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Analysis of molecular interactions in poly(methacrylic acid-*g*-ethylene glycol) hydrogels

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Abstract

Molecular and structural changes of the P(MAA-*g*-EG) hydrogels were investigated in their hydrated state using attenuated total reflectance Fourier transform infrared spectroscopy. FTIR studies identified the formation of hydrogen-bonded complexes at low pH and polyelectrolyte complexes at high pH. Hydrogen bonding and electrostatic repulsion were not affected by the grafted PEG molecular weight in the hydrogels. Additionally, investigation of the macroscopic swelling properties showed that the presence of the grafted PEG chain in the P(MAA-*g*-EG) hydrogels contributed to the formation of hydrogen bonds.

Keywords: Polymer complexes; ATR-FTIR spectroscopy; pH-sensitive

1. Introduction

In recent years, considerable efforts have been made to use environmentally or physiologically responsive hydrogels for biochemical and biomedical applications such as biosensors, membranes, molecular imprinting and drug delivery devices [1–11]. Environmentally responsive materials show drastic changes in their swelling ratio due to changes in their external pH, temperature, ionic strength, nature and composition of the swelling agent, and electrical or magnetic stimulus.

Our laboratory has developed complexation hydrogels of poly(methacrylic acid-*g*-ethylene glycol), henceforth designated as P(MAA-*g*-EG), which can respond to their surrounding pH by the formation of polymer complexes. These polymer complexes occur due to interactions between specific repeating units in the polymer chains and are classified by the kind of dominant interaction into stereocomplexes, polyelectrolyte complexes, and hydrogen-bonded complexes [12]. Typically, polymer networks containing poly(methacrylic acid) (PMAA) or poly(acrylic acid) (PAA) can form polyelectrolyte or hydrogen-bonded complexes that are strongly dependent on the environmental pH and ionic strength [13–19].

Numerous studies have been done to use the P(MAA-*g*-EG) hydrogels as oral drug delivery carriers. In the acidic environment of the stomach, these hydrogels are collapsed, as a result of hydrogen bonding, thus holding and protecting drug (protein) incorporated in the hydrogels. In the basic and neutral conditions of the intestine, the hydrogels are swollen to a high degree, due to electrostatic repulsions, thus releasing drug [20–25].

In this study, pH-responsive complexation phenomena of the P(MAA-*g*-EG) hydrogels were investigated using attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy. This ATR-FTIR spectroscopy is a useful technique to study biomaterials in their biological conditions since the samples can be analyzed in their hydrated states [26]. In addition, further investigation of hydrogen bonding of the polymer was performed by swelling studies.

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2. Experimental

2.1. Polymer synthesis

Copolymers of P(MAA-*g*-EG), and methacrylic acid (MAA) and 2-methacryloxyethyl glucoside (MEG), henceforth designated as P(MAA-*co*-MEG), were prepared by free-radical photopolymerization. MAA (Polysciences, Warrington, PA) was distilled under vacuum prior to use. PEGMA with PEG molecular weight 200, 400 and 1000 (PEGMA200, PEGMA400, and PEGMA1000, Polysciences, Inc., Warrington, PA) were used as received, while PEGMA with PEG molecular weight 2000 (PEGMA2000) was synthesized in the laboratory as described in previous study [27]. TEGDMA (Polysciences, Warrington, PA) was used as a crosslinking agent and 1-hydroxycyclohexyl phenyl ketone (Irgacure® 184, Ciba-Geigy, Hawthorne, NY) was used as a UV-light sensitive initiator.

Monomers with feed compositions (molar ratio) of 1:1 EG:MAA for P(MAA-*g*-EG) using PEGMA with various PEG molecular weights, and of 1:0, 1:1 and 0:1 MEG:MAA for P(MAA-*co*-MEG) were mixed. In each set of the monomer mixtures, the TEGDMA was added in the amount of 1.2 mol% of total monomers. The initiator was added in the amount of 0.1 wt% of the total monomers and the resulting mixtures were diluted to 60 wt% of the total monomers with a 1:1 mixture by weight of ethanol and water. Nitrogen was bubbled through the mixture for 15 min to remove dissolved oxygen. The mixture was cast between glass slides (size $75 \times 50 \times 1$ mm^3) and exposed to UV-light (intensity 15.0 ± 0.5 mW/cm^2) for 30 min in a nitrogen environment. The ensuing hydrogel films were cut into disks of 1 cm diameter and placed in deionized water for 7 days; the water was changed every 12 h. The disks were then dried in air for 1 day and placed in a vacuum oven at 25 °C until their weight remained constant within 0.1 wt% over 24 h. Subsequently, the hydrogel disks were stored in a desiccator for future use.

2.2. FTIR spectroscopic studies

To investigate the molecular structure of the polymer networks in the hydrated state, polymer disks of 1 cm diameter were hydrated in phosphate–citrate buffer solutions of pH values between 2.2 and 7.0 for 24 h. The ionic strength of each buffer solution was adjusted to 0.5 M by the addition of KCl. These hydrated samples were then placed on a ZnSe crystal and the spectra were obtained using FTIR spectrometer (Nicolet® Nexus 670, Madison, WI). ATR-FTIR spectra were collected in the wavenumbers range of 4000–650 cm^{-1} at a resolution of 4 cm^{-1}.

For the spectrum analysis, water absorption band was subtracted from the hydrated sample. This spectral subtraction of water absorption made the peaks between 2000 and 800 cm^{-1} clearer and gave more precise information about the polymer structure, while at the same time producing a strong negative peak centered at 3300 cm^{-1} due to the hydrogen bonds between water and the hydroxyl groups present in the hydrated polymer sample. This water subtraction procedure was illustrated in the previous study [28].

2.3. Swelling studies

To determine relevant swelling properties, the dried hydrogel disks were weighed and then placed in phosphate–citrate buffer solutions of pH values of 2.2 and 7.0 at 37 °C. The ionic strength of each buffer solution was adjusted to 0.5 M by the addition of KCl. After swelling, the samples were taken out of the buffer solutions, blotted to remove surface water and weighed.

The swelling of the hydrogels was expressed by the weight swelling ratio, q, determined as the ratio of the weight of the swollen hydrogel, W_s, to the weight of the initially dry hydrogel, W_d. The equilibrium weight swelling ratio was obtained when the weight of the swollen hydrogel reached constant value ($\pm 1\%$).

3. Results and discussion

3.1. Effect of environmental pH on the molecular structure of copolymer networks

In this work, the most distinct peak in the spectra of the polymer networks was the absorption band of the carbonyl group (C=O) observed in the region of 1850–1400 cm^{-1}. This peak contained information about the polymer complexes formed by hydrogen bond and electrostatic interactions.

Fig. 1 demonstrates two spectra of the P(MAA-*g*-EG) networks with PEGMA1000 hydrated in pH 2.2 and 7.0 buffer solutions after water subtraction. When analyzed in a buffer at pH 7.0 the spectrum contains the C(=O)–O$^-$ peak of symmetric stretching vibrations at 1542 cm^{-1} and asymmetric stretching vibrations at 1414 cm^{-1}. However, the spectrum of a gel in a buffer at pH 2.2 no longer exhibits the C(=O)–O$^-$ symmetric and asymmetric stretching vibration peaks but contains the strong peaks of the C=O stretching at 1701 cm^{-1}. The peak locations and corresponding groups of P(MAA-*g*-EG) networks are listed in Table 1.

These results clearly indicate that P(MAA-*g*-EG) networks exhibit macromolecular changes according to the environmental pH change due to the ionization of the carboxylic acid groups of the PMAA chain in the networks.

3.2. Complexation phenomena of copolymer networks at high pH values

Figs. 2 and 3 show the spectra of P(MAA-*g*-EG)

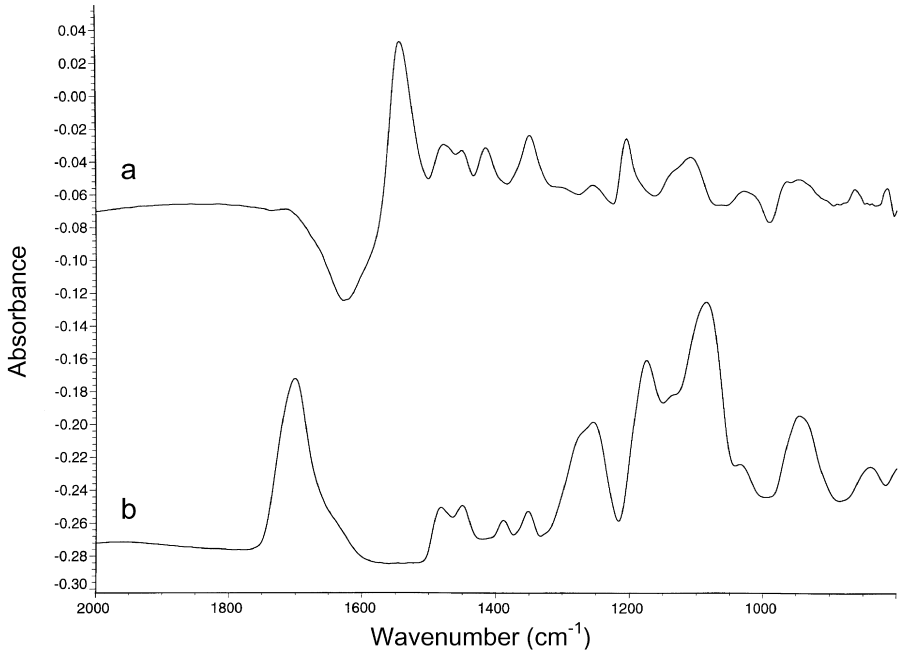

Fig. 1. ATR-FTIR spectra of P(MAA-*g*-EG) networks with PEGMA1000 hydrated with pH 2.2 and 7.0 buffer solutions: (a) pH 7.0 and (b) pH 2.2. The spectra were obtained after water subtraction.

networks with various grafted PEG molecular weights after swelling at pH 7.0. Strong water peaks at 1636 cm^{-1} and peaks of symmetric stretching vibrations of C(=O)–O^- at around 1550 cm^{-1} are observed in Fig. 2, which presents the spectrum before the water subtraction. There was no significant difference of intensity among the various C(=O)–O^- peaks at around 1550 cm^{-1} for samples with varying grafted PEG molecular weights.

After water subtraction, the C(=O)–O^- peaks are clearly defined and their locations can be assigned more precisely in Fig. 3. For instance, the C(=O)–O^- peaks of the symmetric stretching vibrations of P(MAA-*g*-EG) networks prepared with PEGMA1000 before and after the water subtraction are shown at 1551 and 1542 cm^{-1}, respectively. In addition, the C(=O)–O^- peaks of asymmetric stretching vibrations at 1414 cm^{-1} were clearly observed and their intensities did not change with the grafted PEG molecular weights in the network. The C(=O)–O^- peak locations of P(MAA-*g*-EG) before and after the water subtraction are listed in Table 2.

Table 1
Assignment of the FTIR spectra of P(MAA-*g*-EG) networks with PEGMA1000 hydrated in pH 2.2 and 7.0 buffer solutions after 24 h at 37 °C

Functional group	Absorption wavenumber (cm^{-1})	
	pH 2.2	pH 7.0
C=O stretching	1701	–
C(=O)–O^- symmetric stretching	–	1542
CH_2 deformation	1450	1450
C(=O)–O^- asymmetric stretching	–	1414
C–C(=O)–O^- stretching	–	1204
C–O–C symmetric C–O stretching	1030	1028

3.3. Complexation phenomena of copolymer networks at low pH values

Figs. 4 and 5 show the spectra of P(MAA-*g*-EG) networks with various grafted PEG molecular weights after swelling in buffers at pH 2.2. Before water subtraction, the spectra exhibited the water peak at 1636 cm^{-1} and the peaks of the C=O stretching at around 1700 cm^{-1} (Fig. 4). After water subtraction, the C=O peaks were also clearly defined and their locations could be assigned more precisely in Fig. 5. For instance, the C=O peaks of P(MAA-*g*-EG) network with PEGMA1000 before and after the water subtraction are 1699 and 1701 cm^{-1}, respectively. The

Table 2
FTIR peak location of C(=O)–O^- groups of P(MAA-*g*-EG) networks with various grafted PEG molecular weights placed in pH 7.0 buffer solutions after 24 h at 37 °C, before and after water subtraction

MW of grafted PEG	Before water subtraction		After water subtraction	
	Sym (cm^{-1})	Asym (cm^{-1})	Sym (cm^{-1})	Asym (cm^{-1})
200	1553	1414	1544	1414
400	1552	1414	1543	1414
1000	1551	1414	1542	1414
2000	1551	1414	1542	1414

Sym: absorption wavenumber for symmetric stretching vibrations; Asym: absorption wavenumber for asymmetric stretching vibrations.

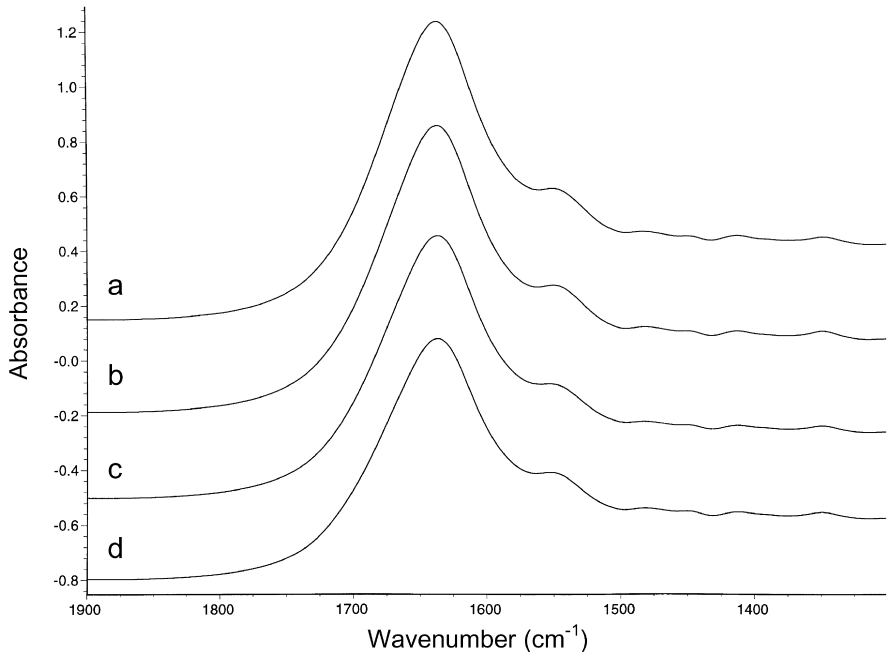

Fig. 2. ATR-FTIR spectra of P(MAA-*g*-EG) networks with various grafted PEG molecular weights hydrated with pH 7.0 buffer solution before water subtraction: (a) PEGMA2000, (b) PEGMA1000, (c) PEGMA400 and (d) PEGMA200.

C=O peak locations of P(MAA-*g*-EG) before and after the water subtraction are listed in Table 3.

3.4. Hydrogen bonding in copolymer networks at low pH values

The C=O peaks shifted from 1704 to 1698 cm^{-1} as the grafted PEG molecular weight increased for the P(MAA-*g*-EG) network after swelling at pH 2.2 (Table 3). These shifts indicated that the hydrogen bonding in the networks at low pH was stronger when the grafted PEG molecular weight increased in the polymer since the frequency of this carbonyl stretching vibration was dependent on hydrogen bonding to the C=O, which resulted in shifting of the absorption band to lower frequency [29,30].

However, a C=O peak shift due to hydrogen bonding was

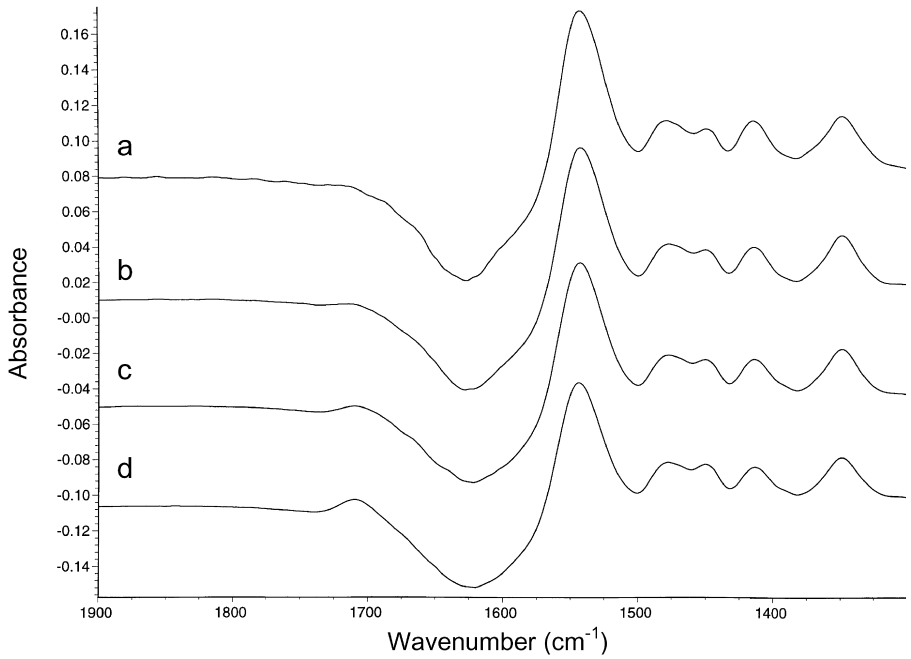

Fig. 3. ATR-FTIR spectra of P(MAA-*g*-EG) networks with various grafted PEG molecular weights hydrated with pH 7.0 buffer solution after water subtraction: (a) PEGMA2000, (b) PEGMA1000, (c) PEGMA400 and (d) PEGMA200.

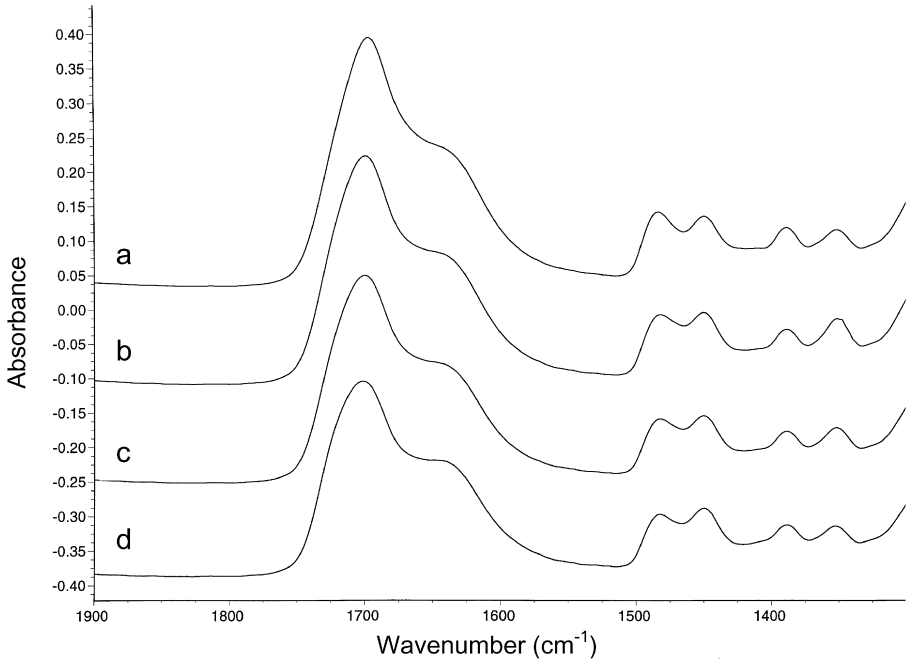

Fig. 4. ATR-FTIR spectra of P(MAA-*g*-EG) networks with various grafted PEG molecular weights hydrated with pH 2.2 buffer solutions before water subtraction: (a) PEGMA2000, (b) PEGMA1000, (c) PEGMA400 and (d) PEGMA200.

independent of whether the bonding is inter- or intramolecular. Therefore, it was difficult to identify which molecules formed the hydrogen bond with the carboxylic groups of the PMAA. In other words, we could only speculate that three different types of hydrogen bonds occurred, i.e. (i) hydrogen bonds between carboxylic groups and water, (ii) hydrogen bonds between carboxylic groups, and (iii) hydrogen bonds between carboxylic groups and oxygen groups in the PEG units [31–36].

Since complexation affects the macroscopic swelling behavior of these hydrogels, the investigation of macroscopic swelling properties could provide additional information about the hydrogen bonding in the polymer networks [37–39]. Fig. 6 shows the equilibrium weight swelling ratio

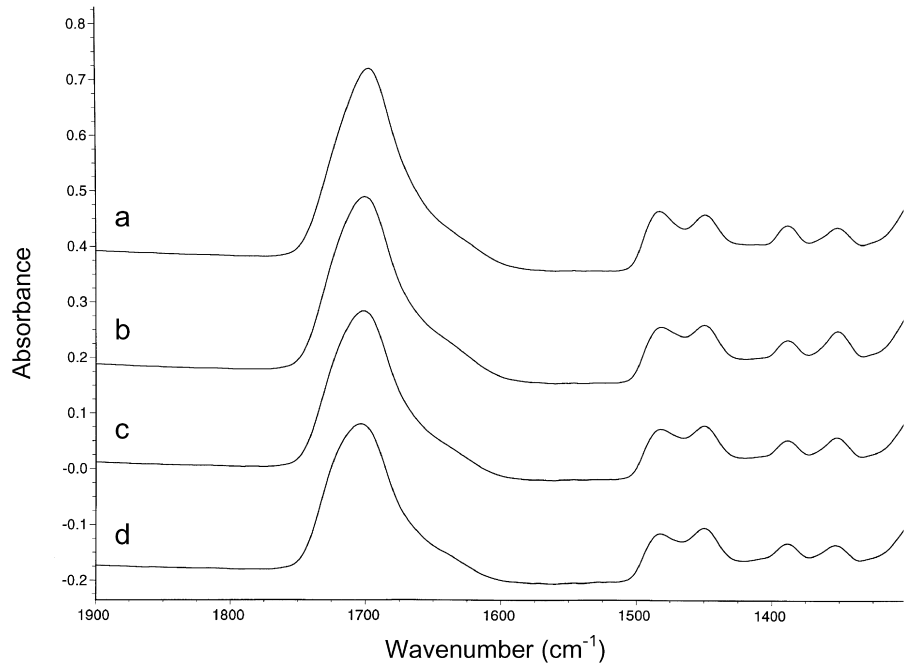

Fig. 5. ATR-FTIR spectra of P(MAA-*g*-EG) networks with various grafted PEG molecular weights hydrated with pH 2.2 buffer solutions after water subtraction: (a) PEGMA2000, (b) PEGMA1000, (c) PEGMA400 and (d) PEGMA200.

Table 3
FTIR peak location of C=O groups of P(MAA-*g*-EG) networks with various grafted PEG molecular weights placed in pH 2.2 buffer solutions after 24 h at 37 °C, before and after water subtraction

MW of grafted PEG	Absorption wavenumber (cm^{-1})	
	Before water subtraction	After water subtraction
200	1701	1704
400	1700	1702
1000	1699	1701
2000	1696	1698

of hydrogels of PMEG, PMAA, P(MAA-*co*-MEG) with 1:1 MEG:MAA, and P(MAA-*g*-EG) with PEGMA1000 (1:1 EG:MAA) networks swollen in a buffer at pH 2.2. It was observed that PMAA networks showed relatively low equilibrium swelling ratio. The P(MAA-*g*-EG) networks exhibited the lowest equilibrium swelling ratio, i.e. the most compact network structure. This indicated that PMAA networks could form hydrogen bonds at low pH between the carboxylic acid groups. Incorporation of the grafted PEG chain in the PMAA contributed to the formation of additional hydrogen bonds, while the presence of pendent MEG disrupted the hydrogen bonding between the carboxylic acid groups of the PMAA.

4. Conclusions

FTIR spectroscopic investigation of P(MAA-*g*-EG) hydrogels showed molecular and structural changes of the polymer networks according to the environmental pH. We were able to identify the formation of hydrogen bonds at low pH and electrostatic interactions at high pH values. Using these structural changes, the macroscopic swelling behavior of the polymer networks could be elucidated. In acidic media, hydrogen bonds forming within the polymer networks rendered them more hydrophobic resulting in collapsed states. However, in neutral or basic conditions, electrostatic repulsion occurred leading to swelling of the networks, often to a rather high degree. However, there was no significant difference of the intensity of carbonyl peaks for samples swollen at low and high pH values as the molecular weight of grafted PEG of the P(MAA-*g*-EG) networks changed.

By analyzing FTIR spectroscopic results, it was difficult to interpret which molecules participate in the formation of hydrogen bonds with the carboxylic groups of PMAA at low pH values. However, investigation of the macroscopic swelling behavior gave additional information about the hydrogen bonds. Incorporation of grafted PEG chain in the PMAA polymer networks contributed to the formation of hydrogen bonds, while the presence of pendent MEG disrupted hydrogen bonding formation among the carboxylic acid groups of the PMAA in gels swollen at low pH values.

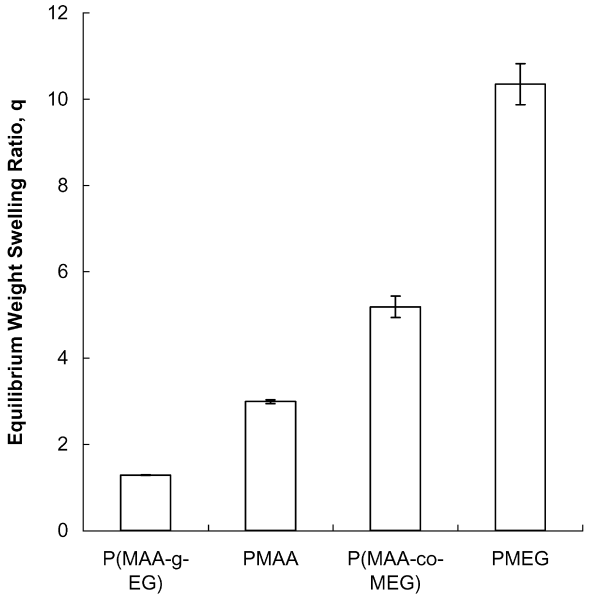

Fig. 6. Equilibrium weight swelling ratio of P(MAA-*g*-EG) with PEGMA1000 (1:1 EG:MAA), PMAA, P(MAA-*co*-MEG) with 1:1 MEG:MAA, and PMEG networks equilibrated in pH 2.2 buffer solutions after 24 h at 37 °C (average ± SD, $n = 3$).

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