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ПОЛИМЕРНЫЕ СЕТКИ

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SYNTHESIS AND CHARACTERIZATION OF NOVEL PEG-TETHERED PMAA HYDROGELS BASED ON A PEG MACROMOLECULAR AZO INITIATOR[1]

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Abstract—A new route was proposed to synthesize polyethylene glycol-tethered polymethacrylic acid (viz., PEG-tethered PMAA or PEG-*t*-PMAA) hydrogels based on a macromolecular azo initiator (MAI), PEG-attached azo initiator. The preparation of the MAI was accomplished by coupling PEG with 2,2'-azobis[2-methyl-N-(2-hydroxyethyl)propionamide] (AMHP) using 1,1-methylene bis-(4-isocyanatocyclohexane) (H_{12}MDI) as bridging molecules. The structure and morphologies of the resulting hydrogels were characterized by FTIR and SEM. The pH and ionic strength responses were investigated by swelling measurements, depending on molecular weight (MW) of PEG, molar ratios of isocyanate-terminated PEG to AMHP and mass percentage of the as-prepared MAIs. The PEG-*t*-PMAA hydrogels synthesized by 100 wt% PEG1000-attached azo initiators and a molar ratio 2 of –NCO-terminated PEG to AMHP exhibit more remarkable pH and ionic strength response than any other hydrogels. The driving force of swelling is believed to be mainly due to the porosity and dissociation balance of PMAA gels as well as gel compositions, while the deswelling behavior may be correlated with the decrease in osmotic pressure caused by the so-called "charge screening effect" of the cations. The PEG-*t*-PMAA hydrogels are expected to find specific applications in oral drug delivery and tissue engineering.

INTRODUCTION

In recent years, hydrogels with good biocompatibility and pH-response have increasingly been attracted attentions because of their applications in the field of peptide, protein, and gene drugs [1, 2]. PEG hydrogels are highly biocompatible hydrophilic polyethers, with the non-toxicity and rapidly spontaneous clearance from human bodies, and can be used as excellent candidates of biomedical materials [3]. While poly(methacrylic acid) (PMAA) is an ionizable hydrophilic polymer. After cross-linked, PMAA can swell in water, and the swelling behavior is largely dependent upon pH. This inspires us to prepare a new type of hydrogels combining the feature of PEG with pH response of PMAA [4]. It seems that PEG tethered onto PMAA hydrogels is a good choice.

It is known that the tethered polymers can effectively enhance cellular adhesion and prevent protein adsorption. Some tethered polymer surfaces act as adhesion promoters by interpenetrating into the mucous gel layer and bridging the interface between the hydrogel-based drug delivery system and the absorption sites [4]. Particularly, this material can enlarge the drug loading capacity, and avoid the non-specific absorption of drug-loaded systems in the reticuloendothelial system. Thus it easily transports drugs to the liver, spleen and other organs [5]. For the tethered polymers, hydrophilic flexible PEG chains are especially valuable because they can be attached bioactive molecules such as peptides and proteins via effective coupling of these molecules with PEG substrates. The well-known synthesizing routes include: precipitation polymerization [4], transesterification [6], and the acid-catalyzed elimination combined with atom-transfer radical polymerization (ATRP) [7], etc. Macromolecular azo initiators (MAIs) are unique azo bifunctional compounds, which can be utilized to synthesize tethered or block polymers consisting of vinyl units. The MAIs containing PEG units can easily polymerize vinyl monomers like methacrylic acid, and thus produce PEG tethered or block polymers as biomedical applications. At the same time, PMAA can form an inter-macromolecular complex with PEG tethers through hydrogen bonding interactions between carboxyl acid groups of PMAA and ether oxygen atoms of PEG. The formation of hydrogen-bonded complex is highly sensitive to change in concentrations and molecular weight (MW) of PEG, temperature, and pH, which is quite different from that of linear PMAA. It has been reported that the absorption of PEG may lead to contraction of PMAA homologues, PMAA gels, and that the degree of swelling is lowered by a factor of 1.5–3.0 [8].

In the above context, our aim is to propose a novel method for molecularly designing a new type of PEG-tethered PMAA (PEG-*t*-PMAA) hydrogels, which

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contain PEG tethered chains providing swelling adjustability upon incubating in various pH media, depending on the concentration and MW of PEG, and methacrylic acid (MAA) moieties supplying pH and ionic strength response. These hydrogels are prepared by a free radical solution polymerization route based on PEG-attached azo initiators. While the preparation of the initiator was accomplished by coupling PEG with 2,2'-azobis[2-methyl-N-(2-hydroxyethyl) propionamide] (AMHP) in the presence of 1,1-methylene bis-(4-isocyanatocyclohexane) (H_{12}MDI). The swelling of the PEG-tethered PMAA hydrogels with different topologies was explained in terms of diffusion theories. Furthermore, we discussed the fast pH-response of the gels to the variation of media acidity in detail, and analyzed the correlation between the porous structure of the gels and the response time, and tried to find which gel composition corresponds to the fastest response. The hydrogels with pH sensitivity are anticipated to have a tempting prospect in applications in oral drug carriers.

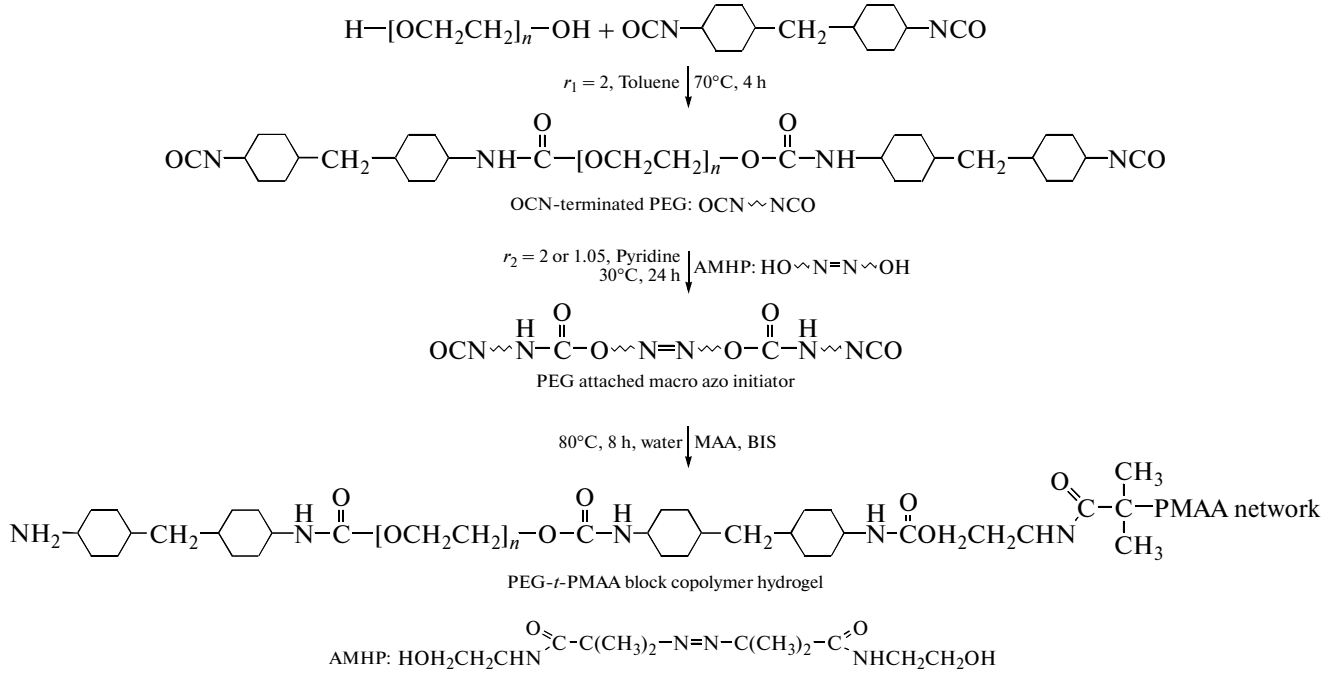
EXPERIMENTAL DETAILS

Materials and reagents

Poly(ethylene glycol) (PEG), biological grade, with MW of 1000 and 4000, was supplied by the National Pharmaceutical Ind. Corp. (Tianjin, China). Methacrylic acid (MAA), analytical grade (A.G), supplied by the Tianjin Jinyu Fine Chemicals Ltd Corp, was distilled in vacuum at 62°C in a pressure of 0.09 MPa. 1,1-Methylene bis-(4-isocyanatocyclohexane) (H_{12}MDI, A.G.) was obtained from the Shanghai Sigma-Aldrich Trading Corp. Ltd. (China). The cross-linker, N,N-methylenebisacrylamide (BIS or NNMBA, A.G), was purchased from the Tianjin Kermol Chemical Regent Developing Center (China). 2,2'-Azobis[2-methyl-N-(2-hydroxyethyl) propionamide] (AMHP, a bifunctional initiator) was purchased from the Wako Pure Chemical Industries, Ltd. (Japan) and used as received. Phosphate buffers with pH of 1.32, 2.81, 7.00, 8.73, 11 and 13 were prepared with Na_2HPO_4, NaH_2PO_4, NaOH and HCl, H_3PO_4 as physiological mediums, and NaCl was used to adjust the ionic strength.

Synthesis method

The synthetic strategies of PEG-*t*-PMAA block copolymers are presented in Scheme 1.



Scheme 1. Schematic illustration of the procedure for synthesizing PEG-*t*-PMAA block copolymer hydrogels.

Typically, 2 g PEG and stoichiometric H_{12}MDI ($r_1 = n_{-NCO}/n_{-OH} = 2$) were dissolved in 7 ml of toluene, and reacted at 70°C for 4 h. After ventilated in a draught cupboard for 8 h, the isocyanate-terminated PEG obtained and AMHP with mole ratio r_2 2 or 1.05 were dissolved in 6 ml of pyridine. The reaction proceeded at 30 °C for 24 h. The product was proved to contain —N=N— groups in its structure

by Raman (–N=N– stretch vibration modes appear at 1575–1630 cm^{-1}) and DSC analyses [9, 10], implying that a macromolecular azo initiator was achieved. Subsequently, 20 mmol of MAA monomer, various mass percentages of the MAIs with respect to MAA (25, 50 and 100%) and 1 wt% of BIS with respect to the monomer were dissolved in 5 ml of pyridine in turn. The resulting copolymer hydrogels were achieved after the reaction was performed at 80°C for 8 h. The as-prepared hydrogel samples were cut into sheets with a thickness of 3 mm, and were immersed with deionized water for one week to remove the residues of unreacted monomers and crosslinking agents. 1 M NaOH solution was employed to titrate the remaining aqueous solution after immersed samples until no acidic substance was detected. All sheets were dried in vacuum oven at 30°C until constant weight. Unless otherwise specified hereinafter, detailed formula designation and sample codes are tabulated in the table.

Formula designation and codes of the synthesized PEG-*t*-PMAA hydrogels

Sample code	MW of PEG	Amount of H_{12} MDI, g	r_2	Mass ratios of PEG-azo initiator to MAA, %
a	1000	1.0480	2	20
b	1000	1.0480	2	50
c	1000	1.0480	2	100
d	1000	1.0480	1.05	50
e	4000	0.2620	2	50

The amount of PEG is 2 g, the NNMBA is 1% and the monomer MAA is 20 mmol.

Structure characterization and properties measurements

A Fourier transformation infrared spectrometer (FTIR, Equinx55, Bruker, Germany) was utilized to inspect the main chemical functional group changes of the synthesized copolymer hydrogel samples by a KBr pellet method. To observe the morphologies of hydrogel networks, a lyophilization equipment (Alpha1-2, Christ, Germany) was used to treat the swollen hydrogels at –50°C for 24 h. The dried hydrogels were knocked out by a forceps, and the fractured sections were coated with a thin layer of gold. The morphological characterization of the samples was carried out on a Quanta 200 SEM equipment produced by the Philips-FEI Corp, the Netherland, with an operating voltage of 20 kV. The swelling ratio R and equilibrium swelling ratio R_e of the above-mentioned xerogel disks were determined in the excess of phosphate buffers mentioned-above at 37°C according to our previous work [11].

$$R = (W_s - W_d)/W_d \quad (1)$$

$$R_e = (W_e - W_d)/W_d, \quad (2)$$

where W_s is the weight of the swollen hydrogels at time t; W_d is the weight of the dried hydrogels and W_e denotes the weight of the gels at equilibrium swelling.

RESULTS AND DISCUSSION

FTIR

FTIR spectra can provide strong evidences of chemical linkage of PEG chains with PMAA networks. Figure 1 displays FTIR spectra of the as-prepared PEG-*t*-PMAA hydrogels. The pure PMAA hydrogel (Fig. 1*a*) produces characteristic absorption peaks at 3450, 2925–3100, 2616, 1702 and 1636 cm^{-1}, corresponding to stretching vibrations of free –OH, CH_3 or $–CH_2–CH–$, bonded –OH, free –C=O and bonded C=O groups, respectively [4, 12, 13]. Newly-synthesized PEG-*t*-PMAA hydrogel samples show variational spectrometric profiles (Figs. 1*b* and 1*c*). The weak peaks at 3500 and 1545 cm^{-1} are due to the –NH– stretch and in-plane bend vibration modes, respectively; at ca. 1400 cm^{-1} reflecting C–N stretching vibrations; at 1485 cm^{-1} attributable to characteristic absorption of –CONH– groups, indicating formation of –OCONH– linkages through the coupling reaction between PEG and H_{12}MDI. The characteristic –C=O stretching peak at 1702 cm^{-1} for the crosslinked PMAA red shifts to 1726 cm^{-1}, and the peak intensity is gradually weaken with increasing PEG tether concentrations. The increased wavenumber and disappearance of the peak at 1636 cm^{-1} indicates –COOH groups exist predominately in a free form with increas-

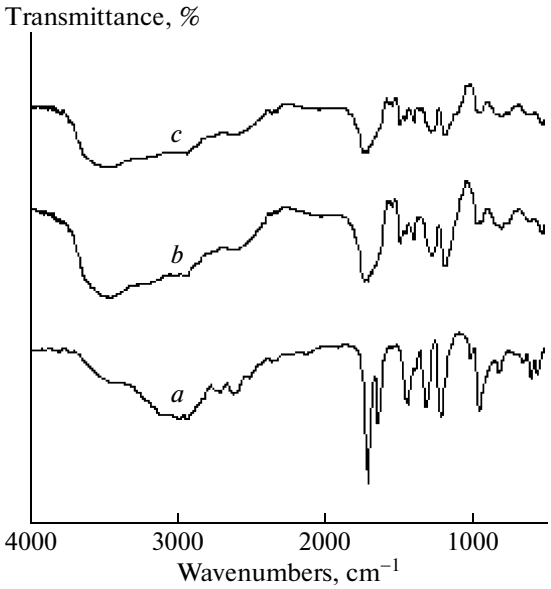


Fig. 1. FTIR spectra of the as-prepared PEG-*t*-PMAA copolymer hydrogels. *a*: PMAA; *b*: $r_2 = 2$, 20% PEG1000-azo initiator; *c*: $r_2 = 2$, 50% PEG1000-azo initiator.

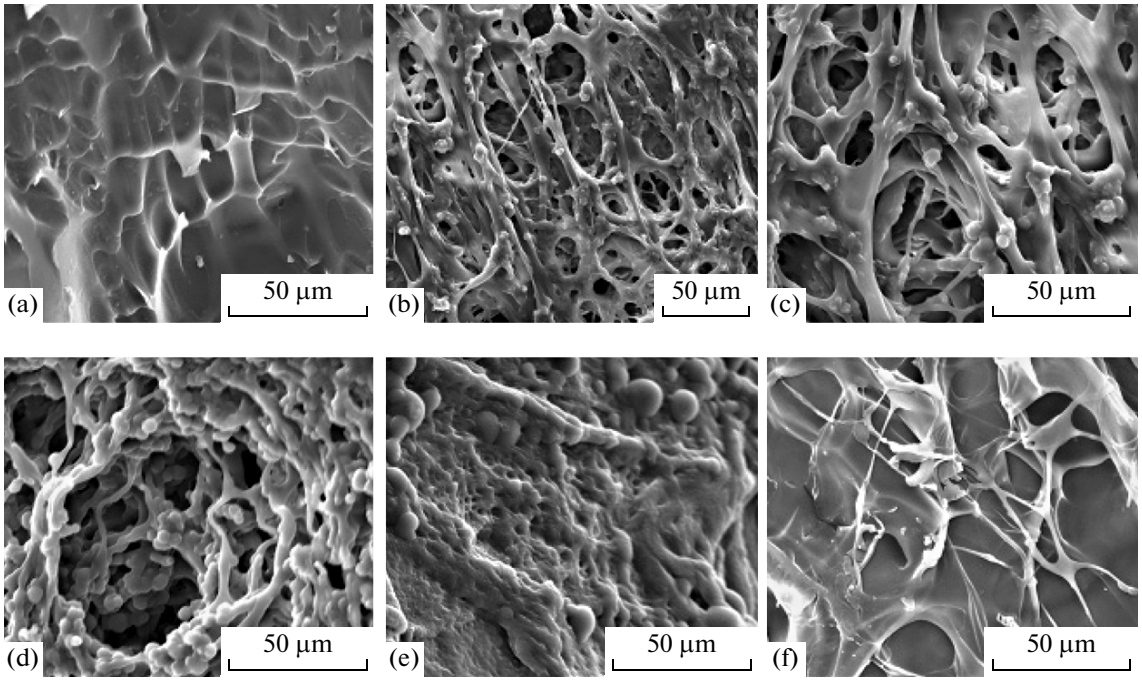


Fig. 2. SEM images of the as-synthesized PEG-*t*-PMAA hydrogel networks. $I = 0.2$. Samples a–e has been specified in the table; and f is PEG1000-*b*-PMAA copolymer without crosslinking.

ing the concentration of the PEG tether. The probability is that as the concentration of the PEG tethered in the network is increased, the concentration of free –COOH groups increases due to the disruption or prevention of dimeric formation with the addition of the PEG macromolecule into the structure [4]. The characteristic –C–O–C stretching of the PEG tether is evident at approximately 1185 cm^{-1}. These results preliminarily testify the formation of PEG-*t*-PMAA hydrogels.

SEM observations

To acquire topologies of the PEG-*t*-PMAA block copolymer hydrogels in an equilibrium swollen state, the samples are observed by SEM after treated via a multilevel freeze-drying technique. It is clear that the hydrogels are a kind of hierarchical microporous three-dimensional morphologies with different pore sizes as expected (Fig. 2), whereas the PEG1000-*b*-MAA copolymer without crosslinking does not exhibit typical network structure, and only a wiredrawing phenomenon. A rough surface can be observed in Fig. 2f.

With increasing the amount of the PEG1000 MAIs, more obvious hierarchical micropores occur, and the pore size is enlarged. PEG1000-*t*-PMAA hydrogels seems to be crystallized in a spherical shape due to linear PEG chains, which is in disagreement with our previous findings, i.e., the crosslink degree is enhanced and mesh size decreases with increasing the initiator concentration [14]. Compared with sample *b* ($r_2 = 2$, r_2 is the ratio of –NCO moles in OCN-terminated PEG to –OH moles of AMHP, viz., $r = (-NCO/-OH)_{mol}$)), the hydrogel with $r_2 = 1.05$ (Fig. 2d) exhibits strong hierarchical microporous networks, which are probably correlated with more PEG crystalline accumulation in PEG-attached hydrogels with higher MW due to the decreased r_2 value. Hydrogels synthesized by a 50% PEG4000-azo initiator do not form the as-expected three-dimensional network, and the mesh size is considerably small, which may be ascribed to the trend of strong crystallization of PEG4000. The morphological alteration is expected to be able to interpret the swelling behavior hereinafter and thus find which gel composition corresponds to the fastest response.

pH response

Considering sensitive pH response of PMAA hydrogels, the equilibrium swelling ratios of the as-prepared PEG-*t*-PMAA copolymer hydrogels in various pH buffer solutions of the same ionic strength ($I = 0.2$ M) were probed, as presented in Fig. 3. It is distinct that all the hydrogels are highly sensitive to change in pH, and the Re values are abruptly increased with increasing pH over 3.0. This behavior is mainly mediated by the ability to accept or release protons for carboxyl groups in various pH media, which has reported by many researchers [4, 11, 12, 15, 16]. It is known that the pKa of PMAA is around 5.5, the carboxyl acid groups are not ionized at low pH (e.g., a pH value less than 3),

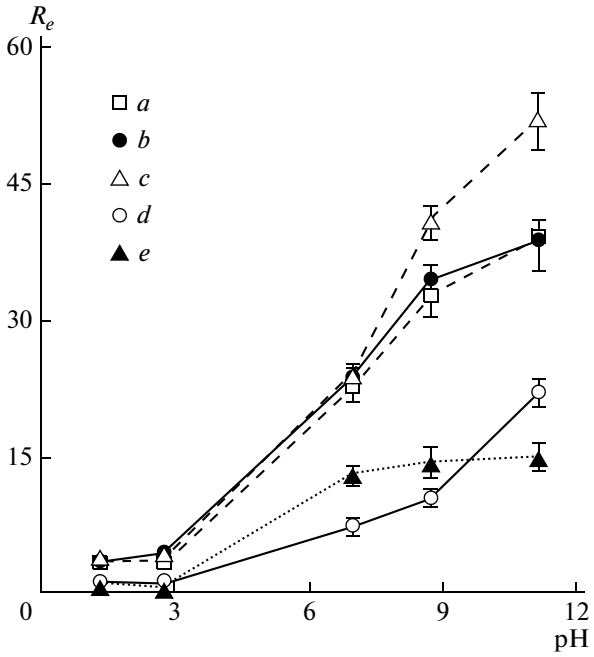


Fig. 3. Equilibrium swelling dependence of PEG-*t*-PMAA block copolymer hydrogels on pH values of buffer solutions at 25°C ($I = 0.2$).

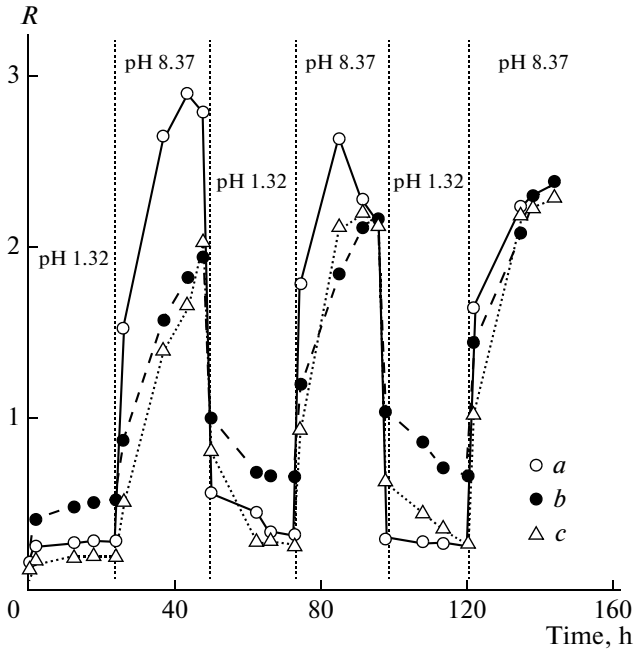


Fig. 4. Reversible swelling of the PEG-*t*-PMAA hydrogels in buffers with alternate pH of 1.32 and 8.73 at 37°C for 24 h ($I = 0.2$).

and therefore the PMAA network is at its collapsed state due to the presence of hydrogen bonding. At high pH, however, the ionization of the acidic groups would cause the dissociation of hydrogen bonds, and thus the charged groups repel each other, leading to expansion in volume of the PMAA networks in water continuously.

However, the pH response is significantly different from each other for specific gels, depending on the concentration and MW of PEG. For the identical MW (1000) of PEG, the R_e values are remarkably increased with increasing mass ratios of PEG-based MAIs above pH 7.0, and have no significant difference below pH 7.0. The fast pH-response to the variation of media acidity is maybe related to the porosity of the as-prepared gel samples that determines the response time. For PEG-*t*-PMAA hydrogels with high porosity, more pores enhanced the uptake of water during swelling when compared with low porous hydrogels. Additionally, PEG crystalline accumulation may affect the formation or perfection of pores in PMAA networks. In this case, it is understandable that high MW and crystallinity of PEG (Fig. 3*e*) and a low molar ratio of OCN-terminated PEG to bifunctional initiator (Fig. 3*d*) result in lowered swelling. It is interesting to note that these results reflect the correlation between gel structure disclosed by SEM and pH response, and the gel composition with high porosity and low crystallinity corresponds to the fastest response.

Compared with our previous works [11, 12, 14], the equilibrium swelling in this work drops by 50% in a relatively low pH value. It has been reported that PMAA can form an inter-macromolecular complex with PEG due to the hydrogen bonding between carboxyl acid groups of PMAA and ether oxygen atoms of PEG [4]. The complex formation may be quite different from that of linear PMAA. It is likely that the absorption of PEG would leads to contraction of the PEG-tethered PMAA gel and decreased swelling. The formation of the hydrogen-bonded complex is highly sensitive to change in the concentration and MW of PEG, and pH, which leads to difference in swelling. While better swelling for sample c (Fig. 3*c*) may also be attributed to the complex destruction and solvation of more PEG molecules, besides porosity and deprotonation of the carboxyl groups. Therefore, swelling properties of the PEG-*t*-PMAA hydrogels can be controlled by varying pH, the MW and the compositional ratio of PEG.

These investigations indicate that the PEG-*t*-PMAA hydrogels should have an intrinsic pH on-off feature. Considering the micro environmental difference between acidic stomach and alkaline intestine, reversible swelling/deswelling experiments of three PEG-*t*-PMAA hydrogels have been conducted alternately in the stimulated gastric fluids (SGF, pH = = 1.32) and stimulated intestinal fluids (SIF, pH = = 8.37) at 37°C for 24 h for three times, as shown in Fig. 4. It is clear that the as-synthesized PEG-*t*-PMAA hydrogels shrink in an acidic medium of pH 1.32, and contrarily expand dramatically in the alkalescent intestines upon repeatedly incubating the hy-

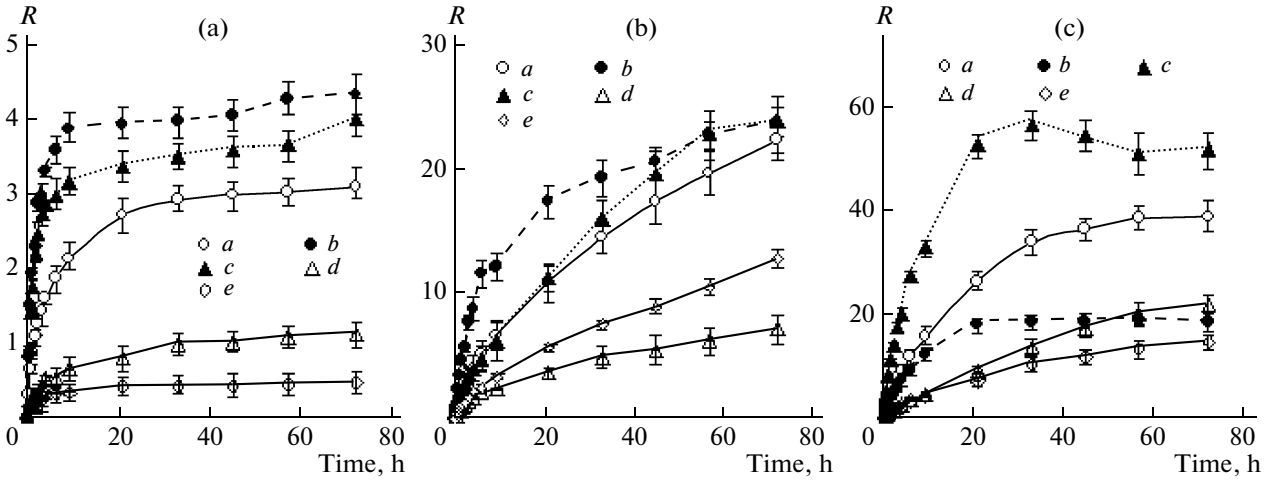


Fig. 5. Dependence of swelling kinetics of PEG-*t*-PMAA hydrogels on component ratios in different pH buffer solutions of (a) pH 2.81, (b) pH 7.40 and (c) 11.13 ($I = 0.2$).

drogels in the stimulated buffers of pH 1.32 and pH 8.37 for at least two more cycles, exhibiting pH switching effect and reversible swelling/deswelling behavior. Therefore, it is believed that the newly-developed PEG-*t*-PMAA hydrogels can find potential applications in drug delivery fields by the pH-switching modulation for each specific hydrogel [17, 18].

Furthermore, swelling kinetics behavior of PEG-*t*-PMAA hydrogels at 25°C in different pH buffer solutions has been assessed, as illustrated in Fig. 5. It is clear that when a dry hydrogel is bought into contact with water, water diffuses into the hydrogel, and the hydrogel swells. Diffusion involves the migration of water into preexisting or dynamically formed spaces among hydrogel chains, while swelling of the hydrogel involves a larger scale segmental motion, ultimately resulting in an increase in the separation distance among the hydrogel chains. From Fig. 5, at the initial stage of swelling (less than 8 h), all hydrogels swiftly swell with time, especially for PEG-*t*-PMAA hydrogels with high concentration of PEG1000 MAIs, reflecting non-Fickian behavior [19, 20]. As swelling proceeds, swelling rates impair, and the swelling ratios-time curves tend to change smoothly. Therefore, the extensive swelling process is produced, and follows the Schott second order dynamic equation [19, 20]:

$$dS/dt = k_S(S_\infty - S)^2 \quad (3)$$

From the whole swelling, whether acidic, neutral or alkaline, we can see that the PEG-*t*-PMAA hydrogel with MW of PEG of 1000, r_2 of 2 and the PEG MAIs concentration of 100% possesses faster swelling rates than any other hydrogels.

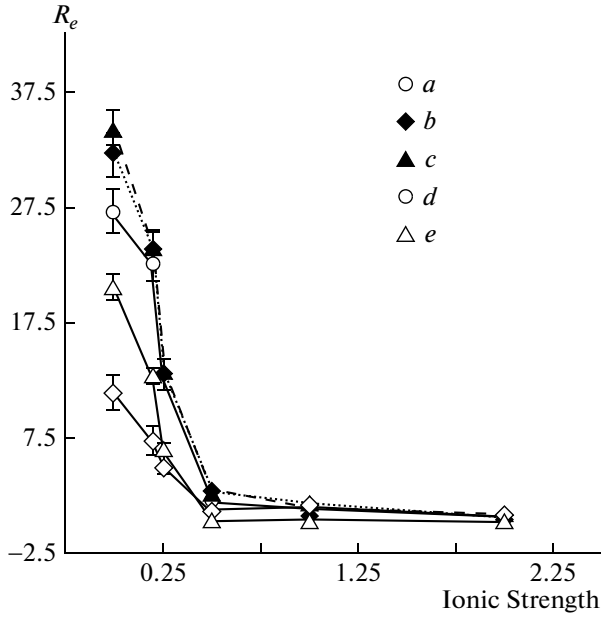


Fig. 6. Effect of ionic strength on swelling of the PEG-*t*-PMAA hydrogels with various compositions of monomers at 37°C (pH 7.4).

Ionic strength

Generally, the hydrogels containing acidic groups respond to not only pH, but also ionic strength I of the media [8]. In this work, the effect of ionic strength on swelling of PEG-*t*-PMAA hydrogels is investigated by using a collection of buffer solutions with various ionic strengths of 0, 0.25, 0.5, 1.0 and 2.0 at pH 7.4, as demonstrated in Fig. 6. It is much clear that the equilibrium swelling ratios abruptly decrease with increasing the ionic strength; as expected, and the extent of decline is reinforced in the order of samples d, e, a, b and c. When the ionic strength is over 0.5, the influence is weakened, and the Re *vs.* ionic strength curve approaches to a straight line. Charged groups attached to the networks have important impact on the ionic strength response, which can be interpreted by Don-

nan theory [12]. In a certain buffer medium, when the ions in gels are confronted with the ions in the solution, the so-called "charge screening effect" of the cations produce [11], and the surrounding solution hardly penetrate into the gels. The osmotic pressures and the driving force for swelling between the gels and the aqueous phases are decreased with the increase in ionic strengths of media, resulting in the undesired swelling loss. It is well known that the ionic forces depend on the ionic concentration and the proportion of attached ionizable groups in the gels according to Donnan theory [21]. Based on a marked charge screening produced by free ions or counterions, a depression in the electrostatic repulsion between the polyions would take place. Therefore, the hydrogel networks are deswelled or shrunk into more compact structures, which makes the diffusion of small molecular ions into the gel networks difficult, leading to lowered osmotic pressures and swelling ratios [22].

CONCLUSIONS

Ionizable PMAA hydrogel networks containing a PEG tether have been successfully synthesized via a free radical polymerization avenue in the presence of a PEG macromolecular azo-initiator. FTIR findings have confirmed the formation of PEG-*t*-PMAA copolymers. The PEG-*t*-PMAA hydrogels have exhibited sharp pH and ionic strength response, which corresponds to porous topologies characterized by SEM observations and the ionization of the acidic groups, while PEG crystalline accumulation and absorption have certain impact on the porosity. Therefore, the swelling properties of the PEG-*t*-PMAA hydrogels can be manipulated by varying pH, the MW and compositional ratios of PEG. The charge screening effect under high ionic strength produced by free ions or counterions can be utilized to explain the deswelling. The newly-developed PEG-*t*-PMAA hydrogels are expected to find potential applications in tissue engineering, adhesion, and drug delivery fields by the pH-switching modulation.

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