pH-Sensitive Swelling and Release Behaviors of Anionic Hydrogels for Intelligent Drug Delivery System

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ABSTRACT: The pH-sensitive swelling and release behaviors of the anionic P(MAA-*co*-EGMA) hydrogels were investigated as a biological on–off switch for the design of an intelligent drug delivery system triggered by external pH changes. There was a drastic change of the equilibrium weight swelling ratio of P(MAA-*co*-EGMA) hydrogels at a pH of around 5, which is the pK_a of poly (methacrylic acid) (PMAA). At a pH below 5, the hydrogels were in a relatively collapsed state but at a pH higher than 5, the hydrogels swelled to a high degree. When the molecular weight of the pendent poly(ethylene glycol) (PEG) of the P(MAA-*co*-EGMA) increased, the swelling ratio decreased at a pH higher than 5. The pK_a values of the P(MAA-*co*-EGMA) hydrogels moved to a higher pH range as the pendent PEG molecular weight increased. When the feed concentration of the crosslinker of the hydrogel increased the swelling ratio of the P(MAA-*co*-EGMA) hydrogels decreased at a pH higher than 5. In release experiments using Rhodamine B (Rh-B) as a model solute, the P(MAA-*co*-EGMA) hydrogels showed a pH-sensitive release behavior. At low pH (pH 4.0) a small amount of Rh-B was released while at high pH (pH 6.0) a relatively large amount of Rh-B was released from the hydrogels. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 105: 3656–3661, 2007

Key words: pH-sensitive; anionic hydrogel; pK_a of hydrogel; biological on–off switch; intelligent drug delivery system

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.[1–7] Environmentally responsive materials show drastic changes in their swelling ratio in response to changes in their external pH, temperature, ionic strength, nature and composition of the swelling agent, and electrical or magnetic stimulus. The drastic swelling change can be used in the design of an intelligent drug delivery system. The anionic hydrogel is one of the attractive materials for an intelligent drug delivery system. Anionic hydrogels are three-dimensional polymer networks and contain ionizable groups, which become ionized as the pH of the external swelling medium increases over the pK_a of the hydrogels. The pK_a is the negative logarithm of K_a, the acid dissociation constant, and the pK_a of the hydrogels is the pH at which the ionizable groups of the hydrogel donate a proton. In general, at a pH above the pK_a of the hydrogel, the anionic hydrogel networks swell abruptly. Thus, if a solute is incorporated into the anionic hydrogel, at a pH above the pK_a the solute is released.

It is important to make a biological on–off switch in the design of an intelligent controlled drug release devices, which can control the release of the solute, such as drugs and biologically active materials, depending on the external stimuli. For example, for the development of an oral drug delivery system for therapeutic proteins, the therapeutic proteins should not be released in the stomach but be released in the small intestine.[8–15] In this system a biological on–off switch triggered by an external pH change is required since there is a significant difference in pH between the stomach (pH $\sim$ 2) and the intestine (pH $\sim$ 6). The swelling behavior, especially the pK_a, of any polymer hydrogels depends on the nature and composition of the polymer. It is therefore essential to know the correlation between the pK_a of the hydrogel and the nature and composition of the hydrogel.

The anionic hydrogels 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.[16–22] In this study, the feasibility of the polymer hydrogels of methacrylic acid (MAA) and poly(ethylene glycol) methacrylate (PEGMA), henceforth designated as P(MAA-*co*-EGMA), was evaluated as the biological on–off switch for an intel-

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ligent drug delivery system triggered by an external pH change. The effect of the hydrogel composition on the pH-sensitive swelling behavior, especially the pK_a, was investigated. In addition, the pH-responsive release behavior of the hydrogel was determined using Rh-B as a model solute.

EXPERIMENTAL

Materials

MAA (Aldrich, USA) was distilled under vacuum prior to use to remove an inhibitor, while PEGMA having various molecular weights (Aldrich, USA) were used as received. Poly(ethylene glycol) dimethacrylate (PEGDMA, Aldrich, USA) and 1-hydroxycyclohexyl phenyl ketone (otherwise known as Igacure®184, Ciba-Geigy, USA) were used as a crosslinker and a UV-light sensitive initiator, respectively. As a model solute for release studies Rh-B (Junsei, Japan) was used.

Synthesis of P(MAA-*co*-EGMA) hydrogels

P(MAA-*co*-EGMA) hydrogels were prepared by free-radical photopolymerization. Monomers with feed compositions (molar ratio) of 1 : 1 EG: MAA for P(MAA-*co*-EGMA) hydrogels were mixed. PEGMA130 (molecular weight 130), PEGMA360 (molecular weight 360), and PEGMA526 (molecular weight 526) were used to introduce various chain lengths of pendent PEG to the hydrogels. In each set of the monomer mixtures, the PEGDMA (molecular weight 330) was added in the amount of 0.75, 1.0, or 1.25 mol % of total monomers. The initiator was added in the amount of 0.1 wt % of the total monomers and these mixtures were then diluted to 50% by weight of the total monomers with a 1 : 1 by weight mixture of ethanol and water. Following complete dissolution of monomers, crosslinker, and initiator, nitrogen was bubbled through the mixture for 10 min to remove dissolved oxygen that would act as an inhibitor of the reaction. The mixture was cast between glass slides to form hydrogel films. The mixture was then exposed to UV light (intensity 1000 mW/cm^2) for 300 s in a nitrogen environment. The kinetics of such polymerization has been discussed extensively.[23,24]

Synthesized hydrogel films were cut into disks of 1-mm thickness and 1-cm diameter. These disks were placed in deionized water for 10 days with the water being changed every 12 h to remove any unreacted monomers, crosslinker, and initiator. The disks were then dried in air for 1 day and placed in a vacuum oven at 25°C until their weights remained constant within 0.1 wt % over 24 h. The hydrogel disks were stored in a desiccator for future use.

Swelling studies

To determine the swelling behavior, the dried hydrogel disks were weighed and placed in phosphate-citrate buffer solutions with pH values in the range from 2.0 to 8.0 at 25°C. The ionic strength of each buffer solution was adjusted to 0.5*M* by the addition of potassium chloride. After swelling, the disks were removed from the buffer solutions, blotted to remove surface water and weighed. The swelling of the hydrogels was expressed by the weight swelling ratio, q, defined as

$$q = \frac{W_s}{W_d} \tag{1}$$

where W_s is the weight of the swollen hydrogel and W_d is the weight of the initially dried hydrogel. The equilibrium weight swelling ratio was obtained when the weight of the swollen hydrogel reached a constant value (±1%).

Rh-B incorporation and release studies

A concentration of 0.01 mg/mL of Rh-B stock solution was prepared and the absorbance of the solution was measured in an UV-visible spectrophotometer (Agilent 8453) at a wavelength of 554 nm. Incorporation of Rh-B was accomplished by soaking the hydrogels disks in 20 mL of a Rh-B stock solution for 24 h. At specific time points, 3 mL samples were withdrawn from the solution and the absorbance measured to determine the Rh-B loading efficiency, calculated as the ratio of the amount of Rh-B incorporated into the hydrogel to the amount of Rh-B in the stock solution. After 24 h, the Rh-B-loaded hydrogel disks were dried under vacuum and stored at 25°C prior to use.

To release Rh-B from the hydrogels, Rh-B-loaded hydrogel disks were placed in 50 mL of buffer solutions with pH values of 4.0 and 6.0 at 25°C. At specific time points, 3 mL samples were withdrawn from the solution and the absorbance was measured. The amount of incorporated and released Rh-B was obtained from the calibration curve of Rh-B concentrations versus their absorbance.

RESULTS AND DISCUSSION

pH-Sensitive swelling behavior of P(MAA-*co*-EGMA) hydrogels

In general, the pH-sensitive swelling behavior of anionic hydrogels results from the ionization or deionization of functional groups in response to external pH changes. Figure 1 shows the equilibrium weight swelling ratios of PEG526 and P(MAA-*co*-EGMA526) hydrogels as a function of pH in the

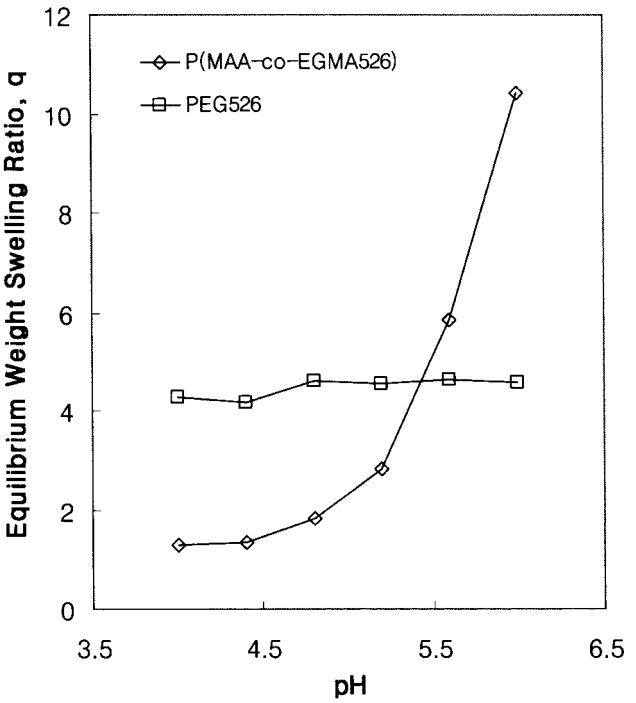

Figure 1 Equilibrium weight swelling ratio of PEG526 (□) and P(MAA-*co*-EGMA526) (◇) hydrogels as a function of pH.

range from 4.0 to 6.0. The PEG526 hydrogel was prepared with only PEGMA526 as a monomer and P(MAA-*co*-EGMA526) hydrogel was synthesized with MAA and PEGMA526 as monomers. Since the PEG526 hydrogels contained no ionizable functional groups their swelling ratios were essentially independent of pH. However, the presence of MAA in the P(MAA-*co*-EGMA) hydrogels resulted in a typical pH-sensitive swelling behavior of the anionic hydrogel, i.e., low swelling ratios at low pH and high swelling ratios at high pH. There was a drastic change in the equilibrium weight swelling ratio of P(MAA-*co*-EGMA526) hydrogels at a pH of around 5, which is the pK_a of PMAA. At a pH below 5, the hydrogels were in a relatively collapsed state but at a pH greater than 5, the hydrogels swelled to a high degree. The reason for this was that at a pH higher than the pK_a of the hydrogel, the carboxylic acid groups of MAA became ionized and there was electrostatic repulsion between the charged groups leading to the high swelling ratio. This sharp transition between the swollen and collapsed states at a specific pH indicates that the hydrogel can be used as an on–off switch with which the release of the solute from the hydrogel can be controlled by the external pH change and the pK_a of the hydrogels. Thus, it is important to have a method to control the pK_a of the hydrogels to create the biological on–off switch in the design of intelligent controlled drug release devices.

The effect of the pendent PEG molecular weight on the equilibrium swelling ratio of the hydrogels is shown in Figure 2. The monomers of PEGMA130, PEGMA360, and PEGMA526 were copolymerized with MAA to provide various chain lengths of the pendent PEG. At a pH below 5, there was no significant difference in the swelling ratio, regardless of the pendent PEG molecular weight. However, at a pH above 5, when the molecular weight of the pendent PEG increased the swelling ratio decreased. This was because when the molecular weight of the pendent PEG increased the number of long chains of the pendent PEG increased, which hindered the electrostatic repulsion between ionized groups. Thus, the swelling ratio of the hydrogels at high pH decreased. To investigate the pK_a shift in relation to the pendent PEG molecular weight, the ratios of the change of equilibrium weight swelling ratio (Δq) to the change of pH (ΔpH) in specific pH ranges were calculated. The highest ratio value falls in the pH range corresponding to the pK_a of the hydrogel. In Figure 3, as the pendent PEG molecular weight increased the pK_a of the hydrogels moved to higher pH ranges. For example, the pK_a of the P(MAA-*co*-EGMA130) hydrogels was in a pH range of 5.2–5.6 while the pK_a of the P(MAA-*co*-EGMA526) hydrogels was in a pH range of 5.6–6.0.

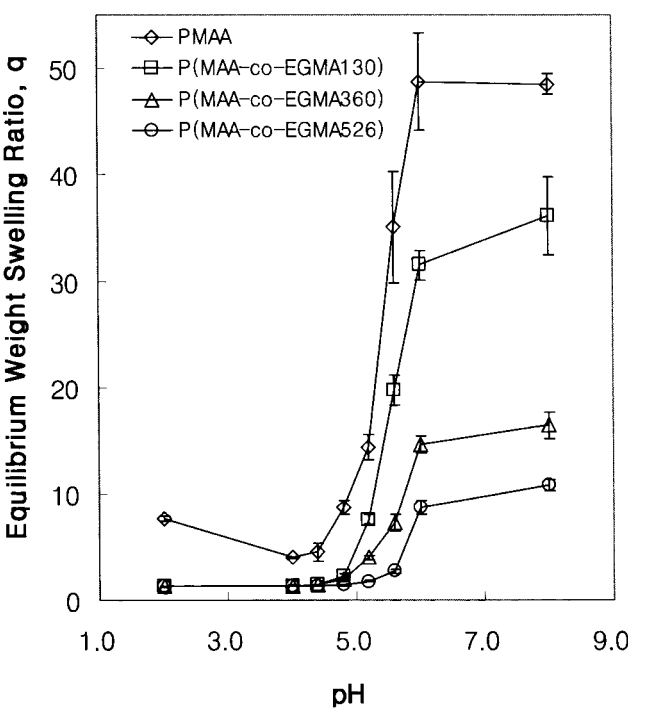

Figure 2 Equilibrium weight swelling ratio of P(MAA-*co*-EGMA) hydrogels having various molecular weights of the pendent PEG as a function of pH; PMAA (◇), P(MAA-*co*-EGMA130) (□), P(MAA-*co*-EGMA360) (△), and P(MAA-*co*-EGMA526) (○) (average ± SD, n = 3–5).

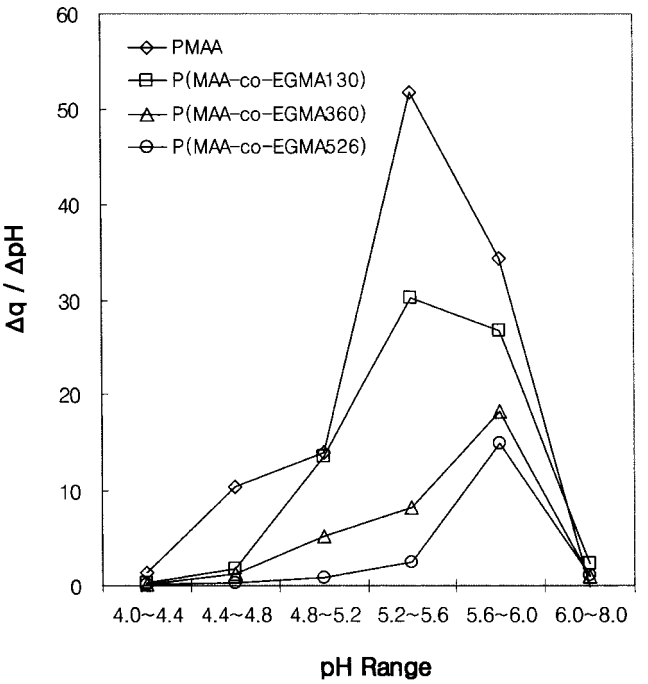

Figure 3 Ratio of Δq to ΔpH of P(MAA-*co*-EGMA) hydrogels having various molecular weights of the pendent PEG as a function of pH range; PMAA (◇), P(MAA-*co*-EGMA130) (□), P(MAA-*co*-EGMA360) (△), and P(MAA-*co*-EGMA526) (○).

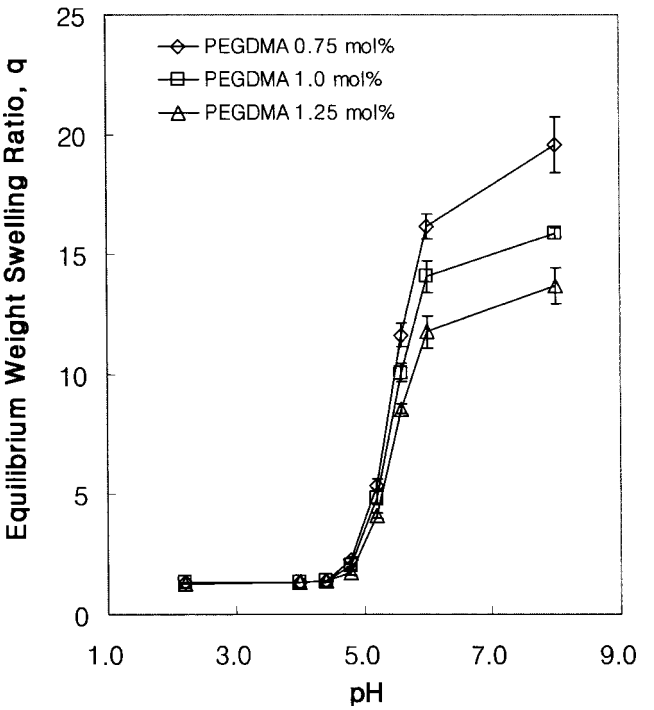

Figure 4 Equilibrium weight swelling ratio of P(MAA-*co*-EGMA360) hydrogels as a function of pH; PEGDMA 0.75 mol % (◇), PEGDMA 1.0 mol % (□), and PEGDMA 1.25 mol % (△) (average ± SD, n = 3–5).

Figure 4 presents the effect of the concentration of the crosslinker of the hydrogel on the equilibrium swelling ratio of the hydrogel. The P(MAA-*co*-EGMA360) hydrogels having 0.75, 1.0, or 1.25 mol % of the crosslinker of PEGDMA were used. At a pH higher than 5, as the concentration of the crosslinker of the hydrogel increased, the swelling ratio of the hydrogel decreased. As expected, when the concentration of the crosslinker increased, the hydrogel networks became denser making it difficult to expand. The pK_a change of the hydrogel according to the concentration of the crosslinker is shown in Figure 5. There was no change in the pK_a with the concentration of the crosslinker in this crosslinker concentration range.

pH-Sensitive release behavior of P(MAA-*co*-EGMA) hydrogels

Rh-B was incorporated into the hydrogels by soaking the dried hydrogels in a Rh-B stock solution. As the dried hydrogels absorbed water, the Rh-B was transported with water due to the concentration gradient of Rh-B between the outside and the inside of the hydrogel. The loading efficiencies of P(MAA-*co*-EGMA526) and PEG526 hydrogels were 40.8% and 41.5%, respectively. To investigate the pH-sensitive release behavior of the hydrogel, the initially dried, Rh-B loaded hydrogel disks were placed in pH 4.0 and pH 6.0 buffer solutions. The cumulative amount of released Rh-B per hydrogel as a function of time

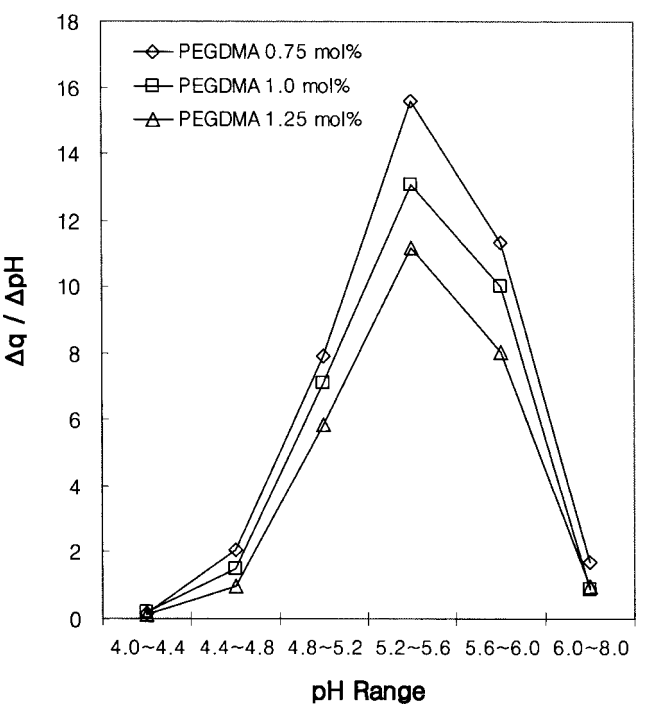

Figure 5 Ratio of Δq to ΔpH of P(MAA-*co*-EGMA360) hydrogels as a function of pH range; PEGDMA 0.75 mol % (◇), PEGDMA 1.0 mol % (□), and PEGDMA 1.25 mol % (△).

is shown in Figure 6. The P(MAA-*co*-EGMA526) hydrogels showed a pH-sensitive release behavior. At low pH (pH 4.0) small amounts of Rh-B were released from the hydrogels while at high pH (pH 6.0) relatively large amounts of Rh-B were released from the hydrogels. However, for the PEG526 hydrogels, there was no significant difference between pH 4.0 and pH 6.0 in the cumulative amount of Rh-B released from the hydrogels. The average cumulative amounts of Rh-B released from hydrogels after 100 h are listed in Table I. The ratios of the average amount of the released Rh-B at pH 6.0 to the average amount of the released Rh-B at pH 4.0 after 100 h were 4.73 and 1.98 for P(MAA-*co*-EGMA526) hydrogels and for PEG526 hydrogels, respectively. This pH-sensitive behavior of P(MAA-*co*-EGMA) hydrogels indicates that the P(MAA-*co*-EGMA) hydrogels can be used as a biological on–off switch for an intelligent drug delivery system triggered by the external pH change in the body. In addition, the P(MAA-*co*-EGMA526) hydrogels did not release the Rh-B for about 10 days, which means the P(MAA-*co*-EGMA) hydrogels can keep the solute such as drugs and biologically active materials inside of the hydrogels for a long period and release the solute from the hydrogels in response to an increase in the external pH above the pK_a of the hydrogel.

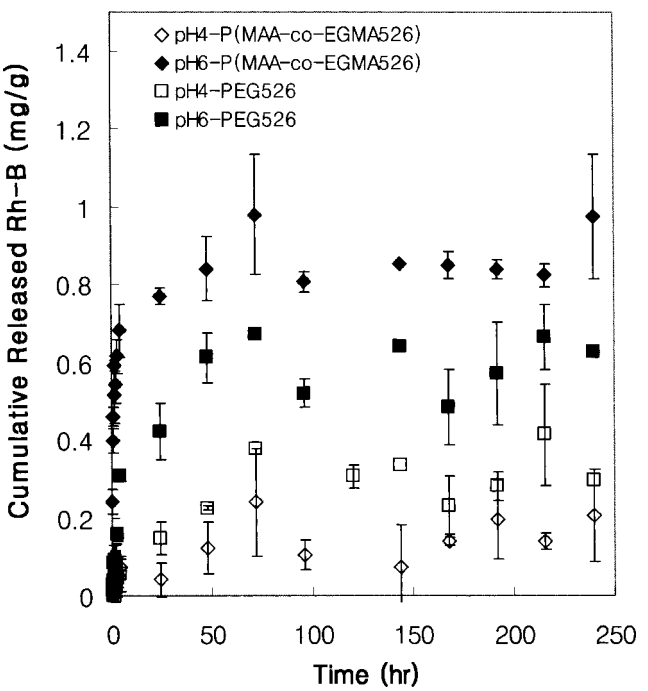

Figure 6 Cumulative amount of Rh-B released from PEG526 and P(MAA-*co*-EGMA526) hydrogels in pH 4.0 and 6.0 buffer solutions; P(MAA-*co*-EGMA526) at pH 4.0 (◇), P(MAA-*co*-EGMA526) at pH 6.0 (◆), PEG526 at pH 4.0 (□), and PEG526 at pH 6.0 (■) (average ± SD, $n = 3$).

TABLE I
Average Cumulative Amount of the Released Rh-B at pH 4.0($M_{R4.0}$) and Average Cumulative Amount of the Released Rh-B at pH 6.0 ($M_{R6.0}$) after 100 hours (Average ± SD, $n = 3$)

Hydrogels	$M_{R4.0}$ (mg/g)	$M_{R6.0}$ (mg/g)	$M_{R6.0}/M_{R4.0}$
P(MAA-*co*-EGMA526)	0.186 (±0.076)	0.879 (±0.062)	4.73
PEG526	0.318 (±0.071)	0.630 (±0.102)	1.98

CONCLUSIONS

pH-Sensitive P(MAA-*co*-EGMA) hydrogels having various molecular weights of pendent PEG and compositions of the crosslinker, PEGDMA, were prepared by free-radical photopolymerization. As the PEG526 hydrogels contained no ionizable functional groups, their swelling behavior was essentially independent of pH. However, the presence of MAA in the P(MAA-*co*-EGMA) hydrogels resulted in a typical pH-sensitive swelling behavior of anionic hydrogels, i.e., low swelling ratios at low pH and high swelling ratios at high pH. There was a drastic change in the equilibrium weight swelling ratio of P(MAA-*co*-EGMA) hydrogels at a pH of around 5, which is the pK_a of PMAA. The hydrogels were in a relatively collapsed state at a pH lower than 5 while at a pH higher than 5, the hydrogels swelled to a high degree. When the molecular weight of the pendent PEG of P(MAA-*co*-EGMA) hydrogels increased, the swelling ratio decreased at a pH higher than 5 and the pK_a of the hydrogels moved to higher pH ranges. When the concentration of the crosslinker of the P(MAA-*co*-EGMA) hydrogels increased the swelling ratio of the hydrogel decreased at a pH higher than 5. The P(MAA-*co*-EGMA) hydrogels showed a pH-responsive release behavior. At low pH (pH 4.0) small amounts of Rh-B were released while at high pH (pH 6.0) relatively large amounts of Rh-B were released from the hydrogels.

These results indicate that the P(MAA-*co*-EGMA) hydrogels can be used as a biological on–off switch with which the release of materials from the hydrogel can be controlled by the external pH change and pK_a of the hydrogels. In addition, the pK_a determining the on–off switch can be tailored by changing the type or composition of monomers and crosslinkers used to prepare the hydrogel.

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