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Synthesis and characterization of pH- and temperature-sensitive hydrogel of *N*-isopropylacrylamide/cyclodextrin based copolymer

Yu-Yang Liu, Xiao-Dong Fan*

Department of Chemical Engineering, Northwestern Polytechnic University, Xi'an 710072, People's Republic of China

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Abstract

A reactive β-Cyclodextrin (β-CD) based monomer carrying vinyl carboxylic acid functional groups was synthesized via reaction of β-CD with maleic anhydride (MAH) in *N*,*N*-dimethylformamide (DMF) at 80 °C. By copolymerization of the monomer with *N*-isopropylacrylamide (NIPA), a novel hydrogel, poly(NIPA-*co*-MAH-β-CD) with pH and temperature sensitivities plus molecular inclusion function, was obtained using free radical polymerization in aqueous solution. The hydrogel's composition was determined by element analysis and infrared spectroscopy. Equilibrium swelling ratio (ESR) of hydrogels was tested under different environment of pH, temperature and ionic strength. The results indicated that ESR of hydrogels presents marked variations following the change of experimental conditions used.

Keywords: β-Cyclodextrin; *N*-Isopropylacrylamide; pH- and temperature-sensitive hydrogel

1. Introduction

β-Cyclodextrin (β-CD) is a torus-shaped cyclic oligosaccharide consisting of seven α-1,4-linked D-glucopyranose units with an internal hydrophobic cavity. It is well known that this structure possesses remarkable ability to include many organic compounds [1–10]. Because of this unique behavior, β-CD and its derivatives including β-CD-containing polymers have been studied extensively in many research fields such as drug delivery system [6], separating and absorption of materials [7,8], environmental protection devices [9], as well as functional catalysts [10].

Hydrogel, which is defined as a cross-linked hydrophilic polymer network, can expand substantially and retain large amount of water without being dissolved [11]. To date, considerable research attentions have be focused on so-called smart hydrogels which can transfer their volume in response to environmental stimuli [12–27]. Based on their swelling and syneresis behaviors, these hydrogels were already used in biomedical and pharmaceutical research fields [16].

Interestingly, if a hydrogel contains a component with a molecular inclusion component such as β-CD, and a temperature sensitivity component such as NIPA units, the copolymer obtained may not only possess the function of including organic compounds, but also may sensitively respond to external stimuli, such as pH, temperature and ionic strength. Furthermore, such dual-functionalities may be effectively applied to many industries to develop new functional biomedical and pharmaceutical products. Unfortunately, so far, there are few studies conducting in this direction [29–31].

In this paper, we synthesized a novel hydrogel, which can respond to different external stimuli, at the same time, can present molecular inclusion functionality. In order to fulfill this goal, we first prepared a β-CD based monomer with vinyl carboxylic acid groups, and then, a smart hydrogel via copolymerization of the monomer with NIPA in aqueous solution was prepared. The hydrogel of poly(NIPA-*co*-MAH-β-CD) shows a good combination of pH-, temperature sensitivities with a molecular inclusion ability. Distinguished from poly(*N*-isopropylacrylamide-*co*-acrylic acid) (poly(NIPA-*co*-AA)), a thermal and pH sensitive hydrogel, poly(NIPA-*co*-MAH-β-CD) also demonstrates many unique swelling characters, especially, a much better temperature sensitivity at higher –COOH group content under a weak base condition.

* Corresponding author. Tel.: +86-2984-93347; fax: +86-2984-91000.
E-mail address: xfand@yahoo.com (X.D. Fan).

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2. Experimental

2.1. Materials

NIPA was purchased from ACROS (more than 99% purity), UK. β-CD was from Northwestern Geological Institute, China, and was purified two times by recrystallization from water prior to use. All other reagents including ammonium persulfate (APS), sodium bisulfite (SBS) and MAH were analytic grade made in China, and used as received without further purification.

2.2. Synthesis of β-CD based reactive monomer (MAH-β-CD)

In order to obtain a β-CD based reactive monomer which can be copolymerized and cross-linked with NIPA component to form a hydrogel, a modified β-CD carrying five vinyl carboxylic acid groups was designed and synthesized. Specifically, 5.68 g of β-CD (0.005 mol) was dissolved in 30 ml DMF, and 4.90 g of MAH (0.05 mol) was added afterwards. The mixture solution was heated at 80 °C for 10 h under the vigorously stirring. The molecular structure and reaction mechanism was shown in Fig. 1. After the reaction was completed, the mixture was allowed to cooling to room temperature, and then, 30 ml of trichloromethane was added. A white precipitate obtained was filtrated, and washed at least three times using large amount of acetone, finally, dried in a vacuum oven at room temperature for 1 day, and 80 °C for 3 days.

The product yield: 5.90 g (72.6%).

IR measurements (KBr, cm^{-1}): 3500 (s, OH), 2900 (w, CH_2), 1720 (s, C=O), 1620 (m, CH=CH), 1040 (s, C–O).

^{13}C NMR(D_2O): The spectrum was shown in Fig. 2; the carbon groups related to the chemical shifts were assigned as showed in Fig. 2.

Element analysis: Specifically, for a molecular structure of $C_{42}H_{65}O_{35}[OCOCH{=}CHCOOH]_5$, the theoretic calculation is C: 45.78%; H: 4.92%, and the actual measurements is C: 45.70%; H: 5.27%.

2.3. Preparation of hydrogel

Hydrogels were copolymerized via NIPA and MAH-β-CD in aqueous solution at 20 °C using APS and SBS redox system as the initiator. Specifically, total 0.60 g of MAH-β-CD and NIPA were dissolved in 2.4 ml of distilled water (based on the feed composition in Table 1), then 0.5 ml of SBS solution was added. After bubbling with nitrogen gas for 15 min to remove oxygen, 0.5 ml of APS solution was added by an injector. The copolymerization was conducted at 20 °C for 24 h. The hydrogel obtained was taken out from the bottle, and cut into thin disks of 12 mm in diameter, then immersed in distilled water to remove the unreacted monomer. The samples were kept in fresh distilled water that was changed for every 12 h, and lasted 6 days. Late, they were dried under ambient conditions for 2 days and in a vacuum oven at 60 °C for 7 days.

Fig. 1. The molecular structure and the reaction scheme of β-CD with maleic anhydride.

2.4. Instrument analyses

^{13}C NMR measurements were conducted on Varian INOVA-400 spectrometer, USA, at room temperature using D_2O as solvent.

Infrared spectroscopy measurements were preformed on a Specode 75 model, Germ, using KBr as the sample holder.

Elemental analyses were carried out on a Vario ELIII Instrument, Germ.

2.5. Swelling measurements

The swelling experiments were performed in different pH buffer solution, or in distilled water with constant ionic strength ($I = 0.1$ mol/l), respectively. After reaching to a desired swelling ratio for the hydrogel, it was carefully taken out from the solution, wiped with a filter paper to remove the free water from the surface of the sample, and then weighted. The swelling ratio (SR, g/g) was calculated using the equation as follows.

$$SR = (w_1 - w_0)/w_0$$

where w_0 and w_1 are weights of dry and wet sample, respectively.

Preparation of buffer solution: KCl/HCl, pH 1.4–2.0;

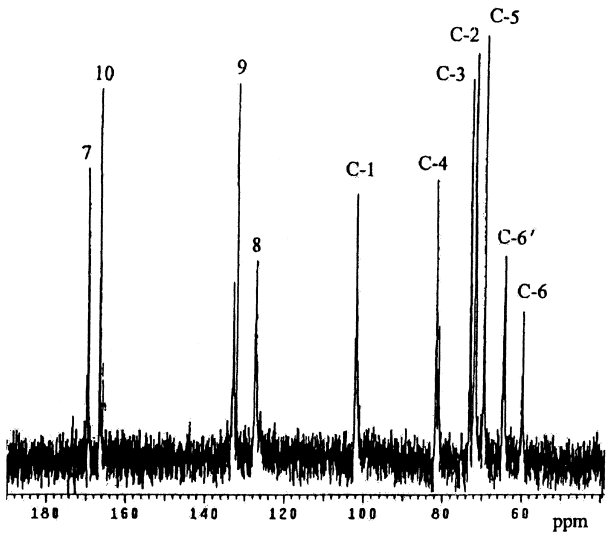

Fig. 2. ^{13}C NMR spectrum of MAH-β-CD monomer using D_2O as the solvent.

Table 1
Hydrogel's chemical composition and the mole ratio of NIPA segment with carboxyl groups

Sample code	Feed composition NIPA/MAH-M-β-CD (wt%/wt%)	Polymer composition NIPA/MAH-β-CD (wt%/wt%)[a]	Environmental-sensitive component composition in polymers NIPA/–COOH (mol%/mol%)[a]
I	70.0/30.0	90.9/9.1	96.6/3.4
II	60.0/40.0	82.6/17.4	93.2/6.8
III	50.0/50.0	78.9/21.1	91.5/8.5
IV	40.0/60.0	73.6/26.4	88.9/11.1
V	30.0/70.0	63.8/36.2	83.5/16.5

[a] Calculated from C and N content measured by element analysis.

HCl/$KHC_6H_4(COO)_2$/NaOH, pH 3.0–5.0; NaOH/KH_2PO_4/Na_2HPO_4, pH 6.0–7.4. In order to obtain a solution with constant ionic strength of 0.1 mol/l, certain amount of NaCl and KCl was introduced into the buffer solution.

3. Results and discussion

3.1. Preparation and characterization of hydrogel

For poly(NIPA-*co*-MAH-β-CD) hydrogel, Our IR spectra show a strong C–OH stretching vibration around 1036 cm^{-1} and a C=O stretching vibration around 1720 cm^{-1} from MAH-β-CD segment. It can also be observed that a C=O stretching vibration around 1640 cm^{-1} and a N–H deformation vibration around 1575 cm^{-1} from PNIPA segment. A strong and wide band at 3250–3600 cm^{-1} is a whole combination of absorption of amide, hydroxyl and carboxyl groups from both MAH-β-CD and NIPA components, respectively. Besides, the chemical compositions of hydrogel synthesized, and its mole ratio of NIPA and carboxyl groups for different samples are given in Table 1 using element analysis techniques.

As can be seen from Table 1, the feed composition and real copolymer composition measured are different. Compared with feed composition, the actual MAH-β-CD component in hydrogel reduces greatly. The reduction of MAH-β-CD may be caused by relatively weak reactive character of 1,2-substituted vinyl groups in β-CD monomer. The result can also be confirmed in Fig. 3 that the yield of hydrogel decreases with the increase in feed composition of MAH-β-CD.

3.2. Effect of pH on ESR of hydrogels

Fig. 4 shows the influence of pH values on hydrogel's equilibrium swelling ratio (ESR). The experiments were performed in buffer solutions in a range of pH 1.4–7.4 with an ionic strength of 0.1 mol/l at 24.5 °C. As can be seen,

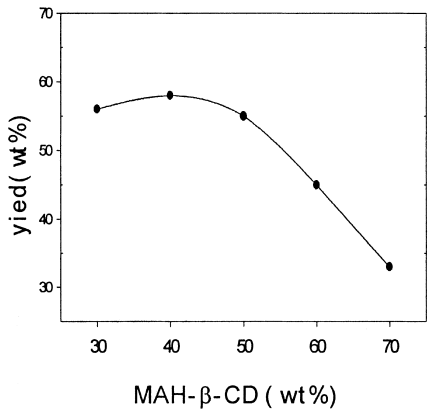

Fig. 3. The yield of poly(NIPA-*co*-MAH-β-CD) versus MAH-β-CD component in feed composition.

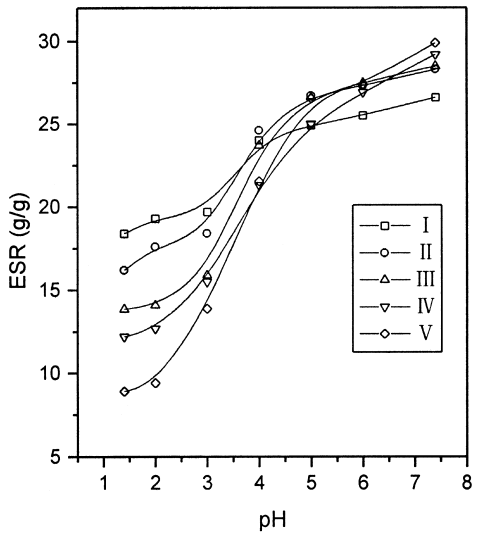

Fig. 4. Influence of pH value on ESR of hydrogels synthesized for samples I–V at 24.5°.

ESR of samples I–III exhibit a marked transition region at pHs 3.0–5.0, and the similar tendency can also be observed at pHs 2.0–5.0 for samples IV and V. The transition phenomena observed may be from ionization behavior of –COOH groups in response to different pH values. At low pH, –COOH groups can not be easily ionized, consequently, it may initiate the formation of hydrogen bonding between –COOH in β-CD and –CONH– in NIPA part, and enhance the interactions between macromolecular chain [15,17,28]. As a result, it causes the decrease in swelling ratio of hydrogels. However, with the increase in pH values, –COOH group begins to ionize. The carboxylic acid group ionized could regain relatively good hydrophilicity due to $-COO^-$ groups' electrostatic repulsive force. This could lead to hydrogel's expanding, and cause their ESR reaching to a relatively larger value accordingly [15,17,28]. The results may clearly explain why there are transition regions for these hydrogels, and indicate that the hydrogel synthesized, indeed, is a pH sensitive copolymer. On the other hand, as shown in Fig. 4, the effect of pH on ESR for hydrogels also depends on the content of $-COO^-$ groups. Because the sequence of pH sensitivity for samples follows the order of I < II < III < IV < V. Interestingly, at pH 7.4, ESR values for all samples, except for sample I, are around 29.0. This may suggest that the carboxylic acid groups at pH 7.4 may subject to be ionized greatly, and at this point, the value of ESR for hydrogels may mainly rely on ionic strength of the solution as well as its temperature.

3.3. Effect of temperature on ESR value of hydrogels

It is well known that poly(*N*-isopropylacrylamide) (PNIPA) homopolymer exhibits a lower critical solution temperature (LCST) around 32.0 °C in aqueous solution. Therefore, the hydrogel of PNIPA swells and shrinks in water below and above this temperature [12–28]. However, if PNIPA hydrogel contains –COOH groups, its thermosensitivity can also be affected by the pH of the solution [15,17,28]. In our study, by incorporating a MAH-β-CD monomer containing –COOH groups into PNIPA, ESR related to LCST of the copolymer should not only be greatly affected, but also the variation of ESR should present differently in accordance with the environment's pH value.

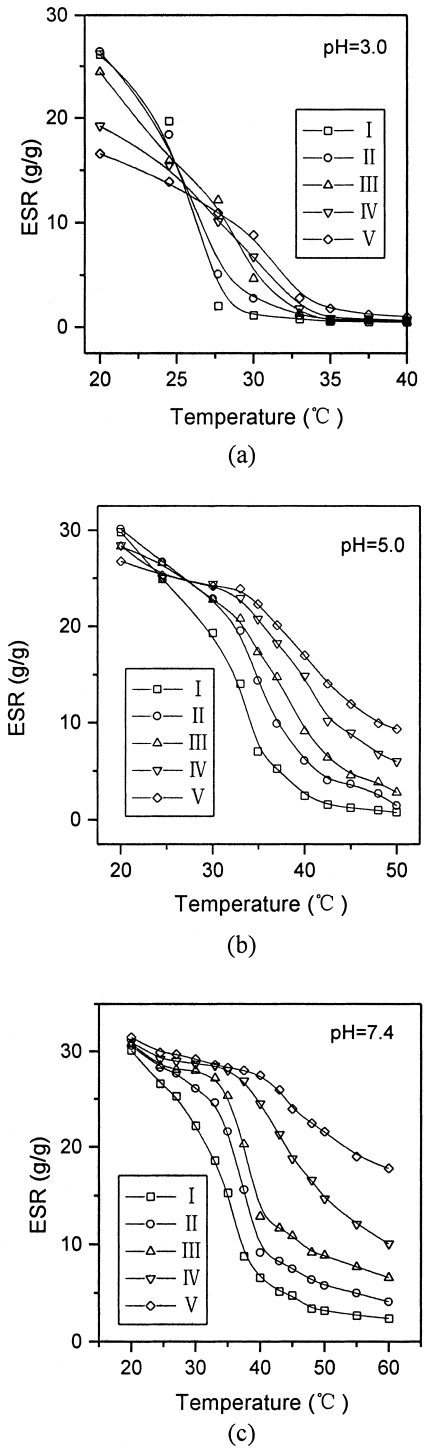

Fig. 5. ESR as a function of temperature at pH 3.0 (a), pH 5.0 (b) and pH 7.4 (c) for samples I–V.

Fig. 5(a)–(c) shows the influence of temperature on ESR values of hydrogels at the difference pH values. First, as can be seen from Fig. 5(a), at pH 3.0, ESR around LCST (30 °C) of samples I–V show evident transition phenomena. It can also be observed that these transition regions decrease with the increase in NIPA component in hydrogels. The result indicates that the temperature sensitive component can still play a dominant role for volume phase transition of hydrogel in response to the temperature at a lower pH value [24–26]. However, temperature sensitivity of hydrogels reduces evidently at pH 5.0 as can be seen from Fig. 5(b). Where the hydrogel's LCST becomes less obvious, and ESR also presents a relatively broad and slow transition region from 20 to 50 °C. This may be attributed to the ionization of –COOH groups, and the electrostatic repulsive force caused by these groups, as a result, may offset the aggregation caused by temperature sensitive component. At pH 7.4, due to more –COOH group's ionization [28], the hydrogels show lowest temperature sensitivity, particularly, for the hydrogel with higher –COOH group content. This result is consistent with poly(NIPA-*co*-AA) hydrogel's behavior. However, it must be noticed that under a weak base condition (pH = 7.4), the variation of ESR of poly(NIPAM-*co*-MAH-β-CD) obviously differs from that of poly(NIPA-*co*-AA) with the same –COOH content as the temperature changes. Usually, for poly(NIPA-*co*-AA) carrying more than 10 mol% –COOH groups, its hydrogel can not exhibit a volume phase transition when the temperature increases [15, 28]. However, for poly(NIPAM-*co*-MAH-β-CD) hydrogel, even with 16.5 mol% –COOH groups (sample V), it still can show a transition region related to its LCST. The result may be attributed to the different structure distribution character of –COOH groups in hydrogel's chain networks. As is shown in Table 1 and Fig. 3, due to low reactivity of 1,2-substituted vinyl monomer, it is reasonable to assume that not all –COOH groups in our hydrogels are bonded directly to polymer backbone. Thus, a plenty of freely pendant –COOH groups may not effectively affect the temperature sensitivity as the case of poly(NIPA-*co*-AA) hydrogel.

3.4. Effect of ionic strength of solution on ESR of hydrogels

Ionic strength of the solution can also influence the swelling behavior of hydrogels synthesized [16,23–25,27]. For understanding this further, ESR of hydrogels as a function of ionic strength in distilled water at 24.5 °C is shown in Fig. 6. As can be seen, for samples I–IV, their ESR drop quickly with the increase in ionic strength in the range of 10^{-4}–10^{-1} mol/l. For sample V, the similar result is also observed at ionic strength in the range of 10^{-3}–10^{-1} mol/l. The result may be caused by shielding effect from counter ions in solution, and the existence in Donnan potential [16,23–25,27]. Because two factors make swelling force of hydrogels reduce quickly.

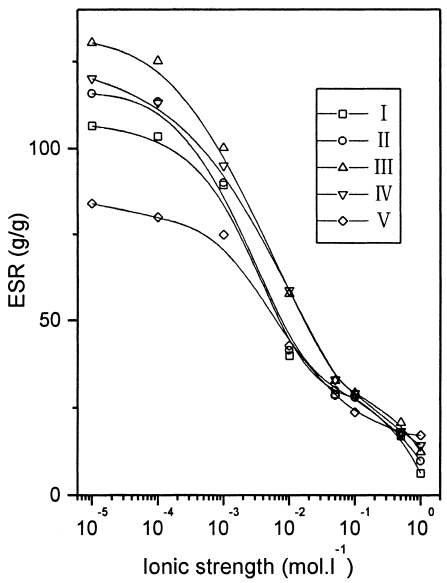

Fig. 6. ESR as a function of ionic strength in distilled water at 25 °C for samples I–V.

3.5. Hydrogels in response to changes in pH, temperature and ionic strength

In order to investigate if the hydrogel synthesized responds to changes of pH, temperature and ionic strength, and at the same time, to understand if the response is reversible and how fast to these stimuli [16]. The oscillatory swelling experiments were conducted under different conditions as shown in Figs. 7–9. As can be seen from Fig. 7, after sample III achieved its swelling equilibrium at pH 7.4, and then was immersed in a pH 3.0 buffer solution, it shrinks quickly. This may be attributed to $-COO^-$ ions transfer into –COOH groups at the higher pH value. When the hydrogel shrinks to a certain extent, the driving force for shrinking decreases, and shrinking rate becomes slow until reaching a new equilibrium. Fig. 7 shows that sample III possesses a good reversible response to the alternating changes in pH.

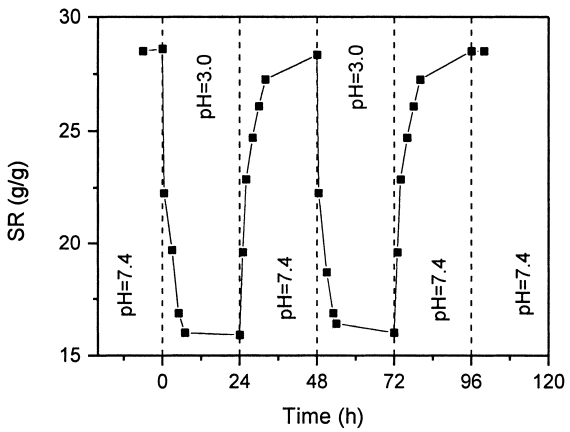

Fig. 7. Oscillatory swelling behavior as a function of time and pH at 24.5 °C for sample III.

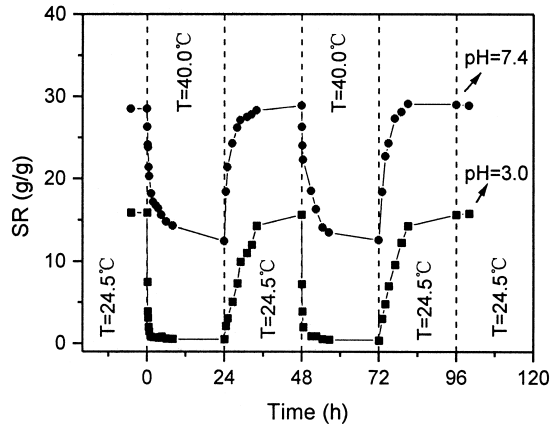

Fig. 8. Oscillatory swelling behavior as a function of time and temperature at pH 7.4 and 3.0 for sample III.

Fig. 8 also shows that sample III responds well to an alternating temperature between 24.5 and 40.0 °C at pH 3.0 and 7.4, respectively. After sample III reaches its ESR at 24.5 °C under pH 3.0, it begins to shrink fast after being exposing to a 40.0 °C circumstance. During 30 min, the swelling ratio of sample III reduces from 15.9 to 0.7.

Fig. 9 is oscillatory swelling ratio of sample III as a function of time and ionic strength at 24.5 °C. As can be seen in Fig. 9, the hydrogel is evidently in response to the alternating changes between distilled water and physiological saline. The hydrogel after achieving its ESR in distilled water begins to collapse in physiological saline. When hydrogel was put into distilled water again, at the same time, keep changing fresh distilled water in every 2 h for 6 h. It is clearly observed that the hydrogel swells faster in distilled water. The phenomenon may be attributed to free salt ions in the hydrogel, which can increase osmotic pressure between hydrogel and solution.

4. Conclusions

1. A novel reactive β-CD based monomer carrying vinyl carboxylic acid groups was synthesized by reaction of MAH and β-CD in DMF solution at 80 °C. The mole ratio of vinyl carboxylic acid group can be effectively controlled by controlling the mole ratio of β-CD with MAH.
2. By copolymeriazation of MAH-β-CD with NIPA, poly(NIPA-*co*-MAH-β-CD hydrogel was prepared by free radical polymerization using redox system as the initiator. The chemical composition of hydrogel can be determined by element analysis. The yield calculation of copolymer indicates that MAH-β-CD have a low reactivity with NIPA.
3. Swelling experiment shows that the hydrogel synthesized possesses a combination of pH-, temperature- and ionic strength-sensitivities, and reversibility in response to these external stimuli.
4. Compared to poly (NIPA-*co*-AA) hydrogel, the hydrogel of poly(NIPA-*co*-MAH-β-CD) with high –COOH group content exhibits better temperature sensitivity under pH 7.4.

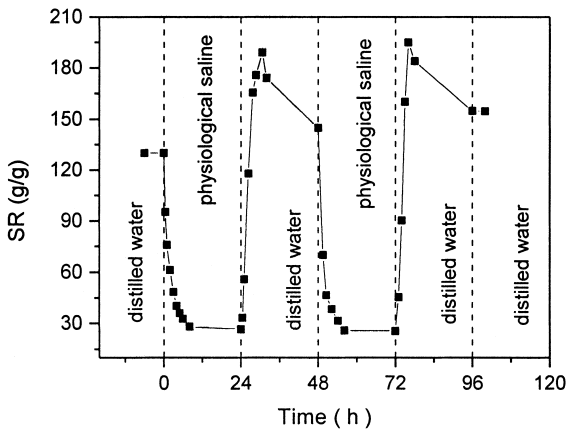

Fig. 9. Oscillatory swelling behavior as a function of time and ionic strength at 24.5 °C for sample III.

Acknowledgments

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