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Investigation of swelling and controlled-release behaviors of hydrophobically modified poly(methacrylic acid) hydrogels

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Abstract

Using hydrophobic acrylic acid-2-ethylhexyl ester (AAEHE) as a comonomer of methacrylic acid (MAA), a series of hydrophobically modified (HM) poly(methacrylic acid) (PMAA) (HMPMAA) hydrogels were prepared by UV solution copolymerization and studied as controlled-release matrices. The result indicates that swelling degree of the HMPMAA hydrogels can sensitively respond to change in pH. However, the presence of hydrophobic AAEHE segments influences swelling kinetics of PMAA hydrogel evidently. Using *p*-hydroxyanisole (PHAS) as a model molecule, controlled-release behaviors of the HMPMAA hydrogels were investigated. It is found that the presence of hydrophobic AAEHE segments can markedly slow down the release rate of PHAS from PMAA-based hydrogels regardless of pH 1.4 or 7.4.

Keywords: Hydrophobically modified poly(methacrylic acid) hydrogel; pH sensitivity; Swelling kinetics

1. Introduction

Syntheses and characterization of controlled-release drug delivery systems based on smart hydrogels have attracted great attention from many polymer scientists in recent years due to their environmental-modulated release behaviors [1–6]. Smart hydrogels are the ones that can conventionally undergo a volume change in response to environmental stimuli including pH, temperature and ionic strength [7–29]. This leads to the fact that the diffusion and permeation of drug (or solute) molecules in a smart hydrogel can be controlled by the external stimuli [3–21]. For example, temperature-sensitive hydrogels like poly(*N*-isopropylacrylamide) (PNIPAm) can regulate drug release by controlling external temperature [8–11,14,15]; pH-sensitive polymer matrices like poly(methacrylic acid) (PMAA) can modulate drug release by change in pH [7,10–12,17,21]. From the viewpoint of potential applications, pH-sensitive hydrogels seem to be of significance. This is because the physiological pH range is from 1.2 to 7.4 and different body parts have a special pH surroundings. However, it should be noted that swelling transition of a pH-responsive hydrogel depends mainly on ionization of ionizable groups linked on the networks. As a result, when the groups are ionized under a certain pH condition, the hydrogel presents a rapid swelling rate, i.e., in a short time period a large amount of water can diffuse into the interior of the polymer matrix. This is due to the electrostatic repulsions between the ionized groups [4,5,11,16,17,21,23]. This leads to a disadvantageous burst-release pattern of drug or solute from the matrix [16,17]. On the other hand, in shrunken state, although a pH-sensitive hydrogel shows much lower swelling ratio than in swollen state, it still possesses hydrophilicity and a certain swelling degree. This does allow the entrapped molecules in the hydrogel to achieve a fast release rate [16], especially drugs with small molecular size and a certain water solubility. For a controlled-release system, these two negative factors should be avoided.

In recent years, many types of polymer carriers have been designed and prepared for overcoming the drawback of drug (or solute) burst-release kinetics from polymer matrices [8,9,11,14–21]. For example, in our earlier studies [14–16], we suggested and prepared novel hydrogels by incorporation

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of hydrophobic network into hydrophilic network via interpenetrating polymer networks technology. In these hydrogels, the moieties formed by hydrophobic networks could evidently retard drug release rate. This is because the hydrophobic microenvironment not only can limit the swelling degree of hydrogels but also may act as reservoirs of drug, from which drug can be released slowly. It was also found that for drugs or solutes with a certain dissolubility in water, their supermolecular interactions with cyclodextrin could effectively reduce their release rate from polymer matrices [17,18]. In addition, Lynch and Dawson [19] and Zhang et al. [20] introduced hydrophobic nanoparticles into hydrogel matrices for retarding drug release. With regard to chain interactions, if hydrophobic segments are randomly distributed onto hydrophilic polymer chains of a hydrogel, the segments can act as reversible physical crosslinks [21,22,30,31]. The crosslinks may form and dissociate according to environmental conditions [22]. This attribute may cause to inhibit polymer chain relaxation, and lower permeation and diffusion of water within the hydrogel at initial swelling stage, leading to a low mass transport behavior of the hydrogels [21,30]. Therefore, if this type of hydrogels is used as carriers of drug (or solute), especially drug (or solute) with small molecular size and a certain water solubility, a sustained release kinetics may be obtained. For this purpose, in this paper, we suggest hydrophobically modified pH-sensitive hydrogels for sustained drug (or solute) release. The HM hydrogels are prepared by copolymerization of methacrylic acid (MAA) with hydrophobic acrylic acid-2-ethylhexyl ester (AAEHE). PMAA was selected as a pH-sensitive polymer because of its both sharp pH-induced volume transition, that is, in the physiological pH range, and broad applications in biomaterial field [7,11].

Based on the above consideration, in this work, our objective is to investigate swelling properties of the HMPMAA hydrogels and feasibility of using them as possible carriers for sustained release *in vitro*. Using *p*-hydroxyanisole (PHAS) as a model molecule, the controlled-release mechanism of the HMPMAA hydrogels, and related structure–property relationship are studied in detail.

2. Materials and methods

2.1. Materials

All reagents including tripropylene glycol diacrylate (TPGDA, crosslinker), benzoin ethyl ester (BEE, photoinitiator), acrylic acid-2-ethylhexyl ester (AAEHE), *p*-hydroxyanisole (PHAS), methacrylic acid (MAA), 1,4-dioxane and dimethyl formamide (DMF) were made in China. They were used as received without further purification.

2.2. Synthesis of hydrophobically modified poly(methacrylic acid)

A series of HMPMAA hydrogels were prepared by UV solution copolymerization of MAA with AAEHE. Specifically, 3.2 g of monomer and comonomer (the compositions shown in Table 1), was added into 3.2 g of DMF/1,4-dioxane (1/1, wt/wt) mixture with 2 mol% of TPGDA and 2.0 wt% of BEE (based on total monomers, MAA and AAEHE). The polymerization was carried out under an UV source (400 W, middle-pressure mercury lamp, HOK4/120, Philips, Belgium) with a distance of 20 cm from lamp to sample. The obtained hydrogel was taken out from the bottle, cut into thin disks of 10 mm in diameter, and immersed in water/acetone mixture to remove the unreacted monomers at room temperature. The samples were kept in fresh water/acetone mixture that was changed for every 6–10 h and lasted 6 d. Later, they were dried under ambient conditions for 1 d and in a vacuum oven at 50 °C for 4 d. The thickness of the dried samples is about 0.7–0.9 mm.

Table 1
Synthesis recipes of the HMPMAA hydrogels

Samples	MAA/AAEHE (mol%/mol%)	UV irradiation time (min)
PMAA	100/0	8
HMPMAA-5	95/5	10
HMPMAA-10	90/10	15
HMPMAA-15	85/15	25
HMPMAA-20	80/20	25

2.3. Swelling measurements

The swelling ratio (SR) of a hydrogel was measured after it was swollen to a desired state at 37 °C. It was carefully taken out from the solution, wiped with a filter paper for the removal of the free water on the surface, and then weighted. SR (g/g) of a sample was calculated as follows:

$$\mathrm{SR} = (w_t - w_\mathrm{d})/w_\mathrm{d} \quad (1)$$

where w_d and w_t are the weights of dry and wet samples at time t, respectively. When a hydrogel reaches its swelling equilibrium state under a fixed condition, its swelling ratio is called equilibrium swelling ratio (ESR). All measurements were triplicated for each sample.

Preparation of buffer solution: KCl/HCl, pH 1.4; HCl/$KHC_6H_4(COO)_2$/NaOH, pH 3.0–5.0; NaOH/KH_2PO_4/Na_2HPO_4, pH 6.0–7.4; H_3BO_3/NaOH, pH 9. In order to obtain a solution with constant ionic strength of 0.1 M, a certain amount of KCl was introduced into the buffer solution.

2.4. Drug loading and in vitro release studies

Loading model drug (PHAS) into samples PMAA, HMPMAA-5, HMPMAA-10, HMPMAA-15 and HMPMAA-20 was performed in water/acetone (3/2, wt/wt) mixture with PHAS of 0.8%, 0.8%, 1%, 2% and 2%, respectively. After the hydrogels were swollen in the solutions at room temperature for 48 h, they were carefully taken out and washed with the mixture for the removal of PHAS on the surface. Then, the loaded samples were dried under an ambient condition for 1 d and in a vacuum oven at 40 °C for 4 d.

A PHAS-loaded disk was immersed in 25 mL of buffer solutions of pH 1.4 (or 7.4) with ionic strength of 0.1 M at 37 °C.

After a given time, a 10 mL of the solution released was withdrawn and at the same time a 10 mL of fresh solution was added. The concentrations of the PHAS released were analyzed by spectrophotometer (UV-2550 model, Shimadzu, Japan) at 222.4 nm. The cumulative fraction of the PHAS released from the loaded gels was calculated by the following equation:

$$\text{Cumulative fraction released} = M_t/M_\infty \quad (2)$$

where M_t is cumulative mass of PHAS released at time t, and M_∞ is the total amount of the PHAS released.

3. Results and discussion

3.1. Synthesis of HMPMAA hydrogels

Synthesis of HMPMAA hydrogels was carried out by UV solution copolymerization of MAA with AAEHE. Dimethyl formamide/1,4-dioxane (1/1, wt/wt) mixture was used as co-solvent and all polymerizations were conducted at 50% weight concentration based on the total monomers. The obtained hydrogels are transparent. Gelling time of the reaction systems was found to increases with an increase in hydrophobic AAEHE content. In order to avoid undesired self-crosslinking reaction during the photo-initiated polymerization, we took different UV irradiation time (Table 1) to prepare these hydrogels with different compositions and the time was obtained by direct observation of solidification of these polymerization systems. Taking the UV irradiation time, self-crosslinking reaction could not occur during the copolymerizations. The result was confirmed by polymerization of a similar system without any TPGDA crosslinker.

3.2. Swelling behaviors of HMPMAA hydrogels

Fig. 1 indicates pH-dependent swelling ratios of the obtained HMPMAA hydrogels. The investigation of swelling properties of the hydrogels was carried out in buffer solutions of pH from 1.4 to 9 with an ionic strength of 0.1 M at 37 °C. It was found that increasing pH led to swelling of the hydrogels and an evident swelling transition could be observed with change in pH. For example, at pH 1.4 the ESRs of samples PMAA, HMPMAA-5, HMPMAA-10, HMPMAA-15 and HMPMAA-20 were 1.5, 0.9, 0.6, 0.5 and 0.2, respectively; whereas at pH 7.4, their corresponding ESR values were 20.9, 21.7, 20.6, 18.9 and 16.5, respectively. This means that the HMPMAA hydrogels show pH sensitivity like homo-PMAA hydrogel. The sensitivity is related to pH-dependent ionization of side carboxylic acid (−COOH) groups of PMAA. As the solution becomes less acidic, the ionization of the carboxylic acid groups occurs, resulting in electrostatic repulsions between the ionized groups, which cause swelling degree of the hydrogels to reach to a relatively larger value accordingly [4–7,11,12,15,16,21–24]. Also, as seen clearly from Fig. 1, at pH = 5.5 (the pK_a value of pure PMAA [11]), the increase in the hydrophobic AAEHE component

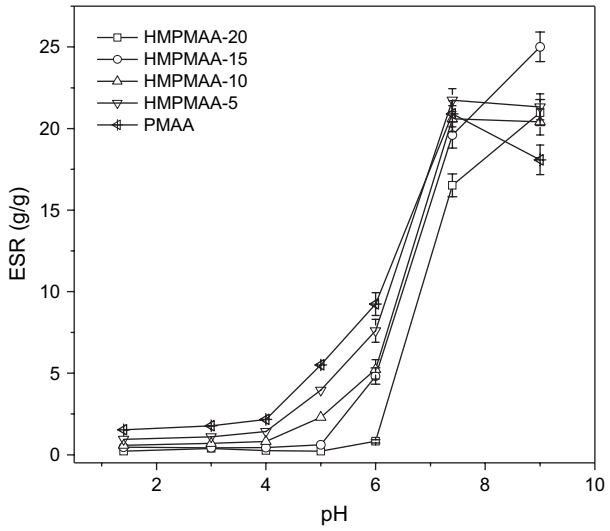

Fig. 1. ESR values of the HMPMAA hydrogels as a function of pH at 37 °C.

decreased the ESR values of the hydrogels evidently. This result can be explained by two possible reasons [5,16,21,22]. One is that the presence of hydrophobic AAEHE units may shield carboxylic acid groups and decrease the local dielectric constant near the network chain, and this can influence the value of dissociation constant of MAA units. As a result, the same equilibrium pH of the surrounding solution will correspond to a lower degree of ionization of a more hydrophobic hydrogel. The other is that the hydrophobic interactions between AAEHE units act as physical crosslinks that drives a HMPMAA hydrogel to form a compact structure. Thus, swelling of HMPMAA network has to overcome the resistances from the hydrophobic aggregation of AAEHE units. Therefore, under fixed conditions, swelling capacity of the HMPMAA hydrogels depends on driving force from −COOH groups, which are related to environmental pH. At low pH, owing to PMAA itself exhibiting coil state, the strong hydrophobic interaction leads to lower swelling ratio of the HMPMAA hydrogels [11,16,21,22]. For example, at pH 1.4 the ESR of PMAA was about seven-fold that of sample HMPMAA-20 with the highest AAEHE content. This evidences that the HMPMAA hydrogels were in a state of more compact structure in low pH solutions. The hydrophobic effect was also observed in the other hydrogel systems [21,22,29]. At pH from 6 to 7.4, the ESR values of all samples increased with pH. At pH 7.4, the ESR values of all obtained HMPMAA hydrogels exhibited small difference. Interestingly, it was found that at pH 9, the ESR values of all HMPMAA hydrogels were higher than that of PMAA (see Fig. 1). This means that the presence of hydrophobic AAEHE segments can increase swelling capacity of PMAA hydrogel at this pH, indicating that the HM hydrogels exhibit a looser structure compared with PMAA. Therefore, the swelling capacity of the HMPMAA hydrogels should depend on both the hydrophobic AAEHE content and environmental pH.

In fact, in aqueous media, drug (or solute) molecule release from its dried loaded polymer matrix is closely related to

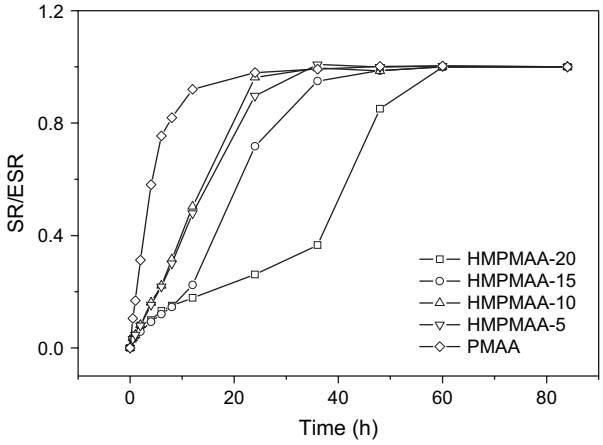

Fig. 2. Reswelling behaviors of the HMPMAA samples at pH 7.4 and 37 °C.

reswelling kinetics of the matrix [19,21]. Therefore, investigation of reswelling kinetics of the HMPMAA hydrogels seems to be of importance. Fig. 2 presents reswelling behavior of the hydrogels at pH 7.4. As seen from Fig. 2, reswelling kinetics of the hydrogels exhibited visible difference. This means that incorporation of the hydrophobic AAEHE units on PMAA chains by random distribution can change reswelling kinetics of PMAA. Obviously, the required time for reaching equilibrium swelling state increased markedly with an increase in the hydrophobic AAEHE content of the polymers. For example, the SR/ESR (the ratio of SR to ESR of a hydrogel) values of samples PMAA, HMPMAA-5, HMPMAA-10, HMPMAA-15 and HMPMAA-20 were 0.81, 0.30, 0.31, 0.15 and 0.15, for first 8 h, respectively. Over 24 h, their SR/ESR values were 0.98, 0.90, 0.95, 0.72 and 0.26, respectively. After 48 h, the SR/ESR value of sample HMPMAA-20 increased to 0.85. These results mean that the presence of hydrophobic AAEHE units can dramatically slow down the swelling rate of PMAA hydrogels. As seen clearly from Fig. 2, the reswelling process of the HMPMAA-15 and HMPMAA-20 hydrogels seems to be evidently classified into two stages, i.e., slow swelling stage followed by fast swelling stage. In the case of the former, the required time was 12 h for sample HMPMAA-15 and 36 h for sample HMPMAA-20. In order to further study this, taking sample HMPMAA-20 as an example, Fig. 3 presents its images in pH buffer solutions with ionic strength of 0.1 M. After sample HMPMAA-20 was kept in the solution of pH 1.4 for 300 h, it was found that its size showed less change compared with its dried sample. This further confirms that the HM hydrogel exhibits low swelling degree in low pH solution. When the sample was transferred to a solution of pH 7.4, its size still showed less change over 24 h, but after 72 h, it had been swollen considerably and its size presented larger change. The result is in agreement with that from Figs. 1 and 2.

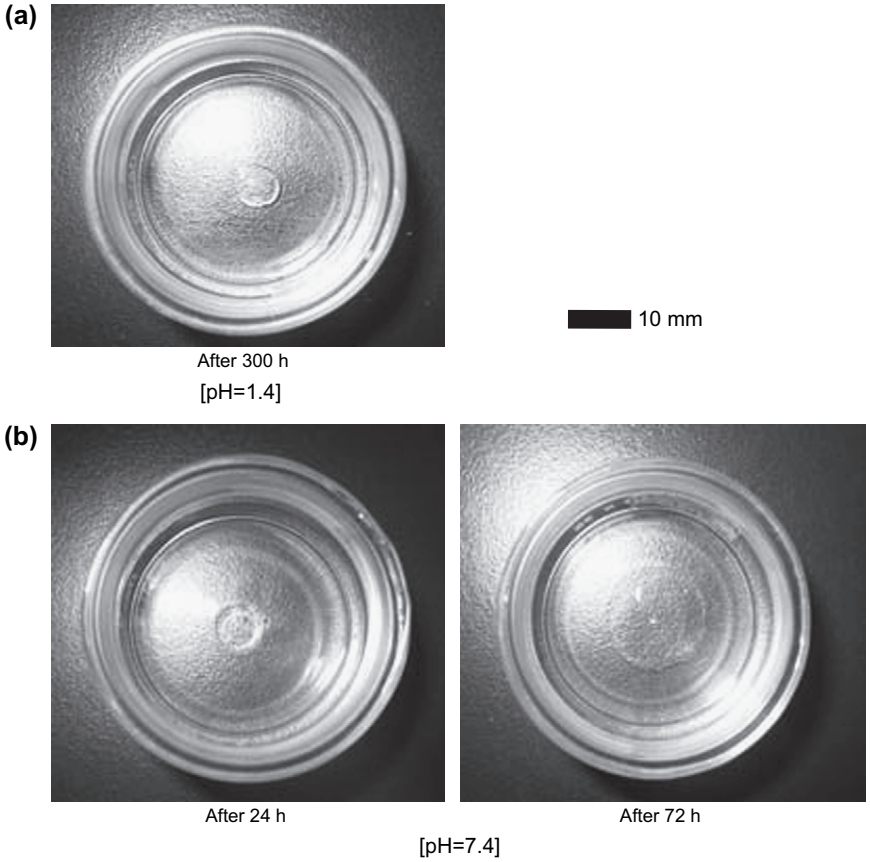

Fig. 3. Images of sample HMPMAA-20 in two pH buffer solutions (I = 0.1 M) at room temperature (the images obtained from a digital camera). (a): pH = 1.4 (b): pH = 7.4.

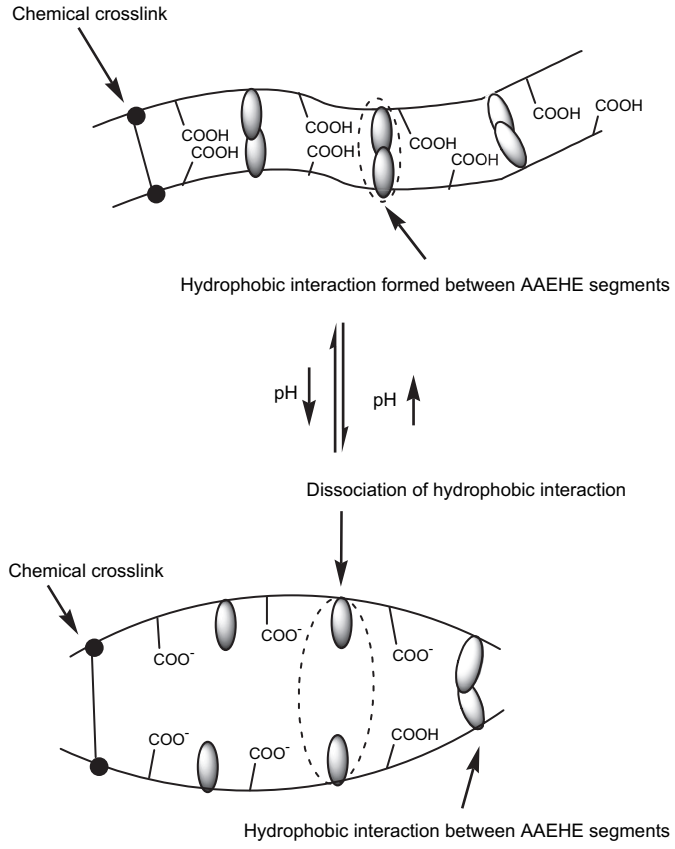

Fig. 4. Schematic illustration for pH-dependence of swelling mechanism of the HMPMAA hydrogels.

A schematic illustration for pH-dependent swelling mechanism of the HMPMAA hydrogels is shown in Fig. 4. Since the hydrophobic interactions act as physical crosslinks, at low pH (e.g., 1.4) the hydrophobic units can form stable hydrophobic domains duo to PMAA exhibiting low swelling ability. As swelling solution pH increased, the ionization of the carboxylic acid groups occurred and their electrostatic repulsions caused swelling degree of the hydrogels to increase [11,16,17,21–23]. In this case, the formed hydrophobic interactions between AAEHE units became weakened and finally dissociated, leading to expansion of the hydrogel network and increase in its swelling degree. Philippova et al. [22] investigated the copolymer hydrogels of acrylic acid (AA) with *n*-alkyl acrylates ($n = 8$,12 and 18) by the fluorescent probe method with pyrene as a probe and NMR spectroscopy. They found that the formation and the breakage of hydrophobic interactions of the hydrogels depended on external pH. The conclusion is in agreement with ours. Moreover, according to Fig. 4, it is easy to understand why the swelling kinetics of the HMPMAA hydrogels shows evident difference (see Fig. 1). This is attributed to slow dissociation of the formed hydrophobic interaction of the copolymer hydrogels under the driving force of $-COO^-$ groups. As depicted in Fig. 4, when the HMPMAA hydrogels were swollen by a solution of pH 7.4, the initially formed hydrophobic interactions acted as physical crosslinks and could effectively offer resistance to diffusion and permeation of water molecules into the hydrogels. The effect increased with an increase in hydrophobic AAEHE units of the polymers. Thus, at initial swelling stage, only front of the hydrogels was first swollen. With swelling process of the hydrogels proceeding and gradual breakage of the hydrophobic aggregation occurring, the whole networks of HMPMAA hydrogels began to expand. When the dissociation of the hydrophobic interactions reached some extent, a fast swelling process of the hydrogel could be observed. Therefore, the presence of hydrophobic groups can change swelling kinetics of hydrogels. Furthermore, it should be noted that at pH 9 (see Fig. 1), the ESRs of all HMPMAA hydrogels were higher than that of PMAA. This may be attributed to the fact that the hydrophobic segments reduce the influence of the shielding effect of counterions on swelling degree of the hydrogels. It is well known that shielding effect of counterions for a polymer network can reduce its swelling degree [11,16,23,26]. Therefore, it is reasonable to conclude that the presence of hydrophobic groups can reduce the shielding effect of counterions, leading to higher swelling capacity of the HMPMAA hydrogels compared with PMAA hydrogel. However, the final swelling degree of a HMPMAA hydrogel should depend on the balance of the both adverse effects.

It was also found that swelling behavior of the copolymer hydrogels differed from that of IPN hydrogel composed of hydrophobic and hydrophilic networks. For example, poly(acrylic acid)/poly(butyl acrylate) (PAA/PBA) IPN hydrogel [16], regardless of pH 1.4 or 7.4, the hydrophobic PBA network could markedly lower the swelling degree of PAA. At pH 1.4, the ESR of PAA/PBA IPN hydrogel was 1.3, while that of PAA hydrogel was 4.8; at pH 7.4, it was 7.8 for PAA/PBA IPN hydrogel and 45.1 for PAA hydrogel. And the change in the ESRs of the IPN with swelling solution pH followed similar trend which PAA hydrogel indicated. But for the HMPMAA hydrogels in this contribution, the presence of hydrophobic AAEHE units could lower ESR only at low pH region, at which $-COOH$ groups cannot be ionized. At pH 7.4, the HMPMAA hydrogels presented a similar swelling degree except that hydrogel HMPMAA-20 showed slightly lower ESR. At pH 9, all HMPMAA hydrogels exhibited higher swelling capacity than PMAA. Also, it was found that the swollen PAA/PBA IPN sample was opaque regardless of pH 1.4 or 7.4, evidencing that the phase separation of hydrophilic PAA and hydrophobic PBA networks of the IPN took place. Therefore, the swollen IPN sample is a multi-phase system. However, in this work all swollen HMPMAA hydrogel samples are transparent (see Fig. 3), indicating that these swollen HMPMAA hydrogels are a homogenous system, at least at macroscopic level. These results mean that swelling properties of a hydrogel depend on the architectures of its components in network.

3.3. Release studies of HMPMAA hydrogels

Fig. 5 presents the release profiles of PHAS from the HMPMAA hydrogels at pH 1.4 and 37 °C. As seen from Fig. 5, the cumulative fractions of the PHAS released from

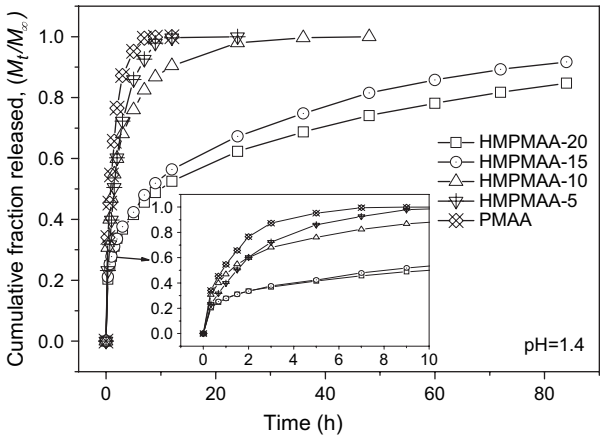

Fig. 5. Release profiles of PHAS from the HMPMAA hydrogels as a function of time at pH 1.4 and 37 °C.

samples PMAA, HMPMAA-5, HMPMAA-10, HMPMAA-15 and HMPMAA-20 were 0.55, 0.40, 0.46, 0.28 and 0.28, respectively, for the first 1 h; whereas over 5 h, the corresponding cumulative fractions of the PHAS released were 0.95, 0.85, 0.76, 0.43 and 0.41, respectively. In the case of PMAA, the loaded PHAS could almost be released within 7 h. But after 72 h the cumulative fraction of the PHAS released from samples HMPMAA-15 and HMPMAA-20 were 0.9 and 0.82, respectively. This result means that in the shrunken state of PMAA hydrogel, the presence of hydrophobic AAEHE segments can markedly retard the release of PHAS.

Fig. 6 shows the release profiles of PHAS from a series of the HMPMAA hydrogels at pH 7.4 and 37 °C. As seen from Fig. 6, the cumulative fractions of the PHAS released from PMAA, HMPMAA-5, HMPMAA-10, HMPMAA-15 and HMPMAA-20 were 0.68, 0.59, 0.32, 0.31 and 0.32, respectively, for the first 1 h; whereas over 2 h, the corresponding cumulative fractions of the PHAS released were 0.96, 0.93, 0.52, 0.37 and 0.39, respectively. For PMAA, the loaded PHAS could almost be released within 3 h. In contrast, the cumulative fractions of the PHAS released from samples

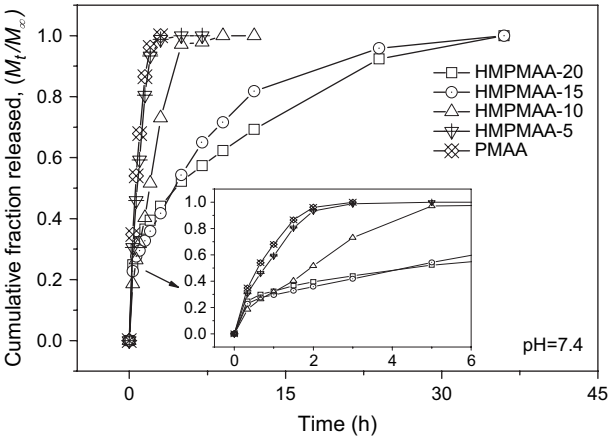

Fig. 6. Release profiles of PHAS from the HMPMAA hydrogels as a function of time at pH 7.4 and 37 °C.

HMPMAA-15 and HMPMAA-20 were only 0.95 and 0.92, respectively, for 24 h. This result indicates that the presence of hydrophobic AAEHE segments can still markedly retard the release of PHAS from PMAA at pH 7.4.

A comparison of the data shown in Figs. 5 and 6 indicates that the release rate of PHAS from the hydrogels is closely related to both the hydrophobic AAEHE content and environmental solution pH. At pH 1.4 PHAS release rate from the HMPMAA hydrogels was slower than at pH 7.4. The lower swelling degree of HMPMAA hydrogels at pH 1.4 is responsible for this release character. Furthermore, it is obvious that the presence of hydrophobic AAEHE units could effectively retard the PHAS release at both pH 1.4 and 7.4. However, regardless of pH 1.4 or 7.4, for every loaded sample, burst release of PHAS could be observed in initial time period. The result is attributed to the presence of PHAS at surfaces of hydrogels. When the loaded samples were immersed in aqueous solution, the PHAS was first released fast [7].

In order to further investigate the release nature of the HMPMAA hydrogels, the kinetics of PHAS release was analyzed using a semi-empirical equation (Eq. (3)) [7,19,21].

$$M_t/M_\infty = kt^n \tag{3}$$

$$\ln(M_t/M_\infty) = n\ln(t) + \ln(k) \tag{4}$$

where n is the diffusional exponent, which determines the release mechanism. The index n can be determined by plotting $\ln(M_t/M_\infty)$ against $\ln(kt^n)$ (see Eq. (4)) and determining the slope of the line obtained. When $n < 0.5$, the release is dominated by Fickian diffusion [19]; when $0.5 < n < 1$, the release follows non-Fickian diffusion; and $n = 1$ there is continuous zero-order release, where the system will be relaxation controlled [7,19,21].

Table 2 shows n values of the HMPMAA hydrogels according to Eq. (4). As seen clearly from Table 2, the presence of hydrophobic AAEHE units had a significant influence on the release nature of PHAS from PMAA hydrogels. At pH 1.4, the n values of the HMPMAA samples were below 0.5 except that the n of sample HMPMAA-5 was slightly higher than 0.5. This suggests that transport of PHAS in the polymer matrices was dominated by Fickian diffusion. At pH 7.4, the n values of samples PMAA, HMPMAA-5 and HMPMAA-10 were above 0.5; whereas the n values of samples HMPMAA-15 and HMPMAA-20 were still below 0.5 (see Table 2). These results indicate that release of PHAS from samples PMAA, HMPMAA-5 and HMPMAA-10 was dominated by non-Fickian

Table 2
Release nature of PHAS from the HMPMAA hydrogels

Samples	n	
	pH 1.4	pH 7.4
PMAA	0.44	0.61
HMPMAA-5	0.52	0.60
HMPMAA-10	0.38	0.55
HMPMAA-15	0.27	0.34
HMPMAA-20	0.26	0.28

diffusion, while that of HMPMAA-15 and HMPMAA-20 was still by Fickian diffusion. The results evidence that transport mechanism of PHAS in the polymer matrices depends on both the environmental pH and the hydrophobic AAEHE content.

The above results mean that release behaviors of PHAS are closely related to the hydrophobic AAEHE content in gel matrices. This further indicates that the presence of hydrophobic interactions plays a dominant role for controlled PHAS release. When a dried PHAS-loaded sample was immersed in water, there were two processes to begin simultaneously: the swelling of the hydrogels and release of PHAS. First, the PHAS at surface of the hydrogels could be fast released. Release of the PHAS located inside the hydrogels was closely related to reswelling behaviors of the hydrogels. This is because a more swollen gel is conductive to increasing diffusivity of the loaded molecules [19]. Owing to the hydrophobic interaction acting as physical crosslinks, at low pH region the HMPMAA hydrogels showed a more compact structure, and the more the hydrophobic AAEHE content the less its swelling degree was (see Fig. 4). This was responsible for lower PHAS release rate from samples HMPMAA-15 and HMPMAA-20. Upon pH being elevated (e.g., pH 7.4), although the HMPMAA hydrogels could be swollen by water and their final swelling capacity showed small difference, their swelling kinetics was evidently different. The swelling process was significantly affected by the hydrophobic interactions. Since swelling of the HMPMAA polymer matrices has to overcome resistance of the formed hydrophobic aggregations, in initial swelling process of the hydrogels, swelling rate was rather slow. In this case, PHAS release was limited, especially from samples HMPMAA-15 and HMPMAA-20 with high content of hydrophobic AAEHE units. Therefore, at pH 7.4 swelling process controlled by the hydrophobic interaction retarded the PHAS release from the polymer matrices. The experiment indicates clearly that the HMPMAA hydrogels used as PHAS carriers can combine properties of both pH sensitivity of PMAA and hydrophobic behavior of the AAEHE units. Therefore, PHAS release nature from HMPMAA hydrogel matrices depends on both external pH and the hydrophobic AAEHE content.

4. Conclusions

Using AAEHE as a hydrophobic comonomer of MAA, a series of hydrophobically modified PMAA hydrogels were prepared by UV solution copolymerization. The hydrogels can sensitively respond to change in pH like PMAA itself. However, their swelling capacity depends on both swelling medium pH and AAEHE. At low pH region, the presence of hydrophobic AAEHE segments can evidently reduce the swelling degree of the hydrogels, whereas at pH 9, the AAEHE segments can increase their swelling capacity. This may be a result of dilution effect of the hydrophobic units. At pH 7.4, the swelling kinetics indicates that the presence of hydrophobic AAEHE units can markedly slow down the swelling rate of the hydrogels. This may be attributed to the fact that the hydrophobic aggregation acts as physical crosslinks and thus inhibits polymer chain relaxation. Using *p*-hydroxyanisole (PHAS) as a model molecule, the release experiment indicates clearly that the HMPMAA hydrogels used as PHAS carriers can combine properties of both pH sensitivity of PMAA and hydrophobic behavior of the AAEHE units. It is found that the presence of hydrophobic AAEHE segments can effectively slow down the release rate of PHAS regardless of pH 1.4 or 7.4, and as a result, a sustained release kinetics can be obtained. The release mechanism is closely related to reswelling kinetics of the HMPMAA hydrogels.

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