Synthesis and Characterization of Novel Polyglycerol Hydrogels Containing L-Lactic Acid Groups as Pendant Acidic Substituents: pH-Responsive Polyglycerol-Based Hydrogels

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Received 3 February 2008; accepted 6 November 2008
DOI 10.1002/app.29666
Published online 26 February 2009 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Novel pH-responsive polyglycerol (PG)-based hydrogels were successfully synthesized through the reaction of epichlorohydrin with L-lactic acid (LLA) in the presence of sodium hydroxide (NaOH), and cetyltrimethylammonium bromide as a phase transfer catalyst at room temperature, followed by hydrolysis, polymerization, and crosslinking reactions. The resultant gel was characterized by carbon nuclear magnetic resonance spectroscopy, X-ray photoelectron spectroscopy, and Fourier transform infrared measurement, and it was found that incorporated LLA was bound to PG network as a pendant acidic substituent by the hydroxyl group of LLA (PGL gel). The PGL hydrogels with different LLA contents and equilibrium swelling ratios (ESRs) were prepared by changing the feed ratios of materials. The results determined by chemical titration showed that under the applied conditions the efficiency of introducing the carboxyl group into PG network was about 86% and the amount of LLA in the hydrogel reached to about 17 wt %. The swelling behavior of the hydrogels in different environmental mediums was investigated, and the results showed that the hydrogels are pH-, ionic strength-, and cationic charge-responsive. The hydrogels also have the reversible swelling/deswelling properties. These pH-responsive PG-based hydrogels will have potential applications in biomedical and related areas. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 112: 3209–3216, 2009

Key words: hydrogels; L-lactic acid; polyglycerol; polyelectrolyte; stimuli-responsive; polymer

INTRODUCTION

Stimuli-responsive polymer hydrogels, which swell or shrink in response to a variety of environmental stimulus in temperature, pH, ionic strength and electric field, etc., are gaining much importance in a wide variety of applications in the biomedical and related field.[1–5] Among these hydrogels, the pH-responsive hydrogels with anionic groups are particularly suitable for biomedical applications because of their ionic nature, such as swelling features, better bioadhesivity, and improved blood compatibility.[6–14] Structurally, pendant acidic groups are linked to the polymeric chain, which ionize at high pH to make the polymer gel swelled. For example, as oral delivery systems, they can minimize drug release in the acidic condition of the stomach but maximize it in the neutral environment of the intestine. Such hydrogels are usually prepared by the polymerization of acrylic acid and its derivatives. Thus, non-poly(acrylic acid) pH-responsive hydrogels such as polypeptides,[11] poly(organophosphazene),[12] and polysaccharides[13–15] hydrogels are also developed to meet various demands.

Polyglycerol (PG) has recently received particular attention for biomedical applications because of its good biocompatibility and structure features of aliphatic polyether–polyol.[16–18] Mammen et al.[19] employed PG as high-loading polymeric supports for multivalent drugs. Burgath et al.[20] revealed that the PCL-multiarm star polymers initiated by PG are promising with respect to slow or controlled drug release. Because of its biocompatibility and excellent water solubility, PG is very suitable for the design of hydrogels. For example, Knischka et al.[21] synthesized a series of functionalizable hydrogels based on poly(ethylene oxide)/polyglycerol multiarm stars, which showed excellent suitability for cell growth. Hennink and coworkers[22] developed PG hydrogels by radical polymerization or photopolymerization of methacrylated PG for drug delivery and tissue

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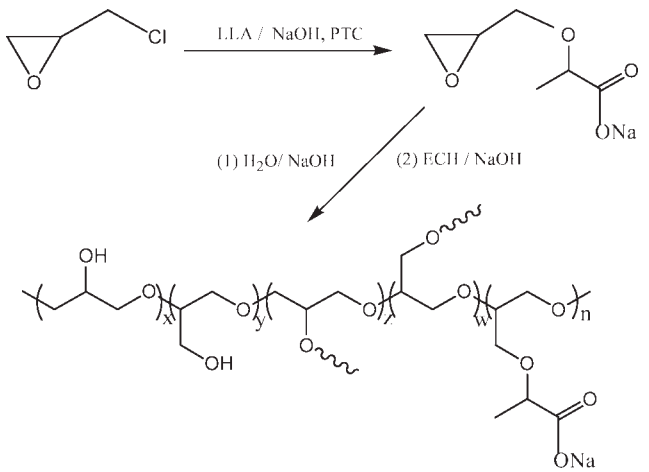

Scheme 1 Schematic route for the synthesis of PGL gel.

engineering purposes. Furthermore, PG is also environmentally friendly material in outdoor natural conditions, because of the presence of the ether group that is very sensitive to photochemical oxidation which causes a chain scissions of the polymer.[23] However, there has been seldom report about the synthesis of stimuli-responsive PG-based hydrogel.

In this article, we report the synthesis and characterization of PG hydrogels containing LLA groups as pendant acidic substituents. The design of PGL hydrogel was based on the previous researches in which crosslinked PG (a hydrogel) was reported to be formed as a by-product during reaction process when ECH reacted with other compounds in the presence of aqueous NaOH.[24–27] Chemically, two reactions are involved in the formation of PG gel, i.e., the nucleophilic ring-opening addition of epoxy group in ECH, and next the elimination of hydrochloride from the reaction intermediate, which causes the reactions of ECH hydrolysis, hydrolysate polymerization, and copolymer crosslinking. Based on the reaction principium, LLA, an excellent biocompatible material having hydroxyl and carboxyl function groups, was selected to react with ECH to synthesize glycidol derivative having LLA units before the reaction of ECH with H_2O took place, and then made it gelated to form PGL gel by the reactions of glycidol derivative hydrolysis, hydrolysate polymerization, and copolymer crosslinking as PG gel was generated (Scheme 1). The structure of PGL gel was characterized by carbon nuclear magnetic resonance spectroscopy (^{13}C-NMR), X-ray photoelectron spectroscopy (XPS), and Fourier transform infrared (FTIR) measurements. The hydrogels with different LLA contents and ESRs were prepared by changing the feed ratios of materials. The equilibrium swelling behavior of the hydrogels in different environmental mediums and the deswelling/swelling kinetics were investigated.

EXPERIMENTAL

Materials

L-lactic acid (LLA) (88%, PURAC, Spain) was distilled to remove water under reduced pressure. Epichlorohydrin (ECH), cetyltrimethylammonium bromide (CTAB), sodium hydroxide (NaOH), and other materials were of analytical grade and used as received. Water was distilled twice before use.

Synthesis of PGL gels

The PGL gels were designed and synthesized according to the reaction sequence shown in Scheme 1. The feed ratios for synthesis of the gels are summarized in Table I. The synthesis procedure was as follows: LLA, ECH-1, and 0.3 g of CTAB were mixed by magnetic stirring and the mixture was stirred at room temperature ($\sim$ 20°C) for 48 h after NaOH-1 was added. Then, H_2O (13 g) was dropped to the reaction mixture over a 20 min period and the stirring was continued for 48 h. During the period of time, NaOH-2 was added after stirring for 4 h. Finally, the polymer gel was formed when ECH-2 and NaOH-3 were added to the reaction mixture and kept at room temperature for 2 days. As a contrast, the copolymerization of ECH with H_2O was conducted under the same conditions except that no LLA was used.

The gels obtained were cut into discs (10 mm in diameter, 3 mm in thickness) by using a punch. The

TABLE I
Synthesis of PGL and PG Gels

Sample ID	LLA (g)	ECH-1 (mL)	NaOH-1 (g)	H_2O (g)	NaOH-2 (g)	ECH-2 (mL)/NaOH-3 (g)
PGL 6 (5.2)	6.0	40	5.4	13.0	5.0	20/5.2
PGL 6 (4.4)	6.0	40	5.4	13.0	5.0	20/4.4
PGL 6 (3.6)	6.0	40	5.4	13.0	5.0	20/3.6
PGL 8 (5.2)	8.0	40	7.2	13.0	5.0	20/5.2
PGL 8 (4.4)	8.0	40	7.2	13.0	5.0	20/4.4
PGL 8 (3.6)	8.0	40	7.2	13.0	5.0	20/3.6
PG	0	40	0	13.0	5.0	20/4.0

disc samples were immersed into distilled water for 3 days at room temperature to remove the impurities, and part of the purified samples were freeze-dried by a LABCONCO system as samples for the characterizations of gels.

Characterizations of PGL gels

^{13}C-NMR measurement was carried out on a Unity Inova 600 (Varian) NMR spectrometer and the freeze-dried powder of PGL gel swelled in DMSO-d_6 for 6 days before detection. XPS were acquired with a XSAM800 (Kratos) electron spectrometer employing Mg-Kα X-rays. The electron take-off angle to the spectrometer was 90° from the specimen surface. FTIR spectra were obtained on a NEXUS 670 FTIR spectrometer.

Titration of carboxyl group content in PGL gel

The carboxyl group content in PGL gels was determined by chemical titration.[28] The analytical procedure was as follows: the freeze-dried powder (0.2500 g) of PGL gel was suspended and acidified in 30 mL standard 0.1000 mol/L hydrochloric acid (HCl) with magnetic stirring for 24 h. Then, the excess hydrogen ion concentration was titrated with standard 0.1000 mol/L NaOH to calculated the HCl consumption for acidifying the carboxyl groups in PGL gel.

Measurement of equilibrium swelling ratio of PGL hydrogels

The ESR of PGL hydrogels was measured gravimetrically by incubating the specimen in different environmental mediums at 37°C up to a constant weight. The average values among three measurements were taken for each sample, and the ESR was calculated as the ratio of the mass of wet hydrogel (m_{wet}) to the dry hydrogel (m_{dry}):

$$\mathrm{ESR} = \frac{m_{wet}}{m_{dry}}$$

Measurement of cyclic deswelling/swelling kinetics of PGL hydrogels

The cyclic deswelling/swelling behavior of PGL hydrogel was investigated in two different pH value solutions with a selected ionic strength at 37°C. Before the deswelling measurement, the hydrogel discs were equilibrated at pH 7.0. Then the pH was changed between 7.0 and 1.0 and the ionic strength was maintained at 0.04 or 0.15*M* during the experimental process. At regular intervals, the weight of the hydrogel discs was recorded gravimetrically. The average values among three measurements were taken for each sample, and the SR was calculated as the ratio of the mass of wet hydrogel (m_{wet}) to the dry hydrogel (m_{dry}):

$$\mathrm{SR} = \frac{m_{wet}}{m_{dry}}$$

TABLE II
Carboxyl Group Content in PGL Gels

Sample ID	Theoretical content (wt %)[a]	Actual content (wt %)[b]
PGL 6 (3.6)	16.34	14.27 (87.33)
PGL 8 (3.6)	19.95	17.31 (86.77)

[a] Calculated in the feed (see Table I).
[b] Determined by chemical titration.

RESULTS AND DISCUSSION

Synthesis of PGL gels

According to the reaction sequence shown in Scheme 1, the synthesis of PGL gels was successfully performed using ECH and LLA as starting materials and CTAB as phase transfer catalyst (PTC) in the presence of NaOH at room temperature. The PGL hydrogels with different LLA contents and ESRs could be synthesized by changing the feed ratios of materials (Table I). The results determined by chemical titration showed that under applied conditions the efficiency of introducing the carboxyl group into PG network was around 86%, and the amount of LLA in the hydrogel reached to about 17 wt % (Table II).

Characterizations of PGL hydrogels

PG gel was first characterized with ^{13}C-NMR spectra in DMSO-d_6-swelled specimen as PG gel did not dissolve in any organic solvent and water. The carbon signals of PG gel appeared mainly between 60 and 80 ppm as shown in Figure 1, which indicated almost all the carbons of PG gel were linked with oxygen atom and is in accordance with characteristics of a PG.[18,29–31] Four possible subunits are suggested from ^{13}C-NMR spectrum in ppm to be as following: (1) —$CH_2CH(OH)CH_2O$—: 73.4 (**a**, $2CH_2$), 69.2 (**b**, CH). (2) —$CH(CH_2OH)CH_2O$—: 80.3 (**c,** CH), 69.8 (**d,** CH_2O), 61.9 (**e,** CH_2OH). (3) —$CH_2CH(O—)CH_2O$— and (4) —$CH(CH_2—)CH_2O$—: 78.6 (**g,** CH), 71.3 (**f,** $2CH_2$). The detected H_2C—OH and HC—OH group indicate the addition of water molecules to the epoxy groups of ECH. Moreover, a low intensity signal of the carbon of chloromethyl group (H_2C—Cl) at 47.8 ppm[32] (Fig. 1, signal **l**) indicated that few chlorine atoms was present in PG gel, which is confirmed by only 0.6% of chlorine determined by XPS (Table III). Obviously, whether the chlorine atom of ECH could be removed by an

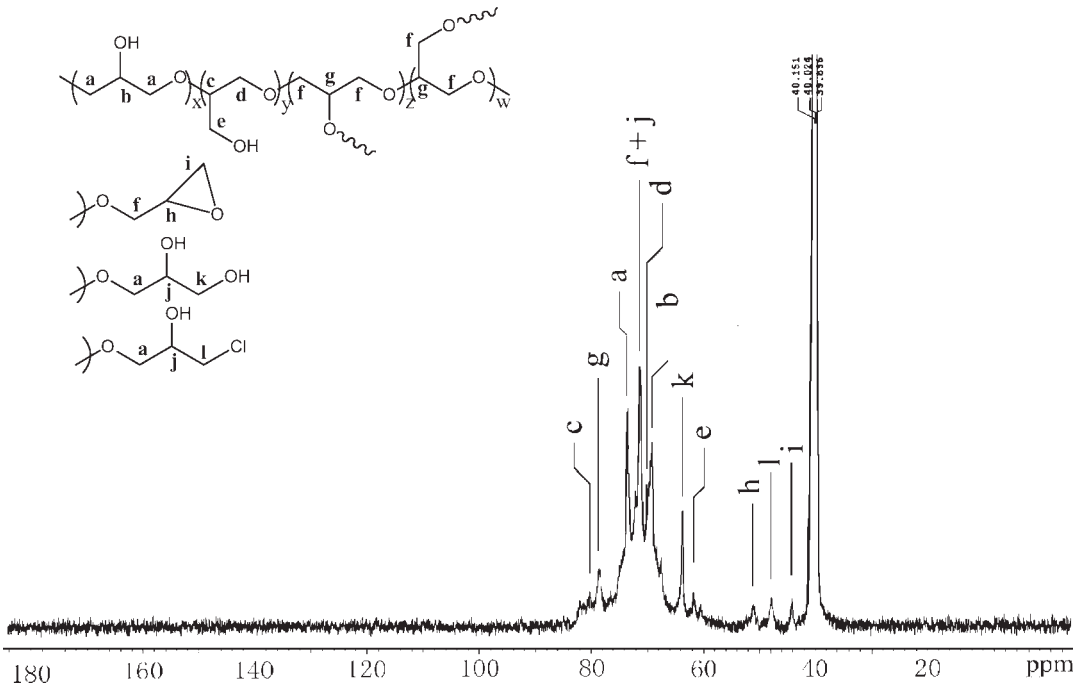

Figure 1 ^{13}C-NMR spectrum (swollen in DMSO-d_6, 30°C) of PG gel.

intramolecular substitution to form new epoxide after ECH was opened by a hydroxyl anion, or chloromethyl groups in PG could be substituted by hydroxyl as well as alkoxy groups. This is the main reason why the ECH can react with H_2O in the presence of NaOH to form PG gel.

In addition, the carbon signals of glyceric group (Fig. 1, signal **j** and **k**: 71.3 and 63.7 ppm) as well as glycidyl group (Fig. 1, signal **h** and **i**: 51.1 and 44.1 ppm[33]) were also observed. Based on the result of characterization, in combination with the swelling property, the structure of resulting PG gel was assigned as crosslinked PG (Fig. 1), which is in agreement on the previous researches.[24–26]

For PGL gel, as shown in Table III and Figure 2, the atomic percentage of chlorine was only 0.3% and the carbon signals (swollen in DMSO-d_6) of the four main subunits and its terminal groups were all measured in the range from 44 to 80 ppm (Fig. 2), showing that the structure of PG was maintained. The additional signals at 176.6 and 19.3 ppm (signal **m** and **p**) were assigned to the carboxyl and methyl group in LLA unit, respectively.[34] The chemical shift of CH group in LLA was 69.2 ppm (signal **o**) but which overlapped with signal **b**. These results demonstrated the fact that LLA unit was incorporated into PG matrix.

A 2.0% of sodium was detected from the PGL gel by XPS (Table III), whereas no sodium atom appeared in the PGL_{HCl} gel that was acidified with HCl before freeze-dried treatment. It implicates a transformation of carboxylic acid group (—COOH) in original LLA to sodium carboxylate group (—COONa) by the neutralization of NaOH during the polymerization course.

To determine the chemical bonding of LLA to PG matrix, the pregel was characterized with ^{13}C-NMR spectra, which was a reaction product without addition of the last amount of NaOH (NaOH-3) that can gelatinize the reaction mixture. As shown in Figure 4, because of incomplete acidification of sodium carboxylate group in hydrochloride-acidified pregel with HCl, the carbon signals of LLA unit showed two carbonyl peaks and two methyl peaks in ^{13}C-NMR spectrum of the hydrochloride-acidified pregel, which should be ascribed to carboxylic acid group (Fig. 3, signal **m**′) and sodium carboxylate group (Fig. 3, signal **m**). However, the ^{13}C-NMR spectrum of a mixture of the hydrochloride-acidified pregel and free LLA showed that the carbon signals of LLA unit in pregel were obviously different from that of free LLA as shown in Figure 4. The carbon peaks of bonded LLA unit appeared at higher field than that of free LLA. But only did the signals of the bonded LLA unit existed in carboxylic acid appeared, and the signals of the bonded LLA unit

TABLE III
XPS Analysis of PG, PGL, and PGL_{HCl} Gels (Atomic Percent)

Sample ID	C	O	Cl	Na
PG	60.5	38.9	0.6	
PGL 6 (5.2)	60.7	37.0	0.3	2.0
PGL 6 $(5.2)_{HCl}$[a]	64.6	34.6	0.8	

[a] Acidified with HCl before freeze-dried treatment.

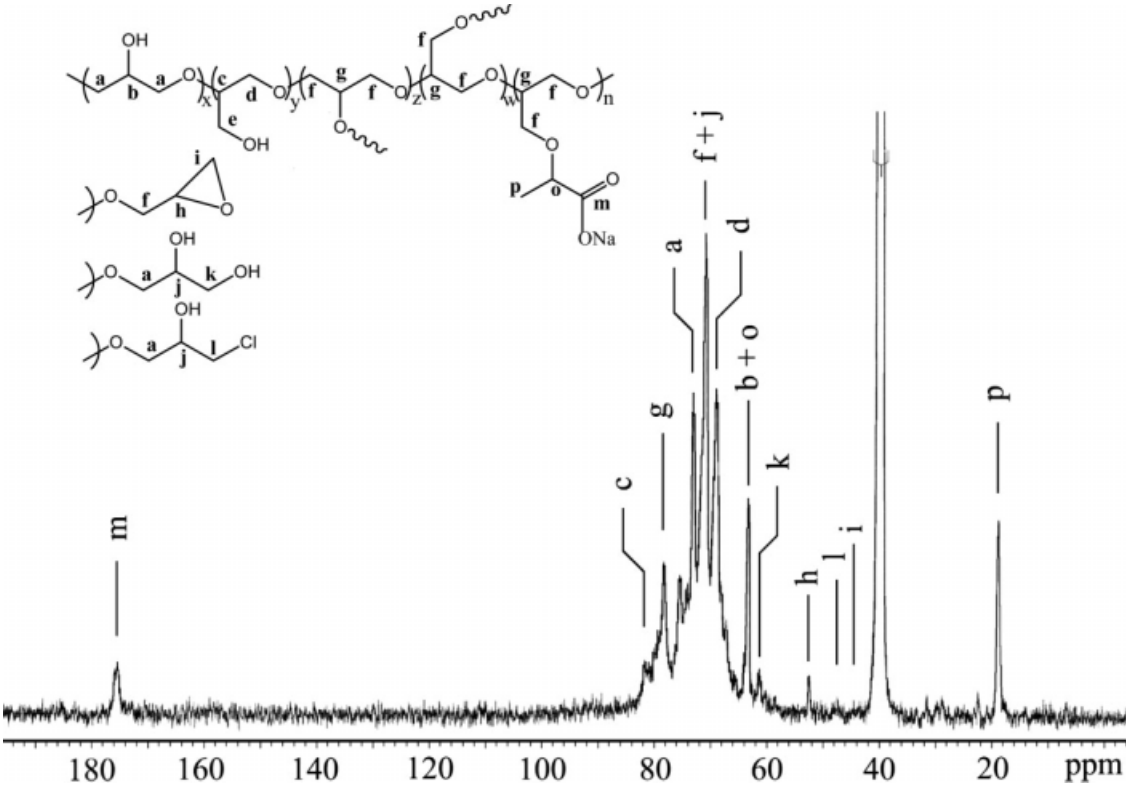

Figure 2 ^{13}C-NMR spectrum (swollen in DMSO-d_6, 30°C) of PGL gel.

existed in sodium carboxylate disappeared in the presence of free LLA because of the exchange of carboxylate with free LLA. Therefore, it is unambiguously confirmed that the LLA unit is bonded to PG matrix by its hydroxyl group and the carboxyl group is free and pendant.

The structure of PGL gel was also supported by the results from FTIR spectra (Fig. 5). As shown in Figure 5, hydroxyl group band (3432 cm^{-1}), alkyl group band (2923 and 2869 cm^{-1}), ether band (1113 cm^{-1}), and epoxy band (852 cm^{-1}, weak) are all recorded for both PG and PGL specimens. The band

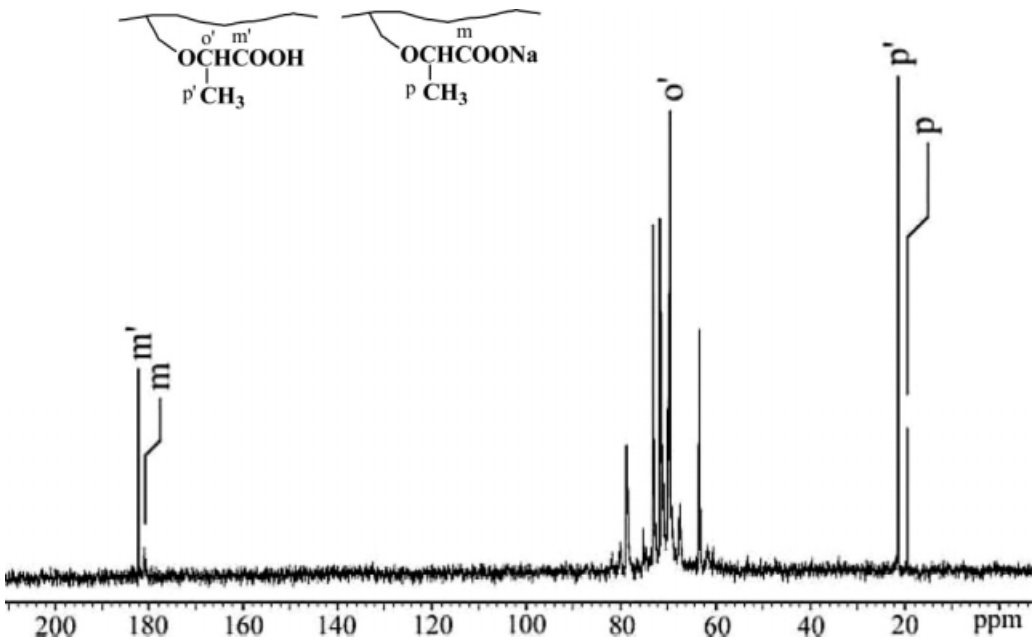

Figure 3 ^{13}C-NMR spectrum (in D_2O) of the acidified pregel.

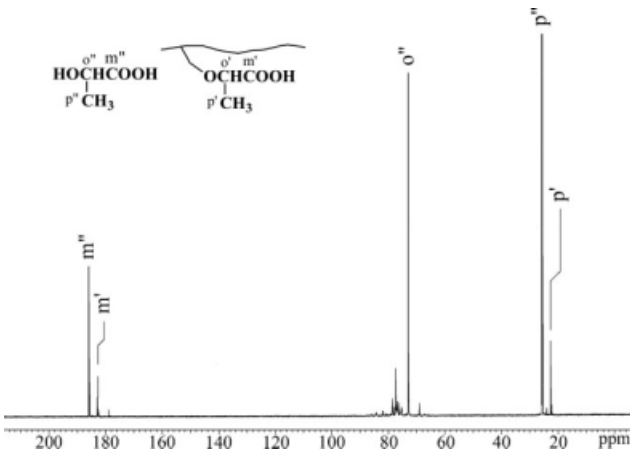

Figure 4 ^{13}C-NMR spectrum (in D_2O) of the mixture of acidified pregel and free LLA.

of carboxyl group (1738 cm^{-1}), however, is observed only in the spectrum of PGL gel.

Equilibrium swelling behavior of PGL hydrogels

The equilibrium swelling behavior of PGL hydrogels was evaluated in terms of ESR by incubating them in different environmental mediums. The effect of amount of LLA and NaOH-3 on ESR of resulting PGL gels in distilled water at 25°C is shown in Figure 6. The average ESR of the PGL hydrogels are 53.1, 38.3, and 24.1, respectively, when the amount of LLA in the feed is 8 g and then 3.6, 4.4, and 5.2 g of NaOH-3 (for the crosslinking reaction) are used, while the amount of LLA are 6 g and subsequently 3.6, 4.4, and 5.2 g of NaOH-3 are used, the average ESR are 34.1, 25.1, and 14.6, respectively. Obviously, the ESR of the hydrogels is in direct proportion to the amount of LLA in the feed, but are in inverse proportion to the amount of NaOH-3, which indicates the swelling of the hydrogels could be favorably tailored by varying the feed amount of LLA and NaOH-3 during the preparation process.

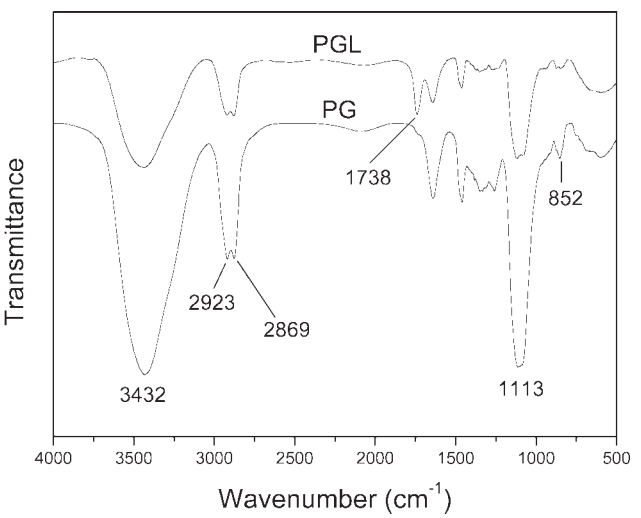

Figure 5 FTIR spectra of PG and PGL gels.

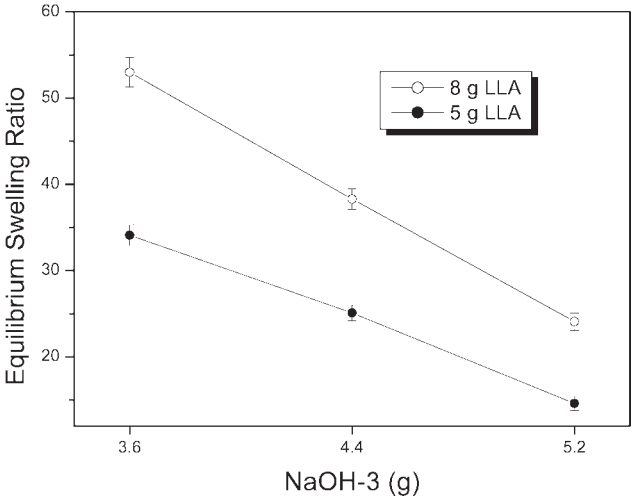

Figure 6 Effect of the amount of LLA and NaOH-3 on ESR of resulting PGL hydrogels in distilled water at 25°C.

Figure 7 shows the ESR of the hydrogels as a function of the solution pH with a constant ionic strength of 0.04*M* at 37°C. The swelling of the hydrogels is pH-depended and its ESR increases with the increase in pH just as poly(acrylic acid) hydrogel does.[5–9] This indicates that with increasing pH of the external solution, the carboxylic acid groups of the hydrogel are converted to carboxylate anions, which causes an expansion of the network chains. The abrupt swelling transformation of the hydrogels occurs at pH 3–5, which is associated with pK_a of LLA (3.87). The hydrogel containing richer LLA unit exhibits larger ESR and ΔESR ($ESR_{pH\ 7–1}$) value. It can be ascribed to the more

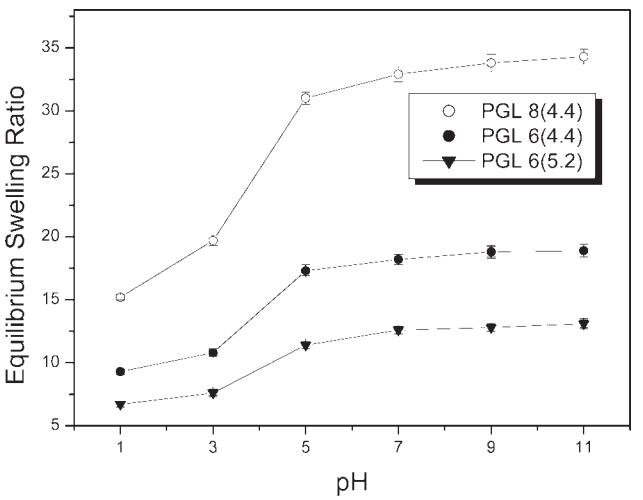

Figure 7 ESR of PGL hydrogels as a function of solution pH ($I = 0.04M$) at 37°C.

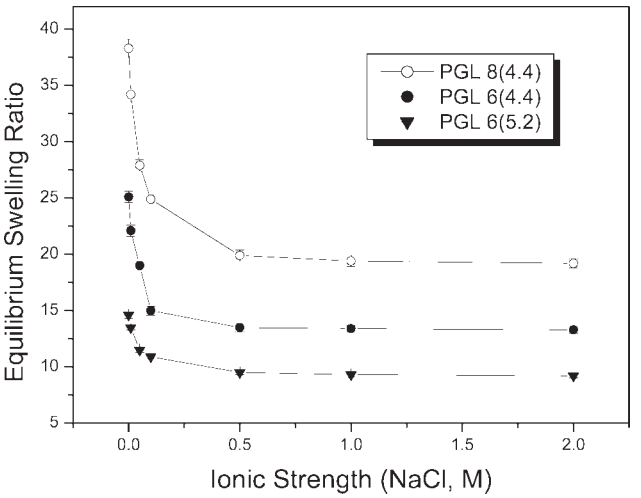

Figure 8 ESR of PGL hydrogels as a function of ionic strength of solution (NaCl) at 37°C.

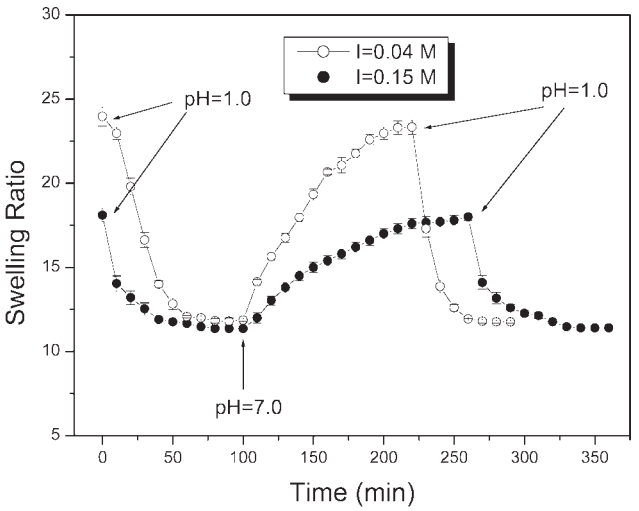

Figure 10 Cycle swelling behavior of PGL 6 (3.6) hydrogel in the solution between pH 1.0 and 7.0 at 37°C.

LLA unit in the hydrogel lead to the more polarity or electrostatic repulsion inside the hydrogel.

It is well known that the Donnan effect is considered as the main driving force for the swelling of polyelectrolyte gels. Increasing ionic strength will strongly suppress swelling and result in the decrease of the gel volume. Figure 8 presents the change of ESR for PGL hydrogels as a function of ionic strength in NaCl solution at 37°C. The ESR decreases drastically with the increase of ionic strength, but further decrease hardly occurs when the ionic strength increases from 0.50 to 2.0*M*.

Figure 9 illustrates the ESR of PGL hydrogels as a function of cation charge of salt solution with a constant ionic strength of 0.10*M* at 37°C. The ESR reduced sharply with increasing the cation charge from 1 to 3, indicating a cationic charge-sensitive swelling in response to a variety of cation charge. Furthermore, the ESR of the hydrogel containing richer LLA unit has the larger change value. The chemical bonding of carboxylate ions with multivalent cation results in the crosslinking of the gel via ionic bridges between carboxylate groups and multivalent cation. Theoretically, the decrease in the hydrogel's ESR with cation charge exhibits a linear change because the chemical bonding of carboxylate ions with multivalent cation is proportional to their ionic valance.[12] For example, the two curves of the PGL 6 (4.4) and PGL 6 (5.2) hydrogel's ESR against cation charge from 1 to 2 have almost the same decline tendency. It is interesting that all the hydrogels have lower ESR value in the solution of Fe^{3+} ion, exhibiting an obvious decrease of the gel volume. The possible reason is the particular structure of the polyether–polyol hydrogels containing pendant carboxyl group, which results in the chelation interaction between the hydrogel and Fe^{3+} ion.

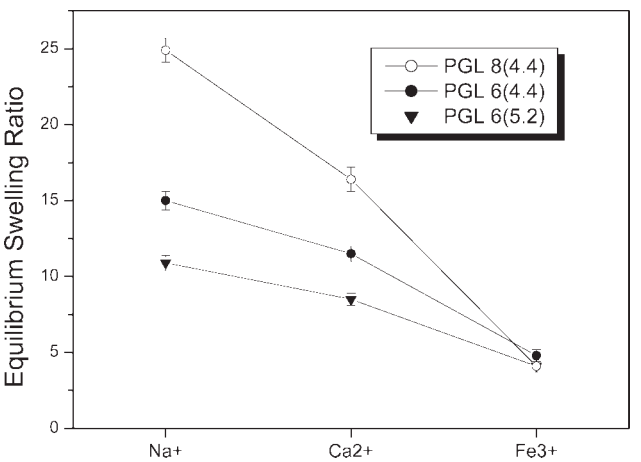

Figure 9 ESR of PGL hydrogels as a function of cation charge of salt solution. The ionic strength of each salt solution was kept constant ($I = 0.10M$, 37°C).

These equilibrium swelling studies indicate that PGL hydrogel is typical of an anionic, weak polyelectrolyte hydrogel, which supports again the structure of PGL hydrogel from ^{13}C-NMR, XPS, and FTIR measurements.

Cyclic deswelling/swelling kinetics of PGL hydrogel

The cyclic deswelling/swelling experiments were carried out in two different pH value solutions with a selected ionic strength (0.04 and 0.15*M*) at 37°C, and results were shown in Figure 10. It can be observed that the PGL hydrogel exhibits a fast response rate to pH changes. At pH 7.0, the hydrogel swells because of electrostatic repulsion, whereas at pH 1.0, it shrinks sharply because of protonation

of the carboxylate anions. It is also observed that its swelling and response rate are affected by ionic strength of the external medium. At a ionic strength of 0.04*M*, the equilibrium shrinkage time and SR of the PGL 6 (3.6) hydrogel are around 60 min and 12, respectively, whereas at ionic strength of 0.15*M*, they are around 40 min and 11, respectively. In addition, the results suggest that its swelling/deswelling properties in response to the changes of solution pH and ionic strength are reversible.

CONCLUSIONS

In this article, we designed an approach to novel anionic, weak polyelectrolyte hydrogels composed of PG and LLA. The PG hydrogels containing LLA groups as pendant acidic substituents were successfully synthesized through the reaction of ECH with LLA in the presence of NaOH and CTAB as a PTC, followed by hydrolysis, polymerization, and crosslinking reactions. The hydrogels with different LLA contents and ESRs were prepared by varying the feed amount of LLA and NaOH. The carboxyl group content in the hydrogel was monitored by chemical titration. The PGL hydrogels exhibit the properties of an anionic, weak polyelectrolyte hydrogel such as pH-, ionic strength-, cationic charge-responsive volume phase transitions, and the reversible swelling/deswelling properties in response to the changes of environmental medium. Consequently, these pH-responsive PG-based hydrogels will have great potential applications in biomedical and related areas, such as drug delivery, waste water treatment, and tissue engineering.

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