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# pH- and temperature-sensitive multiblock copolymer hydrogels composed of poly(ethylene glycol) and poly(amino urethane)

Kasala Dayananda [a], Chaoliang He [a], Dong Kuk Park [a], Tae Gwan Park [b], Doo Sung Lee [a,*]

[a] Department of Polymer Science and Engineering, Sungkyunkwan University, Suwon, Gyeonggi 440-746, Republic of Korea
[b] Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejeon 305-701, Republic of Korea

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ABSTRACT

A series of novel pH- and temperature-responsive multiblock copolymers (poly(PEG/HEP urethane)) consisting of poly(ethylene glycol) (PEG) and poly(amino urethane) (PAU) were synthesized, and their physicochemical properties were studied. The amphiphilic block copolymers were synthesized from PEG, 1,4-bis(hydroxyethyl) piperazine (HEP) and 1,6-diisocyanato hexamethylene (HDI) in the presence of dibutyltin dilaurate as a catalyst. The resulting polymers were examined by FT-IR, $^{1}H$ and $^{13}C$ NMR spectroscopies and gel permeation chromatography (GPC). The solution properties of the copolymers were studied by turbidity measurement and fluorescence spectroscopy. The copolymers showed a pH-dependent soluble–insoluble transition in diluted aqueous solutions. The concentrated polymer solutions exhibited a thermo-induced sol–gel–sol phase transition at pH 6.8–7.4. The gel window covers the physiological conditions. After a subcutaneous injection of the multiblock copolymer solution into mice, a transparent and soft gel was formed immediately. The *in vitro* release of a model anticancer drug, chlorambucil, persisted over 2 weeks under physiological conditions.



## 1. Introduction

Hydrogels have been widely used in biomedical applications such as drug delivery and tissue engineering, because of their good biocompatibility and hydrophilic network structure [1–4]. Hydrogels based on natural polymers, such as collagen [5] and hyaluronic acid [6,7] have been developed. In addition to natural hydrogels, synthetic hydrogels have also been widely used in various drug delivery and tissue engineering applications [8,9]. PEG-based hydrogels are one of the most widely studied materials for biomedical applications, due to their non-immunogenicity and non-toxicity. Interestingly, PEG is not biodegradable, but is readily excreted from the human body via kidneys and liver. Therefore, it forms non-toxic metabolites, which makes it suitable for drug delivery. Some PEG-based hydrogels are used as drug carriers. On account of these properties, PEG-based products have been approved by the FDA for human intravenous, oral and dermal applications [10]. In the last few decades, stimuli-responsive polymers that respond to changes in external stimuli such as the temperature, ionic strength, pH, electric field and magnetic field [11–17] have attracted a great deal of attention. For example, some thermosensitive polymers are soluble at lower temperatures, but separate from the solution when the temperature is raised above their lower critical solution temperature (LCST). In recent years, many researchers have focused on polymeric systems that respond to more than one stimulus, such as pH and temperature [18–28].

Polyurethanes are an important class of polymers that have found many applications as biomaterials, due to their excellent physical properties and good biocompatibility [29–31]. However, the reports on *in situ* forming hydrogels based on polyurethanes are relatively limited. Very recently, a kind of pH- and temperature-sensitive multiblock poly(ester amino urethane)s was developed in our group [32]. The objective of this study was to prepare a series of novel pH/temperature-sensitive copolymers based on double-hydrophilic blocks, which do not contain a hydrophobic block and can be completely dissolved in water at a certain pH and temperature. The hydrogels based on double-hydrophilic blocks may be very interesting and have advantages in some practical applications [33]. The pH/temperature-sensitive multiblock copolymers (denoted as poly(PEG/HEP urethane)) were synthesized by the condensation polymerization of HO–PEG–OH, bis-1,4-(hydroxyethyl)piperazine (HEP) and 1,6-diisocyanato hexamethylene (HDI) in the presence of dibutyltin dilaurate as a catalyst. The resulting polymers were characterized by FT-IR, nuclear magnetic resonance ($^{1}H$ NMR), and gel permeation chromatography (GPC). The aqueous solution properties of the copolymers were studied by turbidity measurement and fluorescence spectroscopy. The pH/temperature-dependent sol–gel phase transition was measured by tube inverting method.

* Corresponding author. Tel.: +82 31 290 7282; fax: +82 31 292 8790.
*E-mail address:* dslee@skku.edu (D.S. Lee).

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## 2. Experimental

### 2.1. Materials and methods

Poly(ethylene glycol) (PEG) ($M_n = 2000$ and 4600), anhydrous toluene, dichloroethane, dibutyltin(II) dilaurate, bis-1,4-(hydroxyethyl)piperazine (HEP), 1,6-diisocyanato hexamethylene (HDI), chlorambucil and phosphate buffer saline (PBS) tablets were purchased from Sigma–Aldrich. All other chemicals were of reagent grade and used as-received. Diethyl ether and chloroform were obtained from Samchun Chemical Co. (Korea) and used as-received.

### 2.2. Synthesis of the poly(PEG/HEP urethane) multiblock copolymers

The PEG based polyurethanes were synthesized by the condensation reaction of 1,6-diisocyanato hexamethylene (HDI) with PEG and bis-1,4-(hydroxyethyl)piperazine (HEP), as shown in Scheme 1. The condensation reactions of MPEG–OH, bis-1,4-(hydroxyethyl)piperazine (HEP) and diisocyanate were conducted at a stoichiometric ratio of the OH and NCO groups, i.e. OH/NCO = 1. The typical reaction procedure is as follows: 1.0 mmol of PEG ($M_n = 2000$) was added to a dry 250 mL round bottom flask equipped with a magnetic stir bar. The flask was placed in an oil bath at 100 °C under vacuum, maintained at this temperature for 2 h and then cooled to 75–80 °C. Then, HEP and a catalytic amount of dibutyltin dilaurate were added and vacuum was applied again for 30 min, after which the flask was kept under a nitrogen atmosphere and maintained under the same conditions. Subsequently, 50 mL of anhydrous toluene/dichloroethane (50:50) solvent was added, and stirring was continued until HEP was completely dissolved. Finally, the requisite amount of diisocyanate was added and the reactants were allowed to react at 75–80 °C. The reaction mixture became turbid and highly viscous within 1 h, after which the flask was cooled to room temperature and the product was diluted with chloroform. The resulting polymer was isolated by precipitating in a 10-fold excess of diethyl ether, washed repeatedly by diethyl ether, and eventually dried under vacuum at room temperature for 48 h. The yields of all resulting copolymers were over 70%.

### 2.3. Acid–base titration and turbidity measurement

One mg/mL copolymer aqueous solution at pH 2 was prepared for the turbidity measurement. The titration was carried out by the stepwise addition of 0.1 N NaOH. The pH value was checked by using a Denver UB-10 pH meter (Denver instrument, USA). The turbidity of the solution during the titration was measured by monitoring the absorbance at 460 nm using a UV–vis spectrophotometer.

### 2.4. Critical micelle concentration (CMC)

The critical micelle concentrations (CMCs) of the synthesized block copolymers were investigated by fluorescence spectroscopy using pyrene as a probe. A stock solution of pyrene in THF was added to 0.01 M PBS buffer solution and then THF was removed by heating at 60 °C for a few hours. The final pyrene concentration was $1 \times 10^{-6}$ M. The excitation spectrum of pyrene was recorded at 392 nm.

### 2.5. Sol–gel phase diagram

The sol (flow)–gel (non-flow) phase transition temperature of the multiblock copolymer in buffer solution was recorded using tube inverting method at temperature intervals of 2 °C. Each sample at a given concentration (20 wt%) was dissolved in 0.01 M PBS solution at pH 1 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 1 M NaOH solution at 2 °C.

### 2.6. In vivo *gel formation*

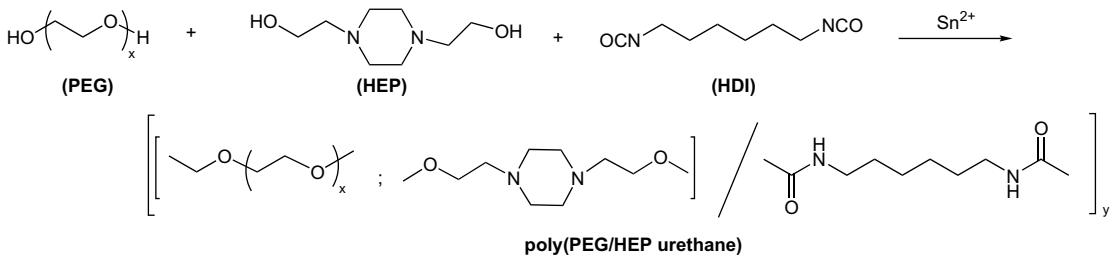
In order to investigate the injectability and *in vivo* gel formation of the polymer solution, the 20 wt% multiblock copolymer (P2) solution at pH 6.7 and 0 °C was subcutaneously injected into ICR mouse. After 15 min, the mouse was sacrificed and the morphology of the *in situ* formed hydrogel was observed.

### 2.7. In vitro *release of chlorambucil*

The polymer (P2) at a given concentration (20 wt%) was dissolved in 0.01 M PBS at pH = 1, kept for 1 day at 2 °C, and eventually adjusted to the pH range of 5–6. Thereafter, the drug was loaded into the polymer solution at a concentration of 4 mg/mL, and stirring was continued for another 24 h. Then, the pH was adjusted to 7.4 and stirring was continued for 12 h under the same condition. Subsequently, 0.5 g of the mixture was placed in a 4 mL vial and then incubated at 37 °C for 30 min, followed by the addition of 3 mL of fresh release medium (0.01 M PBS buffer solution at pH 7.4 and 37 °C). At given time intervals, 1.5 mL of the release medium was withdrawn from the vial, and 1.5 mL of fresh release medium was added to the vial. The chlorambucil concentration was measured by a UV–vis spectrophotometer using the band at 254.0 nm (pH = 7.4) as the characteristic band. The accumulative release was calculated by comparison with the absorbance of chlorambucil standard solutions. The linearity of the standard line was determined by using chlorambucil standard solutions with five concentrations ranging from 0.2 to 0.00032 mg/mL.

### 2.8. Characterization

The resulting polymers were characterized by $^1$H and $^{13}$C NMR spectroscopies (500 MHz JNM-LA FT-NMR). The molecular weight




**Scheme 1.** Synthesis route of the poly(PEG/HEP urethane) multiblock copolymer.

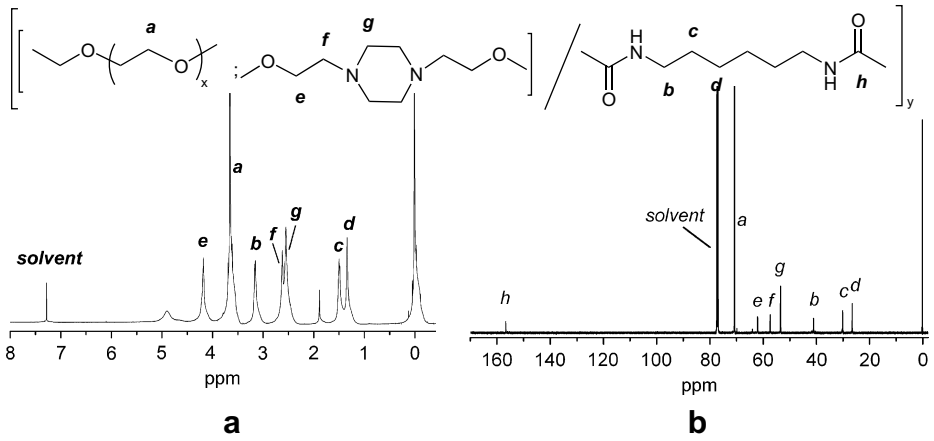



**Fig. 1.** $^{1}$H NMR (a) and $^{13}$C NMR (b) spectra of a poly(PEG/HEP urethane) multiblock copolymer (P2).

and polydispersity index (PDI) were measured by 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 and characterization of the multiblock copolymers

In the present study, we report a kind of multiblock poly(ether amino urethane)s (denoted as poly(PEG/HEP urethane)). Scheme 1 illustrates the synthesis route of the multiblock copolymer. The multiblock copolymer consists of poly(ethylene glycol) as hydrophilic segments and poly(amino urethane) (PAU) as stimuli-sensitive moieties. It is noteworthy that the sequence of the copolymers in our present work may not be a well-defined $[PEG–PAU]_x$ type structure with exactly alternately distributed PEG and PAU blocks, but a [PEG–HDI, PAU–HDI] type structure with random distribution. However, because the PEG molecular weight ($M_n = 4600$ or 2000) is much higher than that of 1,4-bis(hydroxyethyl)piperazine (HEP, $M_w = 174$) and the molar concentration of HEP is much higher than that of PEG (HEP/PEG $\geq 6$, mol/mol), the possibility of formation of PEG–HDI–PEG–HDI type structure should be much lower than that of formation of PEG–HDI–HEP–HDI type structure. Therefore, we think it should be reasonable to call the copolymers as multiblock copolymers composed of PEG and PAU segments, even though the block lengths of the PAU segments in the copolymer may be different.

The chemical structure of the synthesized polymer was examined by $^{1}$H and $^{13}$C NMR as well as FT-IR. The molecular weights were determined by gel permeation chromatography (GPC). Fig. 1 shows the typical $^{1}$H and $^{13}$C NMR spectra of the multiblock copolymers, respectively. The NMR results clearly indicate the coexistence of the PEG and PAU segments. In addition, typical $^{13}$C peak of the isocyanate groups at 122.9 ppm is not observed in Fig. 1(b). This indicates that the isocyanate groups have been completely consumed and are not present in the product. FT-IR spectroscopy is a useful technique to confirm the presence of functional groups. Fig. 2a shows the IR spectrum of a representative multiblock copolymer. The absorbance at 1720 cm$^{-1}$ is attributed to the carbonyl stretching band, and a shoulder band at a lower wavenumber is attributed to the hydrogen bonded carbonyl groups in the poly(amino urethane) segments (Fig. 2(b)) [34]. The absorbance at 3334 cm$^{-1}$ is assigned to the N–H stretching band of urethane. The absorbance at 1104 cm$^{-1}$ corresponds to the C–O–C stretching vibration of PEG. The absence of any absorbance at 2267 cm$^{-1}$ indicates that no unreacted isocyanate groups remain in the resulting polymer. In addition, the molecular weight (MW) and polydispersity index (PDI) were determined by GPC. Typical GPC traces of a multiblock copolymer and the parent PEG are shown in Fig. 3. The observation of a unimodal peak for the copolymer, which does not overlap with the corresponding peak of the parent PEG, indicates the complete consumption of the precursors and the absence of any unreacted materials. The above characterization results clearly indicate the successful synthesis of the poly(PEG/HEP urethane) multiblock copolymers. The results are summarized in Table 1.

### 3.2. Turbidity measurements

The pH-dependent solution property of the multiblock copolymer was measured by monitoring the turbidity. As shown in Fig. 4,

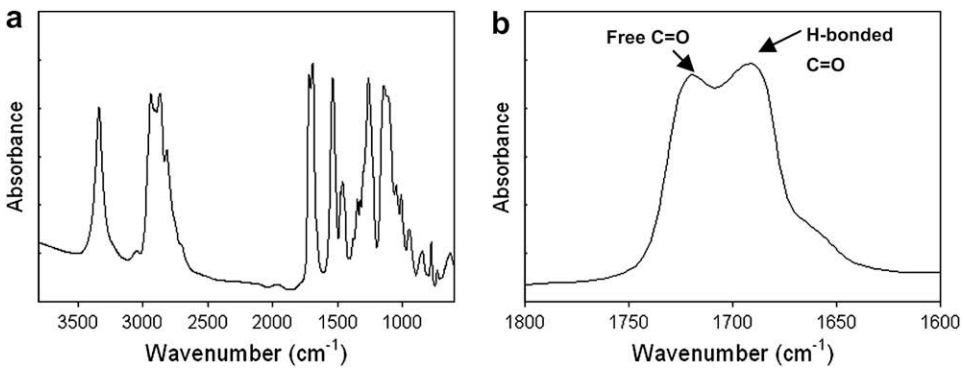



**Fig. 2.** Representative FT-IR Spectrum of a multiblock copolymer (P2).

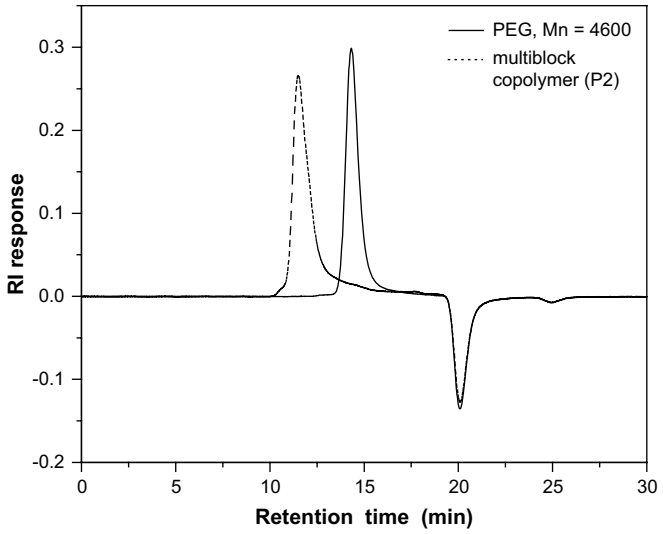



**Fig. 3.** Typical GPC traces of the parent PEG and a multiblock copolymer (P2).

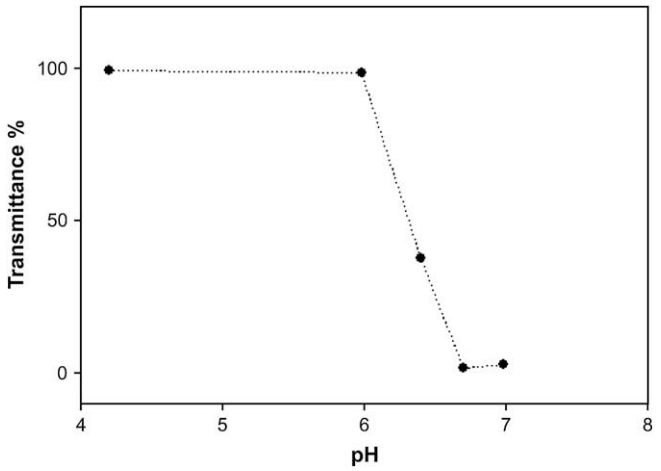



**Fig. 4.** Light transmittance of the P2 aqueous solution (polymer concentration = 1 mg/mL) as a function of pH.

the light transmittance of the 1 mg/mL polymer solution is almost 100% at a low pH. However, the light transmittance decreases markedly as the pH is increased to above 6, due to the decrease in water solubility of the polymer caused by the deionization of the PAU segments. From the phase-transition curve of the P2 aqueous solution, the p$K_a$ of the copolymer is around 6.5. Because the distribution of the multiblock copolymer is not well defined, well-defined micelles with unique distribution are difficult to form in the polymer solution. However, larger micelle-like aggregates composed of hydrophilic and hydrophobic parts should be formed due to the amphiphilic nature of the whole copolymer after the deionization of the PAU segments. This leads to the high turbidity of the polymer solution.

### 3.3. Critical micelle concentration

The formation of micelle-like aggregates from the amphiphilic multiblock copolymers was examined by a fluorescence technique. The typical excitation spectra of pyrene in the aqueous polymer solution at pH 7.4 are shown in Fig. 5a. As the polymer concentration is increased from 0.0016 to 1 mg/mL, the peak at 334 nm shifts to 336 nm, indicating the formation of micelles. Fig. 5b shows the plot of the $I_{336}/I_{334}$ intensity ratio versus the concentration at pH 7.4 for the copolymer P2. The CMC value at pH 7.4 is around 0.095 mg/mL.

### 3.4. Sol–gel phase transition of the copolymers

The sol–gel phase transition diagrams of the poly(PEG/HEP urethane) multiblock copolymers in aqueous solutions were determined by tube inverting method. Fig. 6(a) shows the sol–gel phase diagrams of the block copolymer samples, P1 and P2. At a higher pH (6.8–7.4), the polymer solutions exhibit a sol-to-gel-to-sol transition with increasing temperature. It is noteworthy that, although relatively wide gel windows were observed at pH 7.0 and 6.8 for P1 and P2, respectively, no gel region could be found at a slightly lower pH (Fig. 6(a)). At a lower pH (below 6.8 and 7.0 for P2 and P1, respectively) the multiblock copolymer solutions exist as a sol state at experimental temperature range, due to less hydrophobic interaction between the PAU segments caused by the ionization of the piperazine groups. In contrast, at a relatively higher pH, the piperazine groups are deionized and interconnected micelles comprising the PAU hydrophobic cores and PEG hydrophilic shells are formed. However, at lower temperature, the hydrophobic interaction in the system is not strong enough to form a stable network, or gel. With increasing temperature, the micellar interaction increases and gelation occurs, due to the micellar aggregation and the increase in the hydrophobicity of the whole system [20]. As shown in Fig. 6(a), at pH 7.4, the block copolymer sample P1 shows a lower critical gelation temperature at around 36.0 °C and an upper gel-to-sol transition temperature at around 80.0 °C. The gel-to-sol phase transition at the upper transition temperature may be attributed to the breakage of the interconnected network caused by partial dehydration of the PEG blocks. In addition, the effect of PAU block length on the sol–gel phase diagram was studied. As shown in Fig. 6(a), the block copolymer P2 with higher PAU molecular weight shows a lower sol-to-gel transition temperature and a lower critical gelation pH as compared with P1. This is due to the increase in the hydrophobic interaction between the PAU segments with increasing PAU molecular weight.

In order to investigate the influence of PEG molecular weight (MW) on the sol–gel phase transition, the sol–gel phase transition of a multiblock copolymer with a lower PEG MW was tested. Fig. 6(b) shows the sol–gel phase diagram of a copolymer with PEG MW of 2000 (P3). It shows that this multiblock copolymer exhibits a phase diagram similar to those of the PEG 4600 based multiblock copolymers. It is worth to note that the samples with higher PAU block lengths, i.e. P4 and P5, show syneresis above 30.0 °C, due to the strong hydrophobicity of the above systems. This clearly indicates that the hydrophilic/hydrophobic balance and block lengths are important parameters for gel formation of the multiblock copolymers. Fig. 6(c) shows typical photographs of thermo-induced sol–gel transition of the 20 wt% multiblock copolymer solution at physiological pH. The polymer solution exists as a sol state at 10 °C

**Table 1**
Molecular weights and compositions of the multiblock copolymers

| Sample code | Feed ratio (PEG/HEP, mol/mol) | $M_n$ of PEG[a] | $M_n$ of multiblock copolymer[b] | PDI[b] |
|---|---|---|---|---|
| P1 | 1/8 | 4600 | 20,100 | 1.84 |
| P2 | 1/10 | 4600 | 28,100 | 1.79 |
| P3 | 1/6 | 2000 | 25,400 | 1.89 |
| P4 | 1/8 | 2000 | 32,700 | 1.79 |
| P5 | 1/10 | 2000 | 30,000 | 1.77 |

[a] Provided by Sigma–Aldrich.
[b] Obtained by GPC.

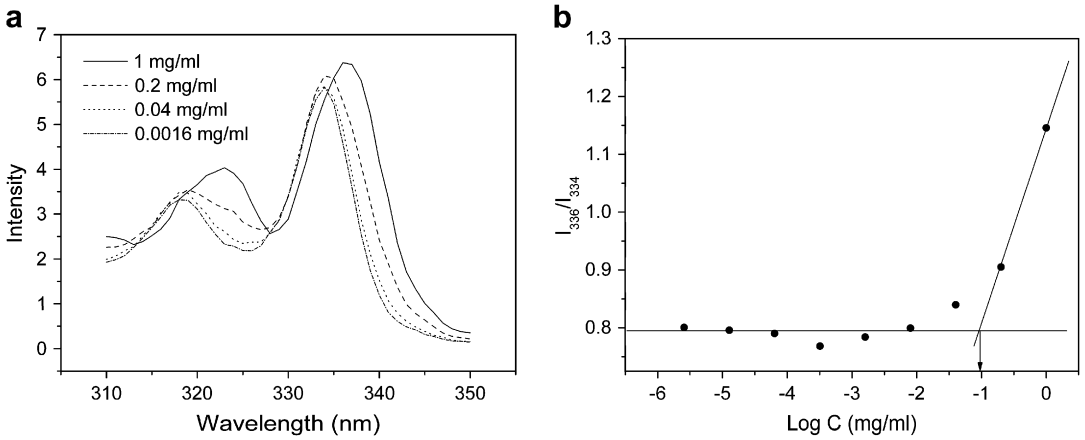



**Fig. 5.** (a) Excitation spectra of pyrene ($1 \times 10^{-6}$ M) as a function of the polymer (P2) concentration at pH = 7.4; (b) plot of $I_{336}/I_{334}$ versus logarithm of the P2 concentration at pH 7.4.

and pH 7.4 and forms a gel at physiological conditions (37 °C and pH 7.4).

### 3.5. 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 ICR mice. In this experiment, 200 μL 20 wt% multiblock copolymer solution at pH 6.7 was subcutaneously injected into a mouse. After 15 min, the mouse was sacrificed and the gel morphology was observed. As shown in Fig. 7, a soft and transparent gel was observed. In addition, the transparent hydrogel was found to be sticky and difficult to separate from the skin of the mouse. The formation of a transparent gel *in vivo*, which is different from the gel formed *in vitro* in Fig. 6(c), may be due to the effect of the body fluid. The *in vivo* injection experiment suggests that the multiblock copolymer can be easily injected into body and form a gel *in situ* in a short time.

### 3.6. In vitro *chlorambucil drug release from the multiblock copolymer hydrogel*

An anticancer drug, chlorambucil, was used as a model drug to examine the release behavior of the pH/temperature-sensitive multiblock copolymer at physiological conditions (37 °C and pH 7.4). The drug loading concentration was 4 mg/mL. The cumulative release of chlorambucil is shown in Fig. 8. As shown in this figure, the continuous release of chlorambucil persists over 2 weeks. The *in vitro* release profile indicates that controllable release of a hydrophobic drug may be fulfilled by the multiblock copolymer hydrogel under physiological conditions.

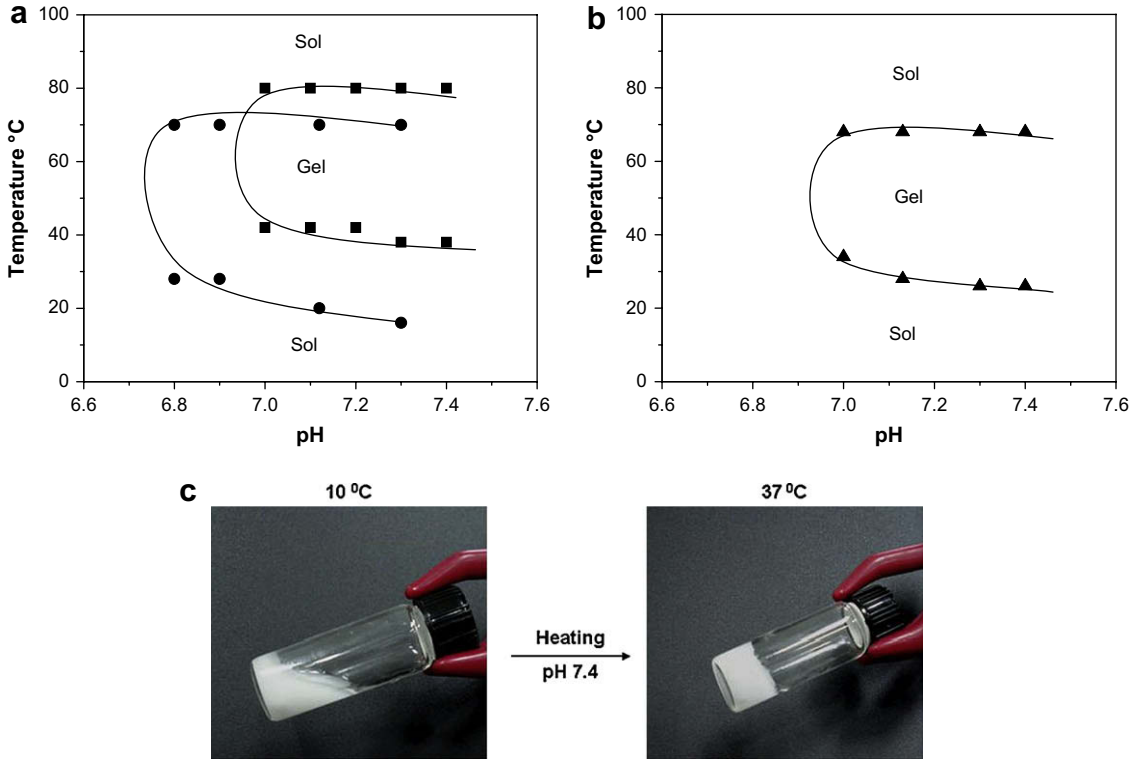



**Fig. 6.** pH/temperature-dependent sol–gel phase diagrams: (a) PEG 4600 based multiblock copolymers (■: P1, ●: P2); (b) PEG 2000 based multiblock copolymer (▲: P3); (c) Photographs of thermo-induced sol–gel transition of the 20 wt% multiblock copolymer (P2) solution at pH 7.4.

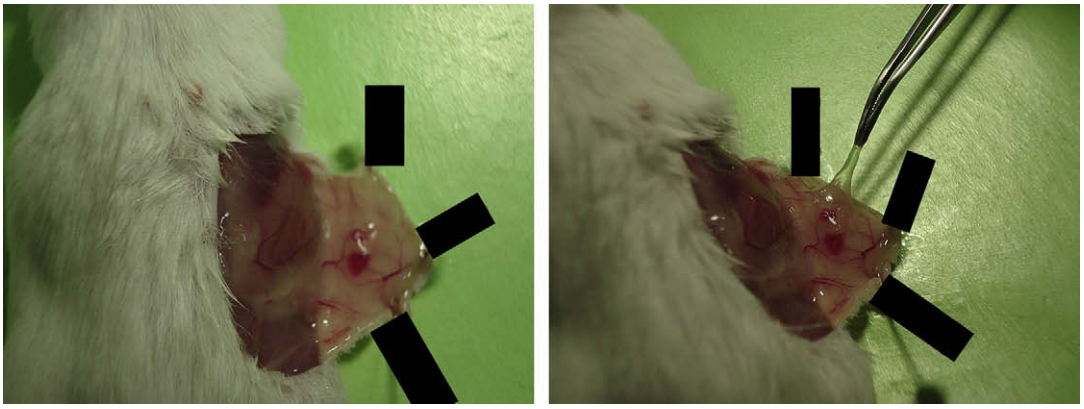


**Fig. 7.** *In vivo* gel formation. Photographs were taken 15 min after subcutaneous injection of the 20 wt% multiblock copolymer (P2) solution into mouse.

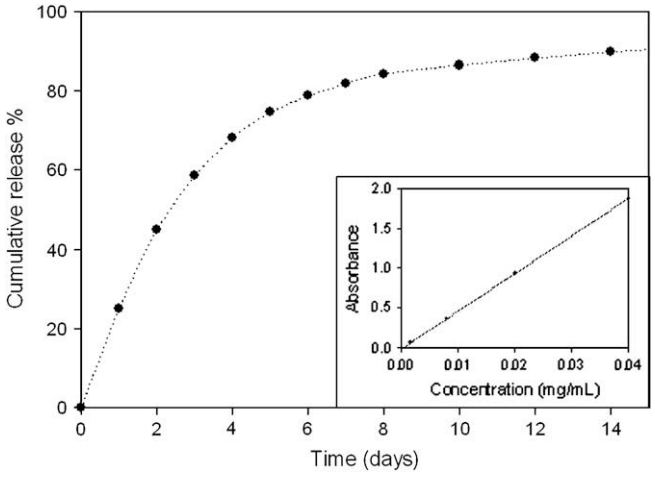



**Fig. 8.** *In vitro* release profile of chlorambucil from the 20 wt% multiblock copolymer (P2) hydrogel. The inset shows the standard calibration line.

## 4. Conclusions

In this article, we report a series of novel multiblock copolymers composed of PEG and poly(amino urethane). The multiblock copolymers were successfully synthesized using HEP as a chain extending agent. The molecular weight and composition were adjusted by varying the feed ratio of PEG, HEP and HDI. The compositions and molecular weights were characterized by NMR, FT-IR and GPC. The copolymers showed a pH-dependent phase transition in diluted aqueous solutions. At a higher pH (6.8 or above), the concentrated polymer solutions displayed a sol-to-gel-to-sol transition with increasing temperature, and the gel window covers the physiological conditions. After a subcutaneous injection of the multiblock copolymer solution into mice, a transparent gel was formed immediately. The *in vitro* release of the model anticancer drug, chlorambucil, from the multiblock copolymer hydrogel persisted over 2 weeks under physiological conditions.

The *in situ* gelling hydrogels reported here are based on double-hydrophilic segments and may have many advantages in practical applications [33]. For example, the frequently used systems containing hydrophobic blocks are difficult to dissolve in water, which bring inconvenience to the drug formulation and administration. In contrast, the copolymers reported in this work can be easily dissolved in aqueous solution at relatively lower pH values and temperatures, due to their double-hydrophilic nature. Therefore, the formulation of drugs and proteins is very easy to carry out by using the present material. In addition, the components of the multiblock copolymers, i.e. PEG and polyurethanes, are biocompatible [10,29–31]. The above advantages allow the present pH- and temperature-sensitive copolymers to be promising materials for biomedical applications.

## Acknowledgements

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