoted as [PCL–PEG–PCL–PAU]$_n$) were synthesized by reacting together hexamethylene diisocyanate (HDI), hydroxyl-terminated PCL–PEG–PCL and bis-1,4-(hydroxyethyl)piperazine (HEP). The condensation reactions of PCL–PEG–PCL, HEP and HDI were carried out at a stoichiometric ratio of the OH and NCO groups (OH/NCO = 1:1). The typical reaction procedure is as follows (Scheme 1): 1.0 mmol of PCL–PEG–PCL was added to a dry 250 mL flask equipped with a magnetic bar, and the flask was placed in an oil bath at 80 °C under vacuum. After 2 h, HEP (10 mmol) and a catalytic amount of dibutyltin dilaurate were added and vacuum was further applied for 30 min. After that the flask was kept under nitrogen atmosphere and maintained at the same condition. Then 50 mL of anhydrous toluene/1,2-dichloroethane (50:50) solvent was added, and stirring was continued until HEP completely dissolved. The reaction was triggered by adding hexamethylene diisocyanate (11 mmol) at 80 °C. The reaction mixture became highly viscous within 1 h, after which the flask was cooled to room temperature and diluted with chloroform. The resulting polymer solution was precipitated in a 10-fold excess of diethyl ether. The product was dried under vacuum at room temperature for 48 h.

2.4. Sol–gel phase diagram

The sol (flow)–gel (non-flow) phase transition temperature of the multiblock copolymer in buffer solution was recorded using the tube inverting method with a 4 mL vial at a temperature interval of 2 °C. Each sample at a given concentration (20 wt%) was dissolved in 0.01 M PBS solution containing 1 M HCl and kept for 1 day at 2 °C. Then, the pH of the block copolymer solution was adjusted to a certain pH (e.g. pH 6.6) by adding a small amount of 5 M NaOH solution at 2 °C.

2.5. In vivo *gel formation*

In order to investigate the injectability and *in vivo* gel formation of the polymer solution, the 20 wt% multiblock copolymer solutions at pH 6.7 and 0 °C were subcutaneously injected into mice. After 15 min, the mice were sacrificed and the *in situ* formed hydrogels were observed.

2.6. In vitro *release of paclitaxel*

Paclitaxel was dissolved in the 20 wt% multiblock copolymer solution (2 °C and pH 5–6) at 5 and 10 mg/mL, respectively. After the pH was adjusted to 7.4 at 2 °C, stirring was continued for 12 h.

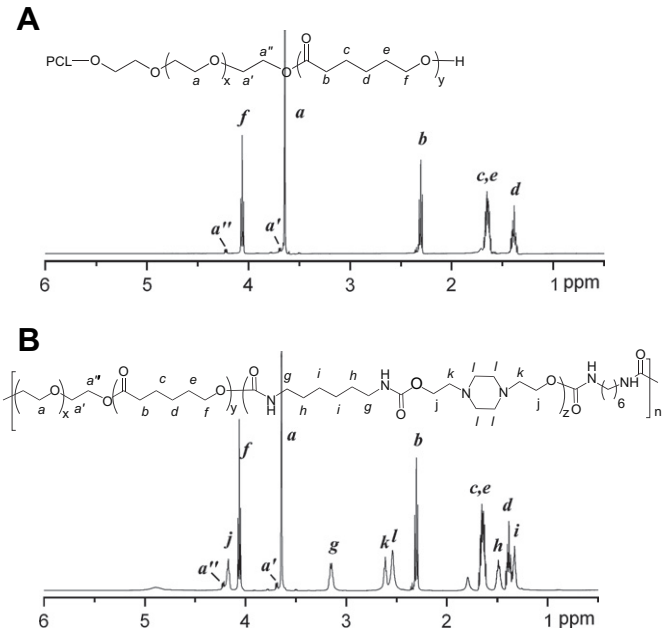

Fig. 1. Typical ^{1}H NMR spectra of the PCL–PEG–PCL triblock ((A) 2110–2000–2110) and multiblock copolymers ((B) $[CL_{19}–EG_{45}–CL_{19}–AU_{10}]_{4.1}$).

Subsequently, 0.5 g drug-loaded solution was placed in a 4 mL vial and allowed to form a gel in a shaking water bath (20 strokes/min) at 37 °C. After 30 min, 3 mL of fresh serum (PBS solution containing 2.4 wt% Tween 80 and 4 wt% Cremophor EL at pH 7.4 and 37 °C) was added to the vial. At given time intervals, 1.5 mL of the release medium was withdrawn from the vial, and 1.5 mL of fresh serum was added. Each aliquot was eluted through C_{18} column (5.0 μm, 250 × 4.0 mm) at a flow rate of 0.5 mL/min and an injection volume 50 μL. The mobile phase was acetonitrile/Milli-Q water (52:48). Chromatograms were generated from the absorbance at 227 nm. The paclitaxel (PTX) concentration in the release medium was obtained according to the calibration curve of PTX.

2.7. Characterization

The multiblock copolymers were characterized by ^{1}H NMR (500 MHz JNM-LA FT-NMR) and FT-IR (Nicolet, IR200) spectroscopies. The molecular weights and polydispersity indexes (PDIs) were measured using gel permeation chromatography (GPC, Shodex-KF 802.5, KF 803L), with DMF as the eluent at a flow rate of 1 mL/min. The molecular weights were calculated against low polydispersity PEG standards.

3. Results and discussion

3.1. Synthesis of the $[PCL–PEG–PCL–PAU]_n$ multiblock copolymer

The multiblock poly(ester amino urethane)s, denoted as $[PCL–PEG–PCL–PAU]_n$, were synthesized by the condensation reaction of hexamethylene diisocyanate (HDI), HO–PCL–PEG–PCL–OH and 1,4-bis(hydroxyl ethyl)piperazine (HEP). The parent triblock copolymers, PCL–PEG–PCL, were synthesized by the ring-opening polymerization of ε-CL using PEG as the macroinitiator and $Sn(Oct)_2$ as the catalyst, respectively. The PCL block lengths were tuned by varying the feed ratio of ε-caprolactone to PEG. The typical ^{1}H NMR spectrum of the triblock copolymer is shown in Fig. 1(A). The ^{1}H NMR result confirms the formation of the PCL–PEG–PCL triblock copolymer. The molecular weight of the PCL block was calculated by comparing the area of the typical PCL ^{1}H NMR peak with that of the representative PEG peak. Additionally, the polydispersity index (PDI) of PCL–PEG–PCL was measured by GPC. The results are summarized in Table 1.

Table 1
Compositions and molecular weights of the triblock and multiblock copolymers

PCL–PEG–PCL (triblock copolymers)				$[PCL–PEG–PCL–PAU]_n$ (multiblock copolymers)			
Composition[a]	PCL/PEG[a] (wt/wt)	$M_{n,tri}$[a]	PDI[b]	Chemical formula[c] $[CL_y–EG_x–CL_y–AU_z]_n$	PAU[d] wt%	$M_{n,multi}$[b]	PDI[b]
1950–1750–1950	2.2	5650	1.24	$[CL_{17}–EG_{40}–CL_{17}–AU_{9.4}]_{5.0}$	36.4	44,400	3.17
1363–1750–1363	1.6	4476	1.16	$[CL_{12}–EG_{40}–CL_{12}–AU_{11.4}]_{5.2}$	46.5	43,800	1.65
2110–2000–2110	2.1	6220	1.30	$[CL_{19}–EG_{45}–CL_{19}–AU_{10}]_{4.1}$	35.6	39,300	2.7
1584–2000–1584	1.6	5168	1.14	$[CL_{14}–EG_{45}–CL_{14}–AU_{10}]_{5.4}$	40.0	46,200	3.0

[a] Determined by ^{1}H NMR.
[b] Evaluated by GPC.
[c] The subscripts represent the number of repeat unit: $z = [(I_k/4)/(I_a/4)] \times (M_{n,PEG}/44)$, I_k and I_a are the areas of the typical ^{1}H NMR peaks of AU and EG units, respectively (Fig. 1); $n = M_{n,multiblock\ copolymer}/[M_{n,triblock\ copolymer} + z \times (168.2 + 174.24)]$, 168.2 and 174.24 are the M_ws of the HDI and HEP units, respectively.
[d] Calculated by ^{1}H NMR: PAU wt% $= z \times (168.2 + 174.24)/[z \times (168.2 + 174.24) + M_{n,triblock\ copolymer}]$.

The multiblock copolymers were synthesized by the condensation reaction between the isocyanate groups of HDI and the hydroxyl groups of PCL–PEG–PCL and HEP. Scheme 1 illustrates the synthesis route of the multiblock copolymer. The synthesized multiblock copolymers were characterized by ^{1}H NMR, FT-IR and GPC. A typical ^{1}H NMR spectrum (in $CDCl_3$) of the synthesized multiblock copolymer is shown in Fig. 1(B). In addition to the typical peaks of PCL–PEG–PCL, the characteristic peaks corresponding to the poly(amino urethane) (PAU) segments are observed in Fig. 1(B). This indicates that the synthesized copolymers consist of both PCL–PEG–PCL and poly(amino urethane) (PAU) segments. Fig. 2 shows the representative FT-IR spectra of the multiblock copolymer and the parent triblock copolymer. For the multiblock copolymer, besides the free C═O stretching region at around 1730 cm^{-1}, a shoulder band at around 1705 cm^{-1} is observed, indicating the hydrogen-bonded C═O stretching band for polyurethane [45]. The band at 3150–3450 cm^{-1} is assigned to the N–H stretching band of urethane groups. In addition, the absence of any absorbance at around 2267 cm^{-1} indicates that no

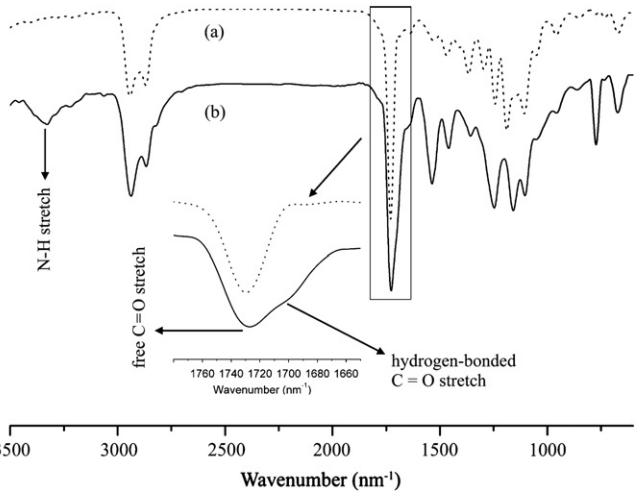

Fig. 2. Representative FT-IR spectra of the PCL–PEG–PCL triblock ((a) 2110–2000–2110) and multiblock copolymers ((b) $[CL_{19}–EG_{45}–CL_{19}–AU_{10}]_{4.1}$).

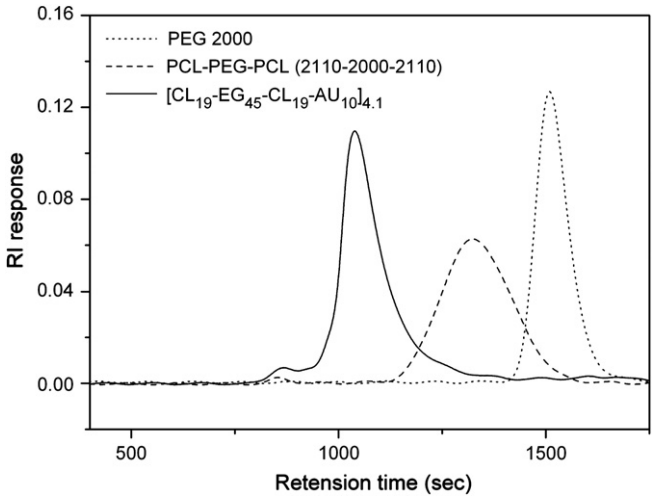

Fig. 3. Representative GPC trace of a multiblock copolymer ($[CL_{19}–EG_{45}–CL_{19}–AU_{10}]_{4.1}$), with those of the parent PEG (2000) and PCL–PEG–PCL (2110–2000–2110) for comparison.

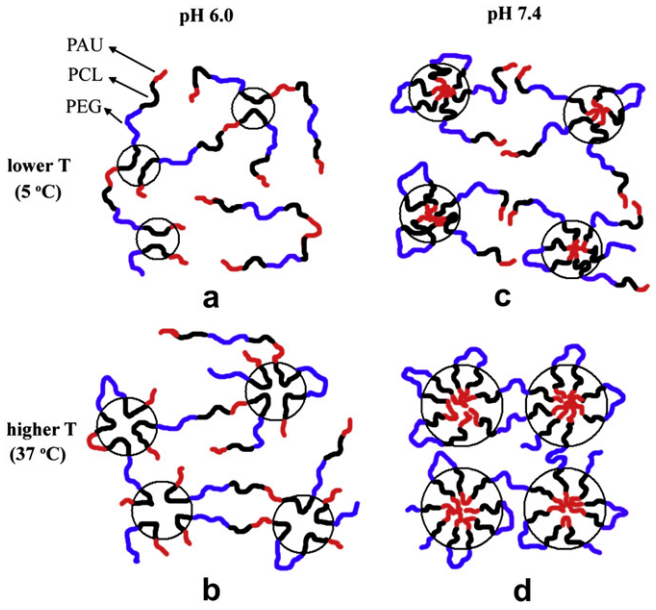

Fig. 5. Schematical illustration for the sol–gel phase diagrams of the multiblock copolymers.

unreacted isocyanate groups are present in the resulting polymer. The FT-IR results further confirm the coexistence of PCL–PEG–PCL and poly(amino urethane) segments in the synthesized copolymers. The molecular weights and polydispersity indexes of the synthesized copolymers were further determined by gel permeation chromatography (GPC). Fig. 3 shows the typical GPC traces of parent PEG, PCL–PEG–PCL and the multiblock copolymer. A unimodal GPC peak is observed for the multiblock copolymer, indicating that the parent PCL–PEG–PCL has been completely consumed. The results of ^{1}H NMR, FT-IR and GPC measurements confirm that the $[PCL–PEG–PCL–PAU]_n$ multiblock copolymers are successfully synthesized and no parent PCL–PEG–PCL is present in the final products. The characterization results of the multiblock copolymers are listed in Table 1.

3.2. Sol–gel phase diagrams

The sol–gel phase diagrams of PCL–PEG–PCL and the multiblock copolymers in PBS solutions were determined by tube inverting method. The thermal sol–gel phase transition of the multiblock copolymers was investigated at various pH values. Fig. 4(a) and (b) shows the sol–gel phase diagrams of the triblock copolymer (PCL–PEG–PCL) and multiblock copolymer ($[PCL–PEG–PCL–PAU]_n$), respectively. As shown in Fig. 4(a), the 20 wt% PCL–PEG–PCL aqueous solutions exhibit a sol-to-gel-to-aggregation transition with increasing temperature [10]. In addition, the gel regions of PCL–PEG–PCL show no pH-dependence within the pH range of 6.5–7.4. In contrast, the gel regions of the multiblock copolymers show marked dependence on pH, as shown in Fig. 4(b). At a pH below a critical pH, the piperazine groups of the poly(amino urethane) (PAU) segments are ionized, resulting in a hydrophilic nature of the PAU segments. Therefore, the multiblock copolymer system exists as a sol state within the experimental temperature range, due to less hydrophobic interaction between the multiblock copolymers. In contrast, at a relatively high pH (7.0–7.4), the multiblock copolymer solution displays a sol–gel-aggregation transition with increasing temperature, and the gel region becomes wider with increasing the pH from 7.0 to 7.4.

The mechanism of sol–gel phase transition in response to pH and temperature is schematically illustrated in Fig. 5. At a lower pH and a lower temperature (such as pH 6.0 and 5 °C in Fig. 5(a)), the PAU segments are ionized and exhibit a hydrophilic nature. The

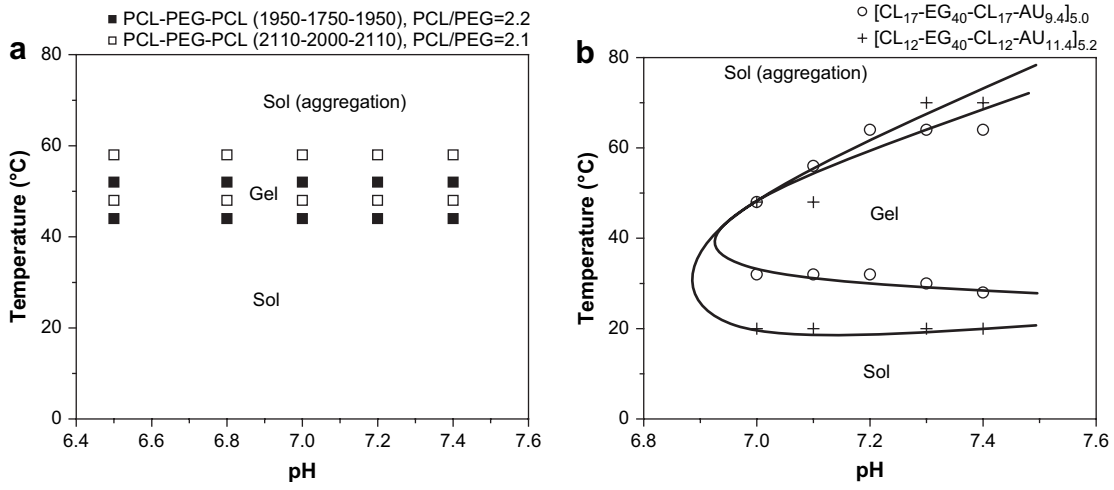

Fig. 4. pH/temperature-dependent sol–gel phase diagrams of the 20 wt% triblock (a) and multiblock (b) copolymer solutions.

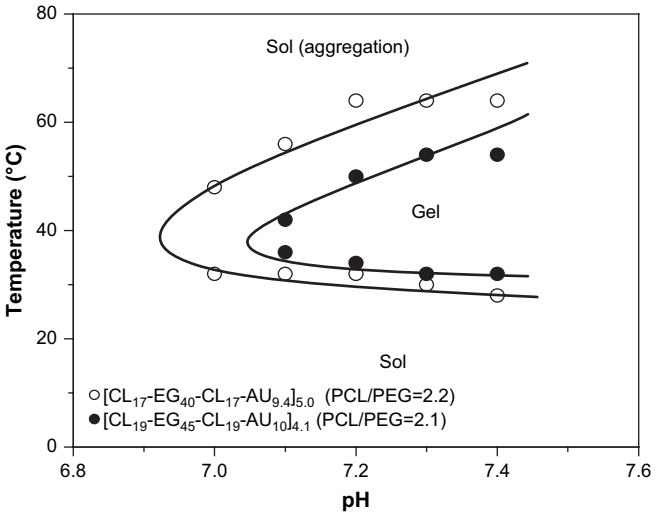

Fig. 6. Sol–gel phase diagrams of the 20 wt% multiblock copolymer solutions with different PEG molecular weights.

electrostatic repulsion between the PAU segments and the relatively weak hydrophobic interaction between the PCL blocks [28] lead to a relatively weak association between the multiblock copolymers. With increasing temperature at a lower pH (pH 6.0 and 37 °C in Fig. 5(b)), the hydrophobic interaction of the PCL blocks increases and the micelles tend to grow [10]; however, a strong micellar interaction cannot form because of the ionized PAU segments and the system still shows a sol state. Similarly, with increasing pH at a lower temperature (pH 7.4 and 5 °C in Fig. 5(c)), although the PAU segments show a hydrophobic nature, the system also stays as a sol state due to the weak micellar aggregation at lower temperatures [10]. In contrast, with increasing temperature and pH simultaneously to physiological conditions (37 °C and pH 7.4 in Fig. 5(d)), the marked micellar growth and aggregation lead to marked increase in micellar interaction and micellar volume, and therefore result in a sol–gel phase transition. The gel-to-sol transition at an upper transition temperature is due to decrease in the micellar volume and micellar interaction caused by the partial dehydration of the PEG blocks.

The influence of composition on the phase diagram and the critical gelation pH (CGpH) was studied, as shown in Fig. 4(b). It is noteworthy that the gel region of $[CL_{12}–EG_{40}–CL_{12}–AU_{11.4}]_{5.2}$ with slightly shorter PCL is wider than that of $[CL_{17}–EG_{40}–CL_{17}–AU_{9.4}]_{5.0}$. This may be attributed to the higher PAU content in the former copolymer. Additionally, the effect of PEG molecular weight on the phase diagrams of the triblock and multiblock copolymers was also investigated, as shown in Figs. 4(a) and 6, respectively. The weight ratios of PCL to PEG blocks in the samples in Figs. 4(a) and 6 are almost equal (2.1–2.2). As shown in Fig. 4(a), both the lower sol-to-gel transition temperature and the upper gel-to-aggregation transition temperature of PCL–PEG–PCL increase with increasing PEG block length. For the multiblock copolymer (Fig. 6), the lower sol-to-gel transition temperature also rises with increasing PEG block length. In contrast, the upper gel-to-aggregation transition temperature decreases as the PEG block length is increased, resulting in the reduction of the gel area and the shift of critical gelation pH to a higher pH region. The decrease in the upper gel-to-aggregation transition temperature may be attributed that the number of repeat units of $[CL_{19}–EG_{45}–CL_{19}–AU_{10}]_{4.1}$ is lower than that of $[CL_{17}–EG_{40}–CL_{17}–AU_{9.4}]_{5.0}$ [46].

3.3. In vivo *gel formation*

In order to examine the injectability and *in vivo* gel formation of the multiblock polymer solution, the polymer solution was subcutaneously injected into mice. In this experiment, 200 μL 20 wt% multiblock copolymer solution at pH 6.7 and 0 °C was subcutaneously injected into mice. After 15 min, the mice were sacrificed and the gel morphologies were observed. As shown in Fig. 7, a hydrogel was observed *in situ* 15 min after injection. The *in vivo* injection experiments suggest that the multiblock copolymer solution can be easily injected into body and form a gel *in situ* immediately.

3.4. In vitro *release of paclitaxel*

Paclitaxel (PTX) was used as a model drug to examine the release behavior of the pH- and temperature-sensitive multiblock copolymer

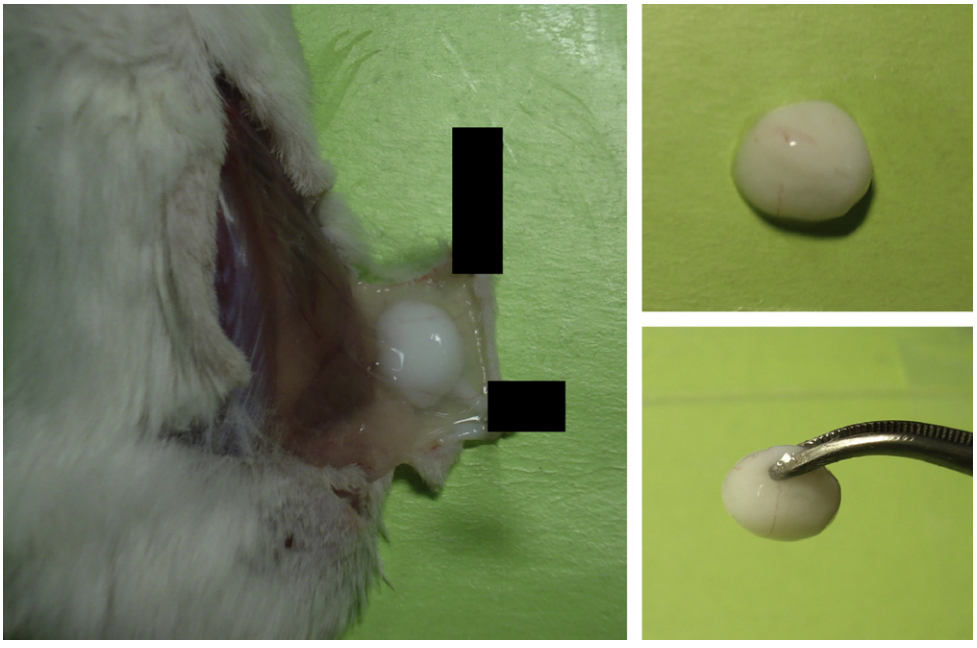

Fig. 7. *In vivo* gel formation. Photographs were taken 15 min after subcutaneous injection of the 20 wt% multiblock copolymer ($[CL_{19}–EG_{45}–CL_{19}–AU_{10}]_{4.1}$) solution into the mouse.

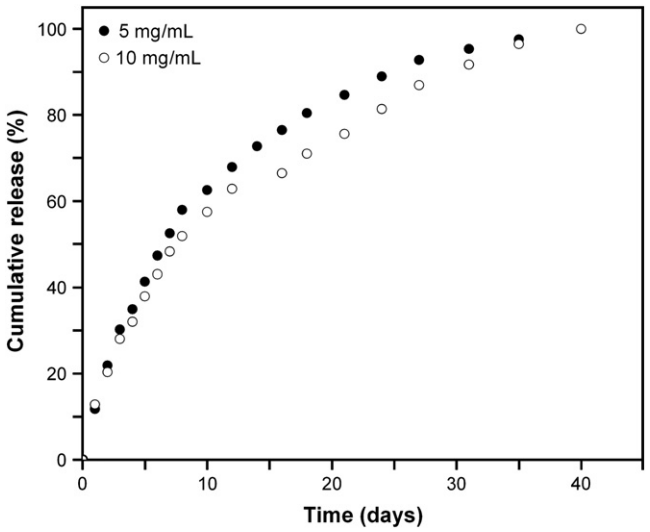

Fig. 8. *In vitro* cumulative release profiles of paclitaxel from the multiblock copolymer ($[CL_{19}–EG_{45}–CL_{19}–AU_{10}]_{4.1}$) hydrogel in PBS solution (containing 2.4 wt% Tween 80 and 4 wt% Cremophor EL) at pH 7.4 and 37 °C. The initial paclitaxel loading concentrations are 5 mg/mL (●) and 10 mg/mL (○), respectively.

hydrogel at physiological conditions (37 °C and pH = 7.4). The drug loading concentrations were 5 and 10 mg/mL, respectively. The cumulative release profiles of PTX are shown in Fig. 8. As shown in Fig. 8, continuous release of PTX persists over 1 month irrespective of the initial drug loading concentration. The *in vitro* release of PTX indicates that the continuous release of the hydrophobic anticancer drug may be fulfilled by the novel multiblock copolymer hydrogel.

4. Conclusions

A series of novel pH- and temperature-sensitive poly(ester amino urethane)s were synthesized and characterized. At pH 7.0 or above, the multiblock copolymer aqueous solution exhibited a sol–gel–sol (aggregation) transition with increasing temperature. In contrast, at pH below 7.0, the copolymer solution existed as a sol state within the experimental temperature range. The sol–gel phase diagram and critical gelation pH can be adjusted by varying the hydrophilic/hydrophobic balance and block length. After subcutaneous injection of the multiblock copolymer solutions into mice, hydrogels were formed *in situ* in a short time. The *in vitro* release of paclitaxel from the multiblock copolymer hydrogel persisted over 1 month under physiological conditions. Therefore, the novel pH- and temperature-sensitive copolymer hydrogels may have potential in biomedical applications.

Acknowledgements

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